Kaiyo Takubo

Pathology of the Esophagus

An Atlas and Textbook

2nd Edition

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With 453 Illustrations, Including 417 in Color

Springer

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This book was financially supported by the Japan Society for the Promotion of Science (Grant-in-Aid for Publication of Scientific Research Results: Grant No. 195203)

Library of Congress Control Number: 2007933157

ISBN 978-4-431-26267-1 Springer Tokyo Berlin Heidelberg New York

Springer is a part of Springer Science+Business Media
springer.com

Printed in Hong Kong

Typesetting, printing, and binding: SNP Best-set Typesetter Ltd., Hong Kong

Printed on acid-free paper

In Memory of My Father

Shuyo Takubo, DLitt

(1906–1979)

Preface

The first edition of this book, published in 2000, received widespread acclaim in reviews of pathology books and in gastroenterological journals such as *Der Pathologe* and *Gut*. A number of journals specializing in surgical pathology and gastroenterology recommended that Japanese physicians publish information in English in those fields, making it accessible in other countries, because many of the original papers had been published only in Japanese. In the first edition, I reviewed a large number of articles that were available in both Japanese and English, and tried to include as many Japanese papers as possible. For this second edition, I reviewed many additional papers in both languages that had been published after 2000, and added more endoscopy photographs to enable readers to acquire a better grasp of the correlation between histologic and endoscopic features.

For the present edition, specialists from all over the world generously provided not only specimens obtained by resection and biopsy, but endoscopic images as well. In the book, they are gratefully acknowledged by name. Among them, I am particularly grateful to Dr. Miwako Arima, Department of Gastroenterology, Saitama Cancer Center Hospital, for supplying many clear and beautiful endoscopic images.

In preparing the second edition, I received valuable suggestions and generous help from Ms. Sachiko Kobayashi, Ms. Eriko Takubo, and Ms. Yoko Takubo. The English manuscript was read through and revised by Dr. Neil K. Lambie, Department of Anatomical Pathology, Canterbury Health Laboratories, Christchurch, New Zealand. I also wish to thank Drs. Ken-ichi Nakamura, Akio Ishii, Naotaka Izumiyama-Shimomura, Junko Aida, Naoko Honma, Ichiro Kasahara, Tomio Arai, and Motoji Sawabe, members of the Research Team for Geriatric Diseases, Tokyo Metropolitan Institute of Gerontology, and Department of Pathology, Tokyo Metropolitan Geriatric Medical Center, for their help in preparing the manuscript.

The publication of this book was supported in part by a Grant-in-Aid for Publication of Scientific Research Results from the Japan Society for the Promotion of Science (195203). Many copies of the previous edition were donated to medical doctors and uni-

versities throughout the world, and a considerable number of copies of the present edition will also be donated to Asian and African countries.

I will feel rewarded for my efforts if this book proves to be of some assistance to readers in finding answers to their questions concerning the pathology of the esophagus and improves the lives of patients with esophageal diseases.

Kaiyo Takubo
Tokyo, March 31, 2007

Preface to the First Edition

The treatment of esophageal cancer with preoperative radiotherapy has become less frequent in Japan over the past twenty years, and this has given surgical pathologists much more opportunity to study resected specimens of the non-irradiated esophagus in detail. Previously, irradiated specimens did not allow a full understanding of the state of non-irradiated carcinomatous tissue, and this discouraged pathologists from studying the pathology of the esophagus, and, in particular, esophageal carcinoma. Formerly, therefore, there were only a limited number of pathologists in Japan who specialized in the study of the esophagus. Despite this our institutional research team has continued to study esophageal diseases, particularly esophageal tumors, mainly from a morphologic standpoint, and the findings have been occasionally reported in domestic and foreign medical journals. I was then given the opportunity to compile these findings into the present book.

Some excellent textbooks containing pathologic descriptions of esophageal diseases have already been published, including one by Vantrappen and Hellemans (Springer-Verlag, 1974), dealing with internal medicine, and one by Enterline and Thompson (Spinger-Verlag, 1984), focusing on pathology. The present book includes many cases previously reported in various medical journals from Japan and other countries. Therefore most of these case descriptions are known to be reliable as they have been reviewed by the editorial boards of the various journals, as well as by our own research team, and have been open to criticism by journal readers.

In this book I have tried to describe, in as detailed a way as possible, not only the major lesions but also the normal tissues and non-cancerous changes which may be observed in the esophagus and surrounding structures in both autopsy materials and resected specimens. In providing detailed descriptions particular consideration has been given to features which have received insufficient coverage in standard textbooks of histology.

Reference is made to both the macroscopic and histologic features of esophageal lesions and this is backed up by enzyme immunohistochemical, cytological and electron microscopic findings. Most of the cases referred to in this book have been my own

autopsy and surgical cases encountered at the Department of Pathology, Saitama Cancer Center Research Institute, the Department of Clinical Pathology, Tokyo Metropolitan Geriatric Hospital, and the Department of Clinical Pathology, Tokyo Metropolitan Institute of Gerontology. These resected specimens were obtained by my co-workers, Drs. K. Fujita, Y. Tanaka and K. Mafune of the Department of Abdominal Surgery, Saitama Cancer Center Hospital, and have also been studied by Professor K. Yamashita, Associate Professor K. Sasajima and Dr. M. Miyashita of the First Department of Surgery, Nippon Medical School. In addition, several rare cases have been provided by other institutions.

I will feel amply rewarded for my efforts if this book proves to be of some assistance to readers in finding answers to their questions concerning the pathology of the esophagus.

In preparing the English version of this book I was given valuable suggestions and generous help by Mses Tomoko Kawata and Yoko Takubo. The English manuscript was read through and revised by Drs. David B. Douglas (Douglas Science Editing Services, Yokose, Saitama, Japan) and Neil K. Lambie (Department of Histology, Green Lane Hospital, Auckland, New Zealand). In this regard, Dr. Lambie was of particular assistance. I am very grateful to them for their efforts. I also wish to thank Ken-ichi Nakamura, Sachiko Kobayashi, Sachiko Nishimura, Ayako Ishiyama and Tomomi Hiraide for their help in preparing the manuscript. The publication of this book was also supported in part by a Grant-in-Aid for the Publication of Scientific Research Results (1010012) which came from a Grant-in-Aid for Scientific Research given by the Ministry of Education, Science, Sport and Culture of Japan.

Finally, the names of my co-workers who assisted me in so many ways during my studies, and who should really be regarded as co-authors of this book, together with those who cooperated in our research by providing relevant information through personal communication, the supply of valuable tissue preparations or photographs, or the giving of technical assistance in the preparation of specimens, are cited on the following pages. I extend my sincere gratitude to them.

Kaiyo Takubo

Foreword to the Second Japanese Edition

The first edition of *Pathology of the Esophagus* by Kaiyo Takubo, M.D., Ph.D. received an enthusiastic reception in Japan, and in fact sold out within a year of its publication in 1992. As a colleague of Dr. Takubo working at the same hospital, I am proud to be associated with the publication of this second edition, which enlarges upon the first, both in terms of quality and quantity. I was sure in my conviction that the first edition would be highly acclaimed. Besides the richness of its content the excellent reputation of the book may also reflect how long a full-length text concentrating on the pathology of the esophagus had been awaited. Medical doctors who need to learn the pathology of the esophagus include not only pathologists but also various other specialists who deal with diseases of the alimentary tract such as endoscopists, gastroenterologists, surgeons and radiologists.

Although *Pathology of the Esophagus* is a book on specific pathology, it is written with reference to general pathology. When the first edition was planned and written Dr. Takubo was working at the Department of Pathology, Saitama Cancer Center Research Institute. In 1992, when the first edition was published, Dr. Takubo had already moved to our facility, the Tokyo Metropolitan Geriatric Hospital, as head of the Division of Clinical Pathology. With this move Dr. Takubo became involved in geriatric medicine, and this is reflected in the increased emphasis on general pathology in the second edition. In his present post as head of the Department of Clinical Pathology, Tokyo Metropolitan Institute of Gerontology, it is anticipated that Dr. Takubo will make further and broader strides in his field of research. I am honored to recommend the second edition of *Pathology of the Esophagus*, a significant text which is the envy of pathologists such as myself who have not had the opportunity to publish such an important work.

Yukiyoshi Esaki
Director, Department of Pathology
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February 12, 1996

Acknowledgments

I am indebted to the following doctors who provided me with illustrations:

Junko Aida, D.D.S., Research Team for Geriatric Diseases, Tokyo Metropolitan Institute of Gerontology, Tokyo.

Tomio Arai, M.D., Department of Clinical Pathology, Tokyo Metropolitan Geriatric Hospital, Tokyo.

Kunimasa Arima, M.D., Department of Ultrastructure and Histochemistry, Tokyo Institute of Psychiatry, Tokyo.

Miwako Arima, M.D., Department of Gastroenterology, Saitama Cancer Center, Ina, Saitama.

Ivan Cecconello, M.D., Department of Surgery, University of São Paulo School of Medicine, São Paulo, Brazil.

Yukiyoshi Esaki, M.D., Division of Pathology, Sayama Hospital, Sayama, Saitama.

Hiromasa Fujita, M.D., Department of Surgery, Kurume University School of Medicine, Kurume, Fukuoka.

Mutsunori Fujiwara, M.D., Department of Pathology, Japanese Red Cross Medical Center, Tokyo.

Shusaku Habu, M.D., First Department of Surgery, Hyogo College of Medicine and Department of Gastro-Intestinal Surgery, Ishinkai, Yao General Hospital, Yao, Osaka.

Akihiko Hamamatsu, M.D., Tokyo Medical Examiner's Office, Tokyo.

Ken Haruma, M.D., Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School, Kurashiki, Okayama.

Noriyuki Horiki, M.D., Department of Internal Medicine, St. Luke's International Hospital, Tokyo.

Reiko Horiuchi, C.T., Laboratory of Pathology, Maruko Central General Hospital, Maruko, Nagano.

Takao Ikeuchi, M.D., Department of Gastroenterology, Inada Noborito Hospital, Kawasaki, Kanagawa.

Kiyoshi Iria, M.D., Department of Pathology, University of São Paulo School of Medicine, São Paulo, Brazil.

Masayuki Itabashi, M.D., Ibaraki Prefectural Central Hospital & Cancer Center, Tomobe, Ibaraki.

Katsuhiko Iwakiri, M.D., Division of Gastroenterology, Department of Medicine, Nippon Medical School, Tokyo.

Hitoshi Iwasaki, M.D., Iwasaki Clinic, Yuwa, Akita.

Toshiyuki Kabuto, M.D., Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka.

Takeshi Kikuchi, M.D., Department of Internal Medicine, Chugoku Chuoh Hospital, Fukuyama, Hiroshima.

Kenji Kino, M.D., Department of Endoscopy, Tokyo Metropolitan Geriatric Hospital, Tokyo.

Hiroshi Kishimoto, M.D., Department of Pathology, Saitama Children's Medical Center, Iwatsuki, Saitama.

Yoichiro Kobashi, M.D., Department of Pathology, Tenri Hospital, Tenri, Nara.

Morio Koike, M.D., First Department of Pathology, Tokyo Medical and Dental University, Tokyo.

Atsushi Kokawa, M.D., Department of Gastroenterology, Inada Noborito Hospital, Kawasaki, Kanagawa.

Teruo Kouzu, M.D., Department of Endoscopic Diagnostics and Therapeutics, Chiba University School of Medicine, Chiba.

Hiroyuki Kuwano, M.D., Department of General Surgical Science (Surgery I), Gunma University Graduate School of Medicine, Maebashi, Gunma.

Mitsuo Maeda, M.D., Department of Internal Medicine, Harima Hospital of Ishikawajima-Harima Heavy Industries, Health Insurance Society, Aioi, Hyogo.

Shotaro Maeda, M.D., Department of Pathology, Tama-Nagayama Hospital, Nippon Medical School, Tama, Tokyo.

Ken-ichi Mafune, M.D., Department of Surgery, International University of Health and Welfare Mita Hospital, Tokyo.

Hiroyasu Makuuchi, M.D., Department of Surgery, Tokai University School of Medicine, Isehara, Kanagawa.

Shinji Masuda, M.D., Department of Pathology, Kouseiren Takaoka Hospital, Takaoka, Toyama.

Katsuaki Matsui, M.D., Department of Pathology, San-in Rosai Hospital, Yonago, Tottori.

Mitsumasa Matsuoka, M.D., First Department of Surgery, Kumamoto University School of Medicine, Kumamoto.

Masao Miyashita, M.D., Department of Surgery, Nippon Medical School, Tokyo.

Shinichi Mori, M.D., Mori Medical Clinic, Musashino, Tokyo.

Yoshihisa Morisaki, M.D., Division of Surgery, Sendai Hospital, Japan Self-Defense Force, Sendai, Miyagi.

Tetsuya Murata, M.D., Department of Pathology and Laboratory Medicine, JA Suzuka Hospital, Suzuka, Mie.

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Shuji Tada, M.D., Department of Gastroenterology, Saiseikai Kumamoto Hospital, Kumamoto.

Kimiya Takeshita, M.D., Department of Endoscopic Diagnosis and Therapy, Tokyo Medical and Dental University, Tokyo.

Masaharu Takeuchi, M.D., Miyoshi Hospital, Nishinomiya, Hyogo.

Yoichi Tanaka, M.D., Department of Abdominal Surgery, Saitama Cancer Center, Ina, Saitama.

Hironori Tokumo, M.D., Department of Gastroenterology, Hiroshima General Hospital, Hatsukaichi, Hiroshima.

Masamitsu Unakami, M.D., Department of Pathology, Watari Hospital, Fukushima.

Michael Vieth, M.D., Institute of Pathology Bayreuth Klinikum, Bayreuth, Germany.

Queng-hong Wang, M.D., Department of Pathology, Shanxi Provincial Tumor Hospital, Taiyuan, China.

Hiroyasu Yamada, M.D., Hiroshima Prefectural Hiroshima Hospital, Hiroshima.

Kiyohiko Yamashita, M.D., Department of Surgery, Nippon Medical School, Chiba Hokusoh Hospital, Chiba.

Koya Yokoyama, M.D., Narita Red Cross Hospital, Narita, Chiba.

Hajime Yonekawa, M.D., Department of Surgery, National Okura Hospital, Tokyo.

Muneki Yoshida, M.D., Department of Surgery, Kitasato University School of Medicine, Sagamihara, Kanagawa.

Tomoharu Yoshida, M.D., Department of Gastroenterological Endoscopy, Yamaguchi University School of Medicine, Ube, Yamaguchi.

Masatomo Yoshioka, M.D., Department of Surgery, Tama-Nagayama Hospital, Nippon Medical School, Tama, Tokyo.

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For Figs. 16-1 and 16-2
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Contents

Chapter 1
Embryology and Developmental Anomalies of the Esophagus

1.1. Embryology of the Esophagus

The esophagus becomes recognizable in the third week of gestation (crown-rump length: CRL, 2.5 mm), becoming distinguishable at this time from the pharynx and stomach. At the embryonal stage the esophageal epithelium is simple columnar type, difficult to distinguish from respiratory epithelium (Fig. 1-1). In the 8th week of gestation (CRL, 13 mm), vacuoles form among the columnar cells. Ciliated cells appear in the 10th week (CRL, 28 mm), and the vacuoles in the epithelium disappear by the 14th week (CRL, 72 mm). At this stage, the epithelium resembles pseudostratified columnar epithelium (Figs. 1-2, 1-3). The formation of squamous epithelium begins to be seen in the 4th month, initially in the midesophagus, but some ciliated cells may persist until birth. At the CRL 160-mm stage, the stratified squamous epithelium of the middle third of the esophagus occurs as discrete patches, separated by thinner areas of stratified columnar ciliated epithelium (Johns).

Esophageal cardiac glands appear in the 4th month. It is said that the mucosal columnar epithelium persists in the form of islets, developing into the esophageal cardiac glands and ectopic gastric mucosa. The histological appearance of the embryonal epithelium in the very early stages is clearly different from that of the epithelium of cardiac glands and islets of ectopic gastric mucosa. At the CRL 160-mm stage, cardiac glands can be seen projecting against the developing muscularis mucosae at the level of the second tracheal cartilage. Similar glands are also found at the lower end of the esophagus at this gestational stage.

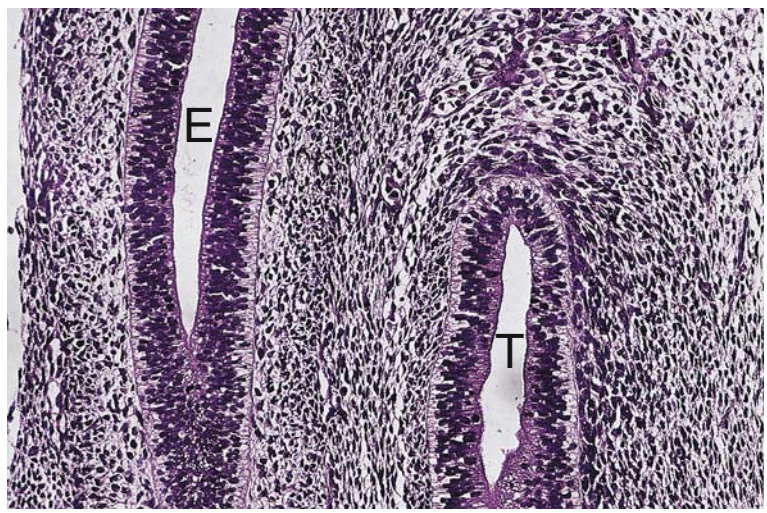


FIG. 1-1. Fetal esophagus and trachea in the 7th week of gestation (10-mm stage). It is difficult to distinguish between the esophageal epithelium (*E*) and the tracheal epithelium (*T*)

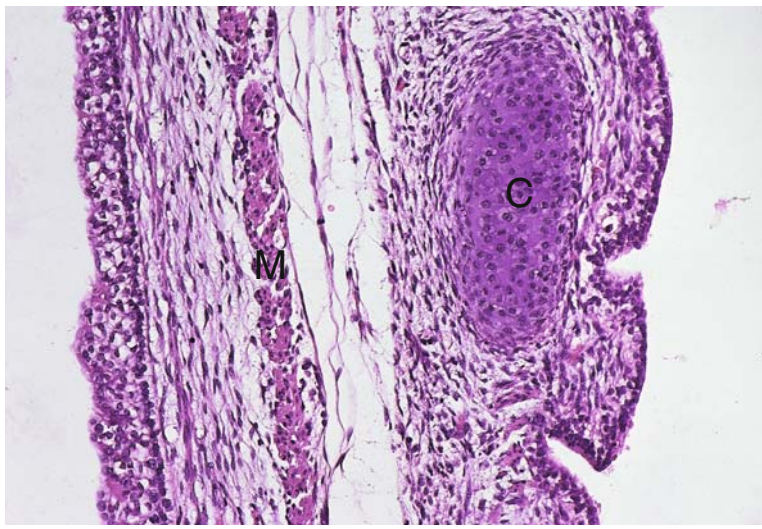


FIG. 1-2. Fetal esophagus and trachea in the 4th month of gestation. The muscularis propria (*M*) of the esophagus and the tracheal cartilage (*C*) are evident

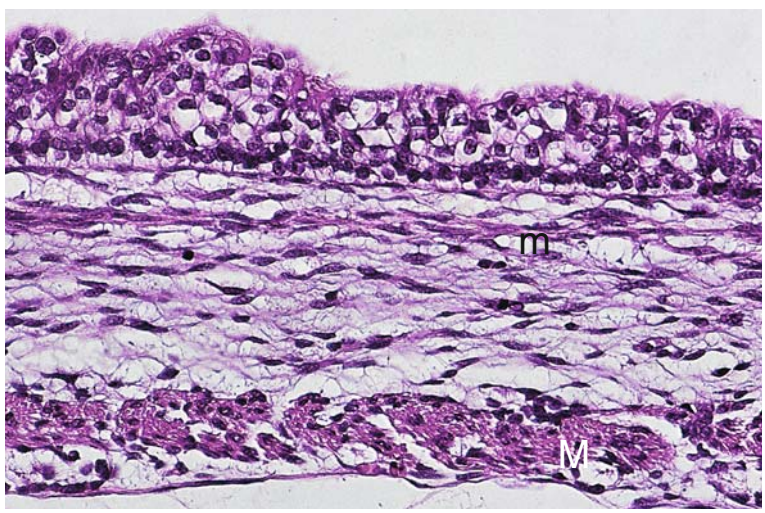


FIG. 1-3. Fetal esophageal wall in the 4th month of gestation. The epithelial cells are ciliated. *m*, muscularis mucosae; *M*, muscularis propria

The esophageal glands proper develop from the mucosal squamous epithelium in the 7th month of gestation. Esophageal glands proper were first seen in an embryo at the CRL 240-mm stage (Johnson). No esophageal glands proper were found in any of the embryonic material examined at the CRL 110-mm stage (Johns).

The inner circular muscle layer of the muscularis propria begins to appear in the 6th week, showing a pattern of spindle-shaped cells arranged regularly, surrounding the lumen; the cell density is higher in the developing muscle than in the surrounding connective tissue. The outer longitudinal muscle layer appears in the 10th week. Although both muscle layers consist initially of smooth muscle alone, striated muscle begins to appear in the upper esophagus in the 4th month.

The muscularis mucosae develops in the 4th to 7th months, beginning from the lower esophagus and proceeding proximally, in the form of one to three layers of aggregated spindle-shaped cells (see Fig. 1-3).

Neuroganglion cells are seen by the 7th week of gestation. Well-developed Meissner's and Auerbach's plexuses can be seen in the 5th month.

1.2. Developmental Anomalies

1.2.1. Congenital Esophageal Atresia

Congenital tracheoesophageal fistula was first reported as early as the 1600s (Rosenthal; Holder and Ashcraft). Congenital tracheoesophageal fistula and/or atresia is the most common developmental anomaly of the esophagus, having a reported incidence of 1 in 2000 live births. There have been many published reviews of esophageal atresia. It is usually classified into five types (Holder and Ashcraft), described as types A–E, types I–V, or types 1–5, according to different reviewers. In these reviews, the "A type" has not always described the same condition. Here, the five types are described as A to E, based on the description by Holder and Ashcraft.

Type A: Esophageal atresia unaccompanied by tracheoesophageal fistula.
Type B: Proximal tracheoesophageal fistula and atresia, or blind ending of the distal esophagus.
Type C: Proximal tracheoesophageal fistula and distal tracheoesophageal fistula, with esophageal atresia.
Type D: Blind ending of the proximal esophagus and distal tracheoesophageal fistula (Fig. 1-4).
Type E: Tracheoesophageal fistula without esophageal atresia (H-shaped tracheoesophageal fistula).

The relative frequencies of these five types have been reported in nearly 20 papers. In outline, more than 85% of patients have type D atresia with blind ending of the upper esophagus and a lower tracheoesophageal fistula (Spitz et al.). Types A and E reportedly account for 8% and 4% of cases, respectively, while types B and C together account for less than 1% of cases (Holder and Ashcraft).

In type D atresia, the upper esophagus is dilated and the fistula to the lower esophagus is located a few centimeters above the tracheal bifurcation, with a fibrous cord often present between the proximal and distal esophageal segments (Rosenthal). It has been reported that the esophageal wall in cases of esophageal atresia shows hypertrophy and atrophy of the muscularis propria as well as abnormalities of Auerbach's plexus (Nakazato et al.). Auerbach's plexus is reported to have a looser histological appearance than normal, particularly in the distal esophagus. Abnormalities have also been found in the muscularis propria (Nakazato et al.).

The diagnosis of H-shaped tracheoesophageal fistula (type E) is likely to be delayed (Kirk and Dicks-Mireaux). Some reported cases have not been found until adulthood.

Tracheoesophageal fistula is accompanied by other anomalies of the digestive and/or cardiovascular systems in more than 50% of cases (Spitz et al.).

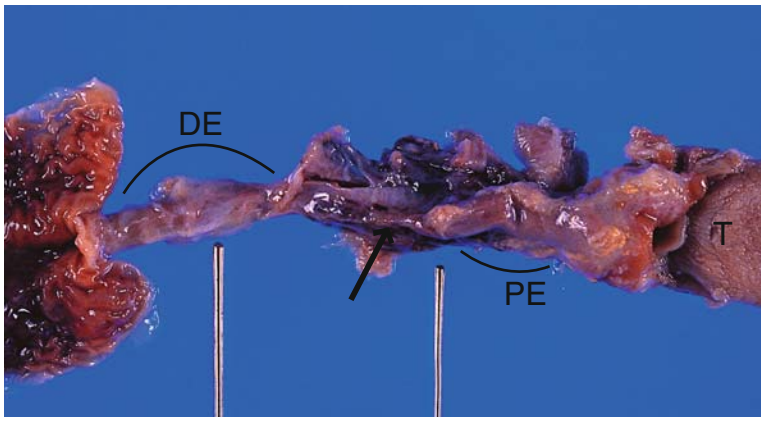


FIG. 1-4. Macroscopic appearance of congenital esophageal atresia (autopsy case). Note atresia of the upper esophagus and a lower tracheoesophageal fistula. *DE*, distal esophagus; *PE*, proximal esophagus; *T*, tongue; *arrow*, fibrous cord

1.2.2. Congenital Bronchoesophageal Fistula

Bronchoesophageal fistula is usually an acquired condition, congenital cases being rare. There have been far fewer published case reports of congenital bronchoesophageal fistula than of congenital tracheoesophageal fistula. The incidence is less than one-tenth that of tracheoesophageal fistula unaccompanied by esophageal atresia (Blackburn and Amoury).

Patients with congenital bronchoesophageal fistula do not usually have concomitant esophageal atresia. The fistula usually opens into the lumen of the right main bronchus, but some cases of a fistula opening into the left main bronchus have been reported (Azcoita et al.). Although some adult cases of congenital bronchoesophageal fistula have been reported (Sawamura et al.), it can be difficult to distinguish between congenital and acquired bronchoesophageal fistulae in adult patients. To make this distinction in adults, the following criteria of Brunner are often used:

1. There is no inflammation in tissue surrounding the fistulous tract or esophagus at the time of surgery.
2. There are no adhesions between the fistulous tract and lymph nodes.
3. There is histological evidence that the fistulous tract consists of esophageal mucosa, including muscularis mucosae.

On histological examination of their cases, Nakamura et al. found that the fistulous tracts were lined by flat stratified squamous epithelium, which showed a transition to respiratory epithelium via transitional epithelium.

1.2.2.1. Acquired Nonmalignant Tracheoesophageal Fistula and Bronchoesophageal Fistula

Most cases of acquired tracheoesophageal or bronchoesophageal fistula are the result of infiltration by esophageal cancer, other causes being rare. Causes other than carcinomatous involvement have been reviewed by Wesselhoeft and Keshishian, who noted a high proportion of inflammatory (e.g., tuberculosis) and traumatic cases, although there were also a number of cases of unknown etiology. Other reported nonmalignant causes have included bronchogenic cyst, esophageal diverticulum with diverticulitis (Braimbridge and Keith), and necrotizing vasculitis.

1.2.3. Esophageal Cysts

1.2.3.1. Congenital Esophageal Duplication Cyst

Congenital esophageal cyst (Figs. 1-5, 1-6) has also been called esophageal intramural cyst or esophageal duplication cyst, and more than 45 cases have been reported in Japan (Iseki et al. 1985). As there are no definite criteria to distinguish between a congenital cyst and congenital esophageal duplication, cases with a bulbar lumen may be classified as cysts and those with a columnar lumen as

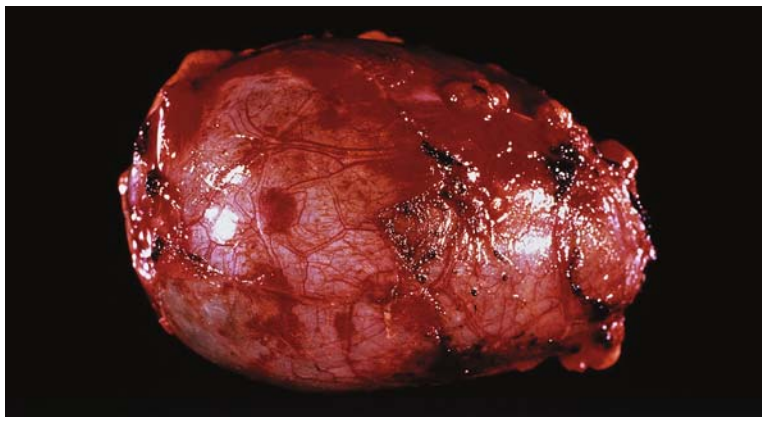


FIG. 1-5. Macroscopic appearance of the outer surface of a congenital esophageal cyst (surgical specimen). Arteries and veins are seen on the outer surface

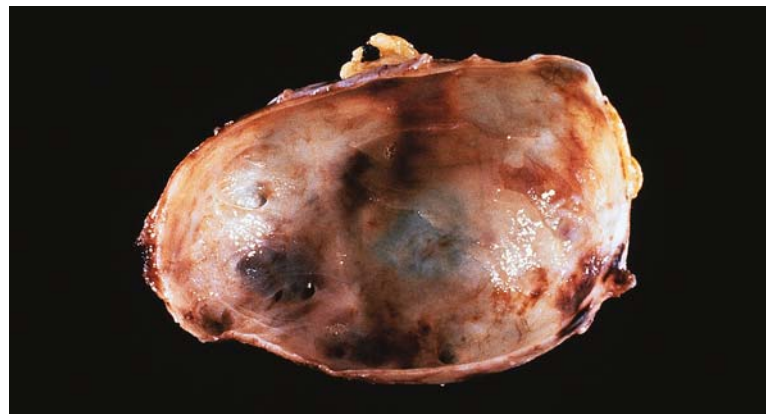


FIG. 1-6. Macroscopic appearance of the inner surface of a congenital esophageal cyst. The inner surface is lined by white mucosa

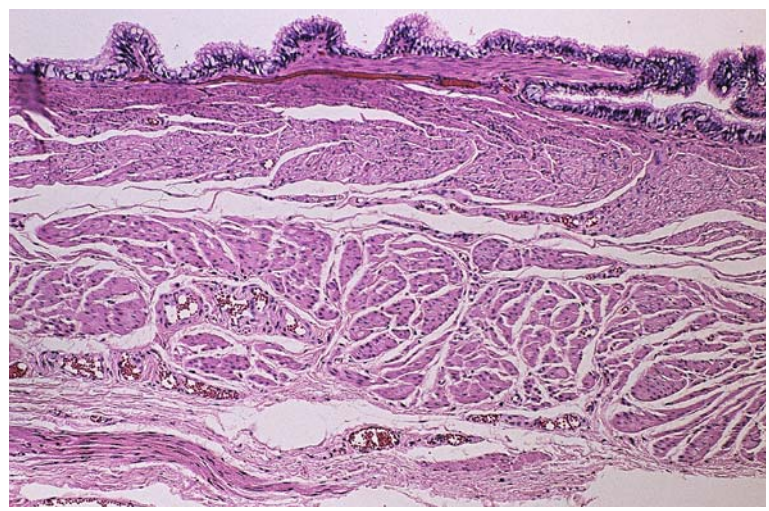


FIG. 1-7. Inner surface of a congenital esophageal cyst. The lining consists of simple columnar ciliated epithelium

esophageal duplications. However, most cases reported to date have had a bulbar lumen. Nowadays, both these are usually called congenital esophageal duplication cysts.

Usually the lumen of a congenital esophageal duplication cyst has no communication with the esophageal lumen, but some cases showing such a communication have been reported from Japan (Iseki et al.) and elsewhere (Robison et al.; Ratan et al.). This situation is sometimes called a congenital esophageal diverticulum.

Congenital esophageal duplication cysts usually occur in the lower third of the esophagus, with very few cases involving the cervical esophagus. The cyst is located in the esophageal wall. The wall of the cyst has the same structure as the wall of the normal digestive tract, having a muscularis mucosae and a muscularis propria (Arbona et al.). Cysts with a different wall structure are not classified as congenital esophageal duplication cysts.

Congenital esophageal duplication cysts are usually lined by stratified squamous epithelium, pseudostratified epithelium resembling the embryonal esophageal epithelium, columnar epithelium, or cuboidal epithelium (Fig. 1-7). However, some cysts lack an epithelial lining (Kaneko et al.). Figures 1-5 through 1-7 show the macroscopic and histological features of a congenital esophageal duplication cyst, reported by

Suzuki et al., which occurred in a 28-year-old man.

Massive hemorrhage into an esophageal duplication cyst was reported by Gatzinsky et al.

Malignancy arising in esophageal duplication cysts has also been reported. A squamous cell carcinoma, which arose in an esophageal duplication and was surgically resected, has been reported from Japan (Shimada and Akai), and two autopsy cases of adenocarcinoma arising in esophageal duplication cysts have been reported (Butler and Ende; Boivin et al.). Lee et al. (1998) reviewed four cases of malignancy arising in esophageal foregut duplication cysts; these included three adenocarcinomas and one squamous cell carcinoma.

1.2.3.2. Gastroenteric Cyst

Some cases of gastroenteric cyst of the esophagus, lined by gastric fundic mucosa (Kaneko et al.) or small intestinal mucosa, have been reported (Salyer et al.).

1.2.3.3. Bronchogenic Cyst

A few bronchogenic cysts of the esophagus have also been reported (Arbona et al.). The wall of bronchogenic cysts consists of pseudostratified ciliated epithelium, and the underlying tissue contains bronchial glands and cartilage, but there is no muscularis mucosae as seen in the digestive tract (Figs. 1-8, 1-9). These cysts are more often located on the right side of the esophagus than the left.

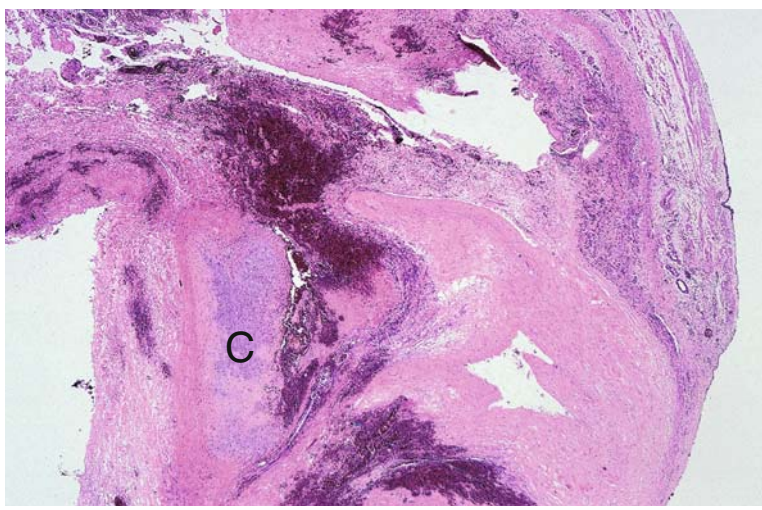


FIG. 1-8. Bronchogenic cyst of the esophagus. There is cartilage (*C*) in the wall

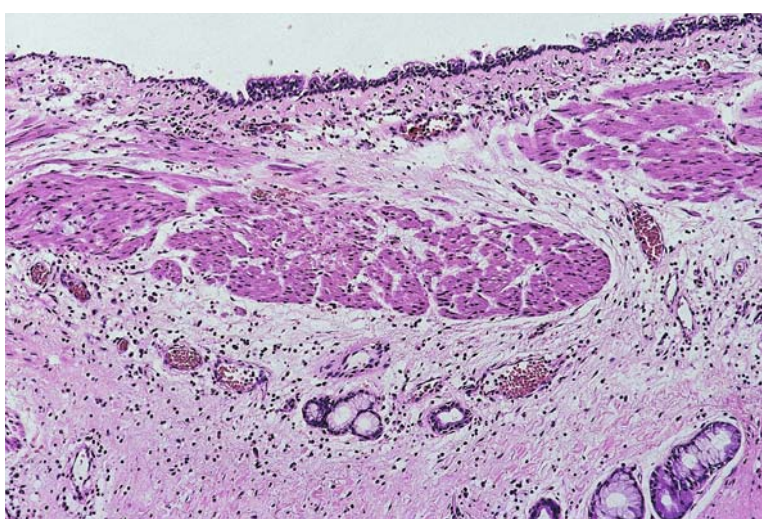


FIG. 1-9. Bronchogenic cyst of the esophagus. Ciliated pseudostratified epithelium and bronchial glands are seen on the inner aspect of a bronchogenic cyst. The wall does not have muscularis mucosae

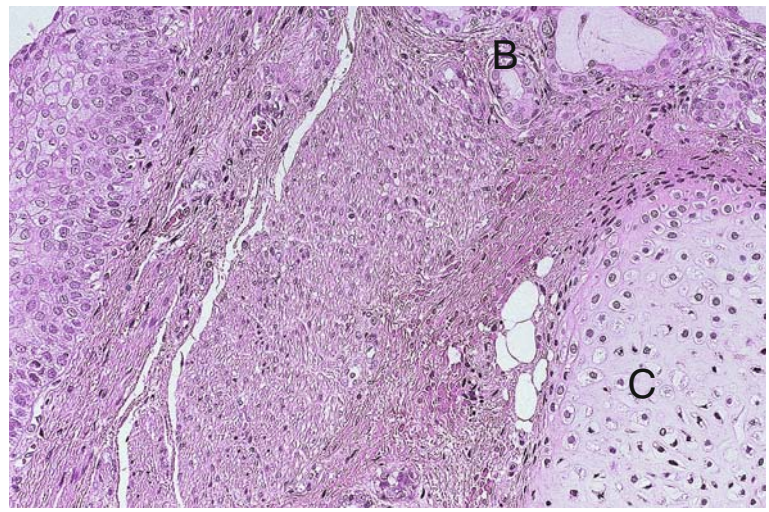


Fig. 1-10. Congenital esophageal stricture. Cartilage (*C*) and bronchial glands (*B*) are seen in the submucosa of the esophageal wall in the stenotic segment

1.2.3.4. Other Cysts

Another described type of cyst that can occur in the esophageal wall has a structure different from that of the wall of the digestive tract and no cartilage. This type is known as a nonspecific or simple cyst because it cannot be classified as either a congenital esophageal duplication cyst or a bronchogenic cyst (Arbona et al.). These cysts, together with esophageal duplication cysts, gastroenteric cysts, and bronchogenic cysts, are collectively called foregut cysts.

1.2.3.4.1. Retention Cyst

This type of cyst is described in Chapter 9, under benign epithelial tumors and tumor-like conditions (p. 109).

1.2.4. Congenital Esophageal Stricture

The incidence of congenital esophageal stricture is extremely low compared to that of congenital esophageal atresia, occurring in only 1 in 25 000 live births. The stenotic segment is usually located in the lower or middle third of the esophagus and measures up to 1.5 cm in length.

Congenital esophageal strictures are classified into three types: tracheobronchial remnant type, fibromuscular type, and membranous type (Akaboshi et al.). In the tracheobronchial remnant type, histological examination often shows the presence of tracheobronchial remnants. Cartilage (Paulino et al.), respiratory epithelium, bronchial glands (Fonkalsrud), and lymphatic tissue may be found in the submucosa or muscularis propria (Kuroda and Akata) of the strictured segment (Fig. 1-10). This type usually occurs in the abdominal part of the esophagus. In the fibromuscular type, there is fibromuscular thickening of the inner circular muscle layer of the esophageal wall at the site of the stricture. This type usually occurs in the thoracic esophagus. The membranous type of congenital esophageal stricture is rare; in a series of 50 cases of congenital esophageal stricture reported from Japan, 3 were of the membranous type (Akaboshi et al. 1973).

1.2.5. Laryngotracheoesophageal Cleft

Laryngotracheoesophageal clefts are rare developmental disorders of the upper aerodigestive tract that range in severity from being virtually asymptomatic throughout life to being incompatible with life. Upper airway clefts range from small soft tissue defects to complete clefts involving the larynx, trachea, and esophagus. The complete type of laryngotracheoesophageal cleft has a mortality of greater than 90% (Myer et al. 1990).

Chapter 2
Structure of the Esophagus

2.1. Anatomy of the Esophagus

The esophagus is a highly distensible muscular organ with a tubular form that connects the pharynx to the stomach. It is compressed anteroposteriorly, and in transverse sections has an ovoid shape, except when food is passing along it.

The human esophagus measures 11 cm in length at birth and about 25 cm in length in adulthood; the distance from the upper incisor teeth to the cardia is generally reported, in Japan, to be 37–40 cm. The average length of the esophagus in 209 adults in Chile was reported to be 27.5 ± 2.1 cm, and a direct correlation was shown between esophageal length and subject height. Adults with a height of 159 cm or less had an esophageal length of 26.1 ± 2.2 cm (Csendes et al.).

The esophagus arises from the hypopharynx at the level of the inferior margin of the cricoid cartilage (at the level of the 6th cervical vertebra), but its mucosal surface cannot be distinguished from that of the hypopharynx. The esophagus connects with the cardia of the stomach at the level of 11th or 12th thoracic vertebra.

The esophagus can be divided into three parts. The first, the cervical esophagus (Ce), is a short segment, ending at the superior margin of the sternal manubrium. It is situated in the midline, running posterior to the membranous portion of the trachea and anterior to the vertebral column. The thoracic esophagus (Te) descends anterior to the vertebral column and thoracic aorta and passes through the esophageal hiatus of the diaphragm. After entering the thorax, the esophagus gradually deviates to the left of the trachea, and at the level of the tracheal bifurcation is more or less situated behind the left main bronchus. The esophagus is initially situated to the right of the thoracic aorta in the upper thorax but it gradually comes to lie in front of the aorta and, when it passes through the esophageal hiatus of the diaphragm, is situated left and anterior to the aorta. The thoracic esophagus is further divided into three subsections: the upper thoracic esophagus (Ut), extending from the level of the superior margin of the sternal manubrium to the level of the inferior margin of the tracheal bifurcation; the middle thoracic esophagus (Mt), extending from the level of the inferior margin of the tracheal bifurcation to a point midway between this and the esophagogastric junction; and the lower thoracic esophagus (Lt), extending from midway between the inferior margin of the tracheal bifurcation and the esophagogastric junction to the level of the diaphragm within the thorax. The abdominal esophagus (Ae) is the shortest of the three segments. It extends from the level of the esophageal hiatus in the diaphragm and, after curving slightly leftward, connects with the cardia of the stomach at a point left and anterior to the 11th or 12th thoracic vertebra. The angle of Hiss is formed on the left side between the esophagus and the adjacent stomach.

In the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*, 10th edition (2007), edited by the Japan Esophageal Society, the location of esophageal carcinomas is described in relation to the five parts Ce, Ut, Mt, Lt, and Ae (Fig. 2-1).

Three areas of constant narrowing are found in the esophagus. The first constriction is located at the upper end of the esophagus, at the level of the 6th cervical vertebra and about 15 cm from the

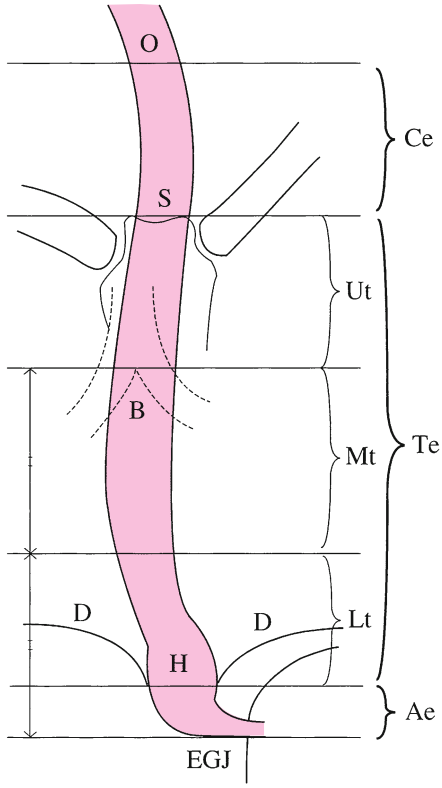


FIG. 2-1. Five parts of the esophagus. The esophagus is divided into five parts, based on the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (9th edition), from the Japanese Society for Esophageal Diseases. *O*, esophageal orifice; *S*, upper margin of the sternum; *B*, tracheal bifurcation; *D*, diaphragm; *EGJ*, esophagogastric junction; *H*, esophageal hiatus

upper incisor teeth. The second is located near the tracheal bifurcation, at the level of the 4th–5th thoracic vertebra and about 25 cm from the incisor teeth. The third is located just above the point at which the esophagus traverses the diaphragm, at the level of the 11th thoracic vertebra and about 40 cm from the incisor teeth.

When empty, the esophagus has longitudinal mucosal folds and a very narrow lumen, with an irregular shape in cross section. When food is swallowed, the folds become flat. The mucosal surface is whitish to light orange in color. The esophageal wall in cross section can be divided macroscopically, by tissue density, into lamina propria mucosae, lamina muscularis mucosae, tunica muscularis propria, and tunica adventitia. After fixation, the smooth muscle of the tunica muscularis propria in the lower and middle parts of the esophagus has an ivory color, but the striated muscle in the upper part is brown. The smooth and striated muscles are thus recognizable macroscopically.

In the upper thoracic region, the azygos vein runs on the right side of the esophagus and the thoracic duct runs posteriorly.

The vagus nerves run on the left and right sides of the cervical esophagus. The left vagus nerve trunk runs anterior, and the right vagus nerve trunk posterior, to the thoracic esophagus.

2.2. Histology, Cytology, and Electron Microscopy of the Normal Esophagus

2.2.1. Tunica Mucosa

The esophageal mucosa is composed of flat stratified squamous epithelium, lamina propria mucosae (lamina propria), and lamina muscularis mucosae (muscularis mucosae).

2.2.1.1. Normal Mucosal Epithelium

The normal mucosal epithelium is a thick, nonkeratinizing, flat stratified squamous type, comprising about 10–20 layers of cells and measuring 300–500 μm in thickness in resected specimens (Fig. 2-2). Resection specimens, including specimens obtained by endoscopic mucosal resection, usually have much thinner epithelium than biopsy specimens, because the superficial layers are likely to be lost in peri- and postoperative handling, and in Japan resected esophagi are stretched to their original length before fixation. Epithelial cells lying on the basement membrane are called basal cells and are cuboidal or polyhedral in shape. Above these, parabasal cells and prickle cells lie in layers. The layers of basal and parabasal cells reportedly account for 15% or less of the thickness of the epithelium. The epithelial cells become flatter as they approach the surface, and those in the uppermost layer are very thin and attenuated, resembling disks. Although they still possess nuclei, these are small and condensed. The prickle cells contain a large quantity of glycogen in their cytoplasm, which stains periodic acid–Schiff (PAS) positive. The cells in the superficial layers some-

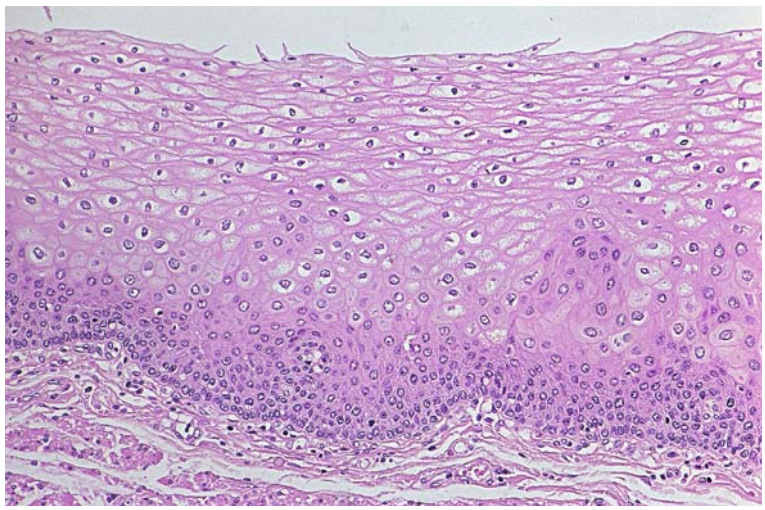


FIG. 2-2. Normal mucosal epithelium of the esophagus. This is a flat stratified squamous epithelium without keratinization

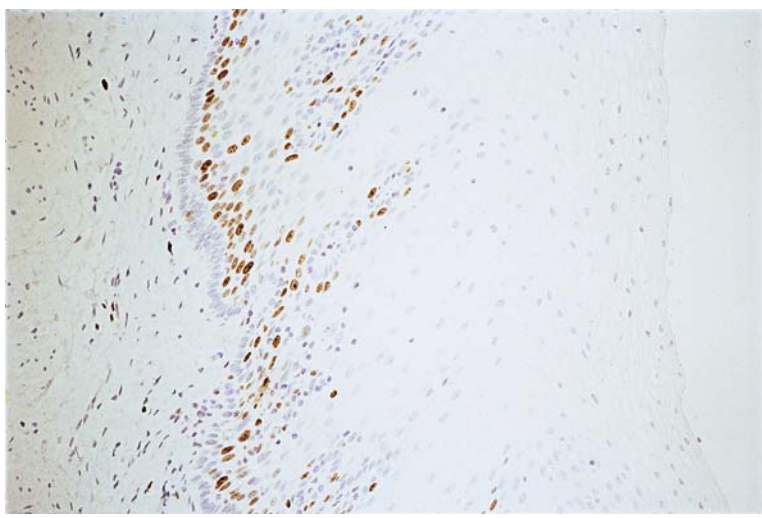


FIG. 2-3. Normal mucosal epithelium (Ki-67 immunostain). The basal cells do not stain but parabasal cells stain positive for Ki-67

times contain keratohyaline granules, but there is usually no keratinization of the esophageal epithelium.

The turnover time of the esophageal epithelium is about 4–7 days in rats and mice. The corresponding period is said to be 10 days or less in humans, although no definite data are available. Mitotic figures have been said to be present normally in the basal layer. Ito and Ishii (1970), however, reported that mitotic figures were found in the deeper parabasal layer, but not in the basal layer. Ki-67 (MIB-1) immunostaining of biopsy specimens usually shows a negative reaction in the basal layer and a positive reaction in the parabasal layer (Fig. 2-3), with very few basal cells being Ki-67 positive (Seery and Watt 2000). Telomerase immunostaining shows a positive reaction in both the basal and parabasal layers (Fig. 2-4). The telomere of the basal cells is longer than that of the prickle cells. These findings suggest that epithelial stem cells may be in the basal layer but that proliferative activity occurs in the parabasal layer (our unpublished data, 2006). It was previously believed that, after mitosis, one of the two daugh-

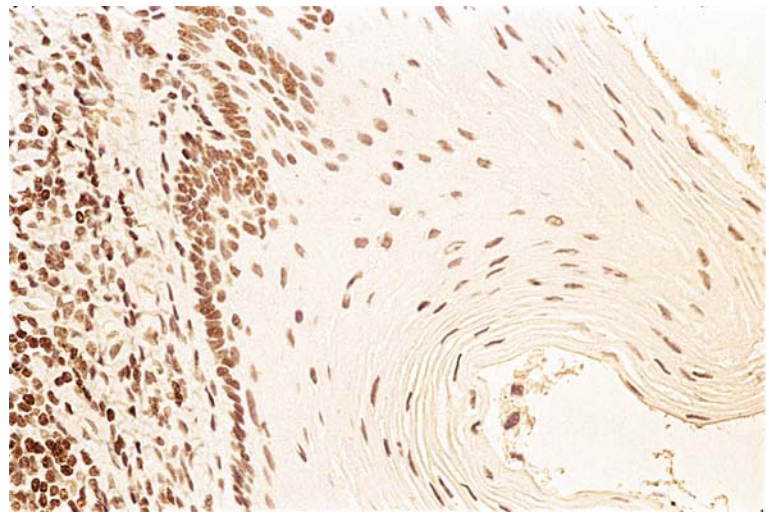


FIG. 2-4. Normal mucosal epithelium (telomerase, hTERT, immunostain). The basal and parabasal cells stain positive for telomerase. Lymphocytes stained positive for telomerase

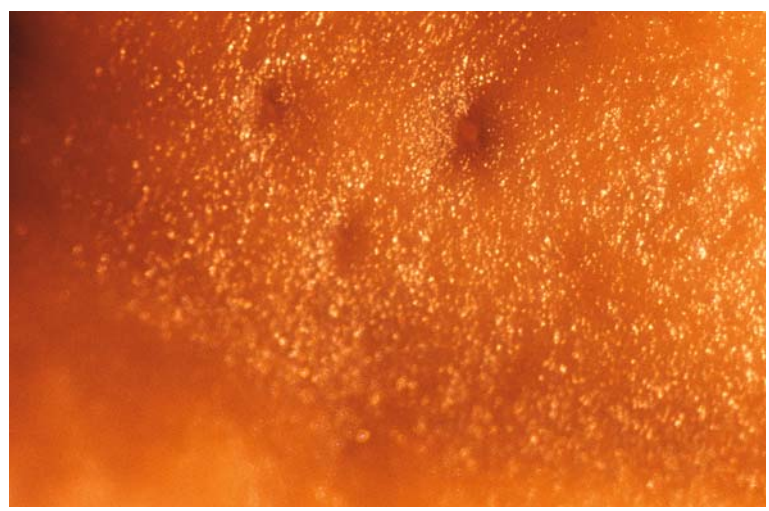


FIG. 2-5. Dissecting micrograph of the esophageal mucosal epithelium (glutaraldehyde-fixed). Openings of esophageal glands proper are evident

ter cells would always stay on the basement membrane while the other would become a prickle cell. However, Marques-Pereira and Leblond (1965) showed that, after mitosis, both daughter cells remain as basal cells and that both, or occasionally only one, later become prickle cells.

In addition, a small number of T lymphocytes (cytotoxic T cells), and fewer granulocytes, are present in the epithelium. The presence of these T lymphocytes is not considered to be pathological. The granulocytes include neutrophils and basophils. Eosinophils appear in various pathological conditions, particularly reflux esophagitis and idiopathic eosinophilic esophagitis.

When examining the esophageal epithelium from the luminal aspect with a dissecting microscope, fine concavities and convexities can be seen in the superficial layer, and the openings of the esophageal glands proper can also be observed (Fig. 2-5).

The cytological features of the epithelium are very simple, reflecting the simplicity of the

histology. Nonkeratinizing superficial cells, having attenuated thin cytoplasm and small nuclei, are often stripped off in sheets. A few keratohyaline granules are sometimes seen in the cell cytoplasm (Fig. 2-6). Keratinizing epithelial cells derived from the oral mucosa may also be seen with esophageal epithelial cells, because oral and esophageal epithelial cells are often intermixed during sampling.

It is apparent by electron microscopy that basal cells are cuboidal and lie on the basement membrane, being bound to the membrane by hemidesmosomes. Their nuclei are nearly elliptical, and they have sparse glycogen but abundant free ribosomes in their cytoplasm (Fig. 2-7). Intracytoplasmic keratin filaments are increased in number in the upper prickle layer. The cells make contact with each other via microvilli and are bound together by numerous desmosomes. They possess abundant glycogen, but relatively few mitochondria (Fig. 2-8). The squamous epithelium is also said to be characterized by the presence of membrane-coated cytoplasmic granules, up to 0.5 μm in size.

Low-magnification scanning electron microscopy, as does examination with the dissecting microscope, allows clear observation of the openings of the esophageal glands proper (Fig. 2-9). Mucus is occasionally seen in these openings. The outlines of the epithelial cells in the most superficial layer are also recognizable (Fig. 2-10). At high magnification, microvilli on the surface of superficial squamous epithelial cells can be seen, resembling a shaggy carpet (Fig. 2-11).

2.2.1.1.1. Free Nerve Endings

Free nerve endings have been described in intraepithelial spaces in the stratified squamous epithelium of the upper third of the esophagus (Spassova 1959; Robles-Chillida et al. 1981). The nerve endings reaching the subepithelial plexus emanate from the submucosal plexus. The axons are surrounded by Schwann cell processes for a short distance as they extend through the basement membrane, but then are devoid of Schwann cells when among the epithelial cells (Figs. 2-12, 2-13a,b). Free nerve endings stain sometimes positively with anti-MAP2 (Sigma, Saint Louis, MO, USA) and ant-SMI 31 (Sternberger Monoclonals, Lutherville, MD, USA) antibodies. In thin histological sections, the nerve endings have been shown to be very short and fine. No detailed information about their function has been reported, but they probably mediate esophageal pain and dysphagia in patients with gastroesophageal reflux disease.

2.2.1.2. Esophagogastric Junction

There are three possible histological patterns that may be observed at the esophagogastric junction: an abrupt change from stratified squamous epithelium to columnar epithelium (clear-cut demarcation type; Fig. 2-14); overlapping of columnar

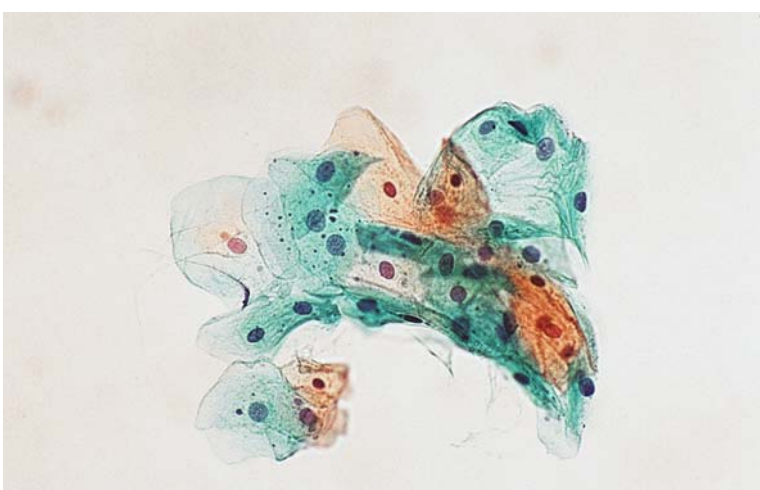


FIG. 2-6. Cytology of esophageal mucosal epithelial cells (Papanicolaou stain). There are keratohyaline granules in the superficial cells

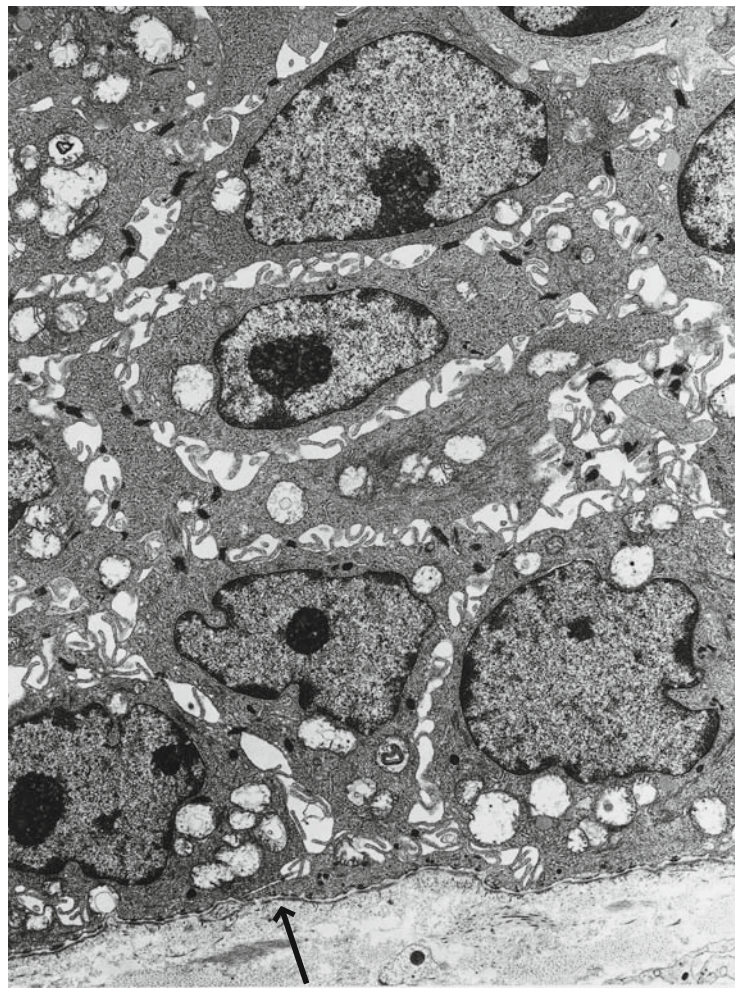


FIG. 2-7. Electron micrograph of the basal cells of the esophageal epithelium. A section perpendicular to the basement membrane (*arrow*) shows cuboidal cells

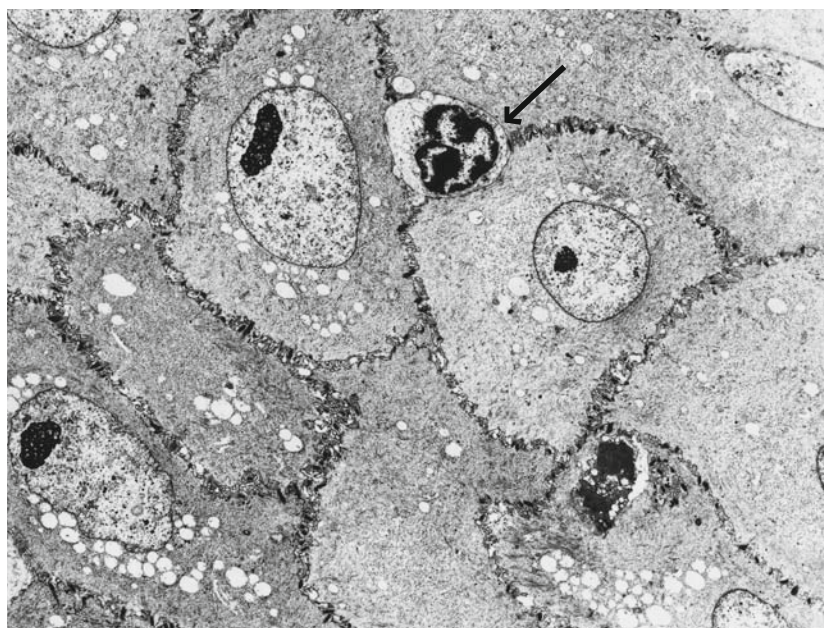


FIG. 2-8. Electron micrograph of the superficial cells of the esophageal epithelium: a section parallel to the basement membrane. *Arrow*, lymphocyte

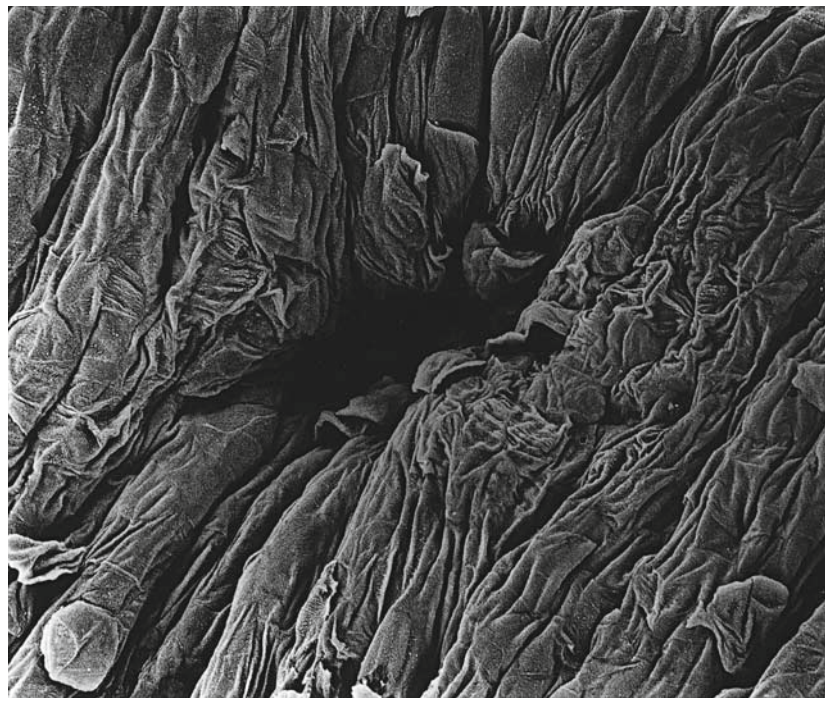


FIG. 2-9. Scanning electron micrograph of esophageal epithelium. An opening of an esophageal gland proper

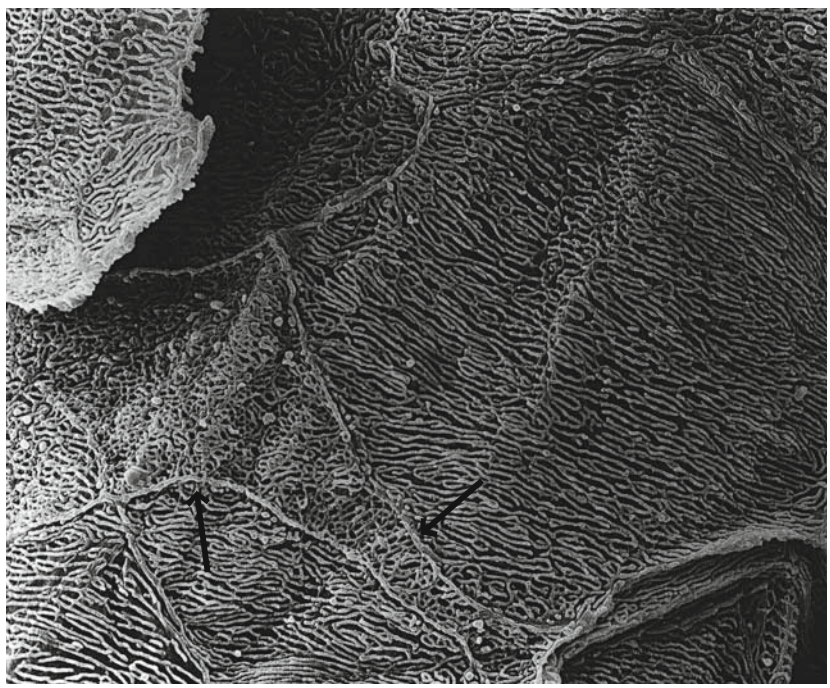


FIG. 2-10. Scanning electron micrograph of esophageal epithelium. The outlines of the superficial cells are evident (*arrows*)

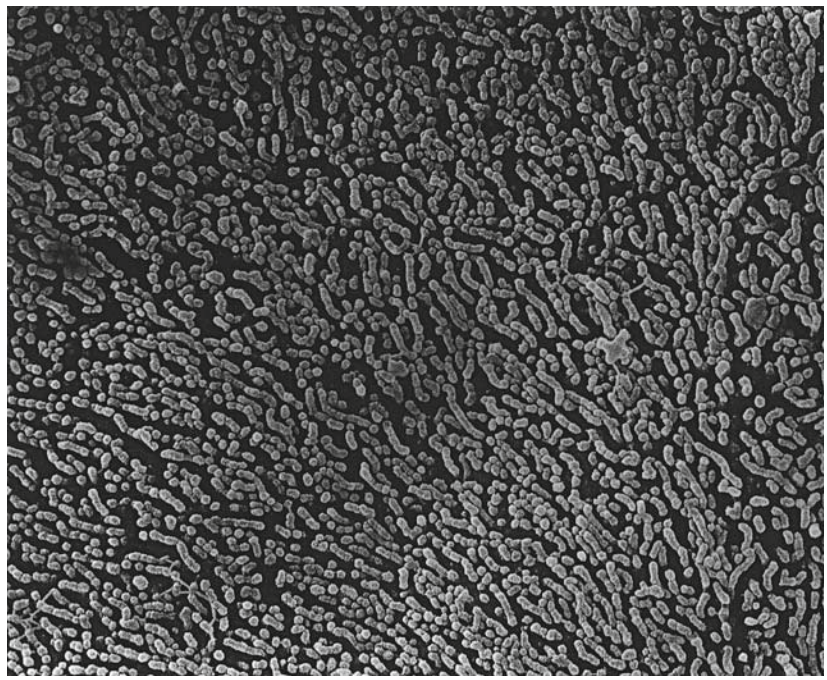


FIG. 2-11. Scanning electron micrograph of an esophageal epithelial cell. There are many microvilli on the cell surface

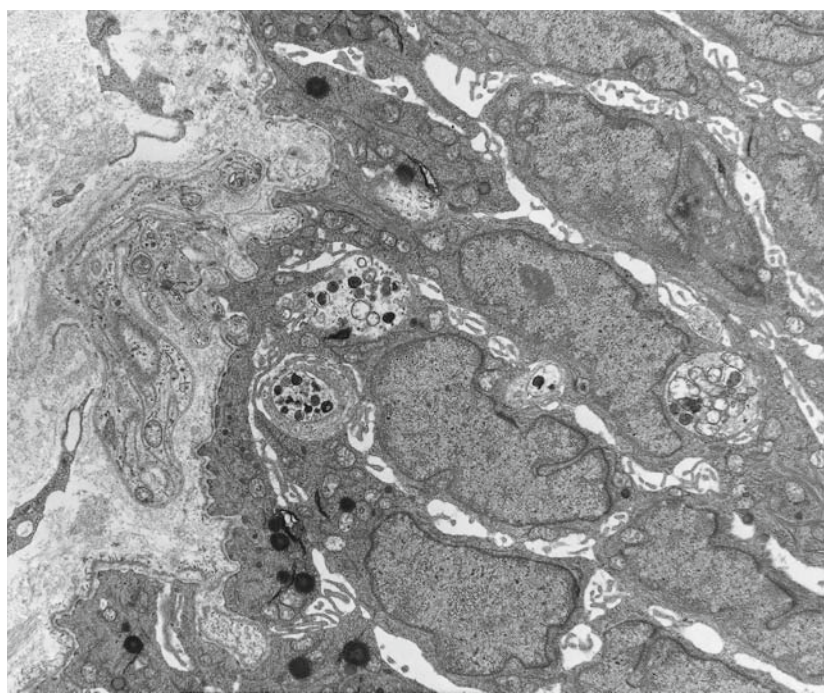


FIG. 2-12. Electron micrograph of free nerve endings. Cross sections of three axons are seen among the prickle cells. The nerve endings contain many granules

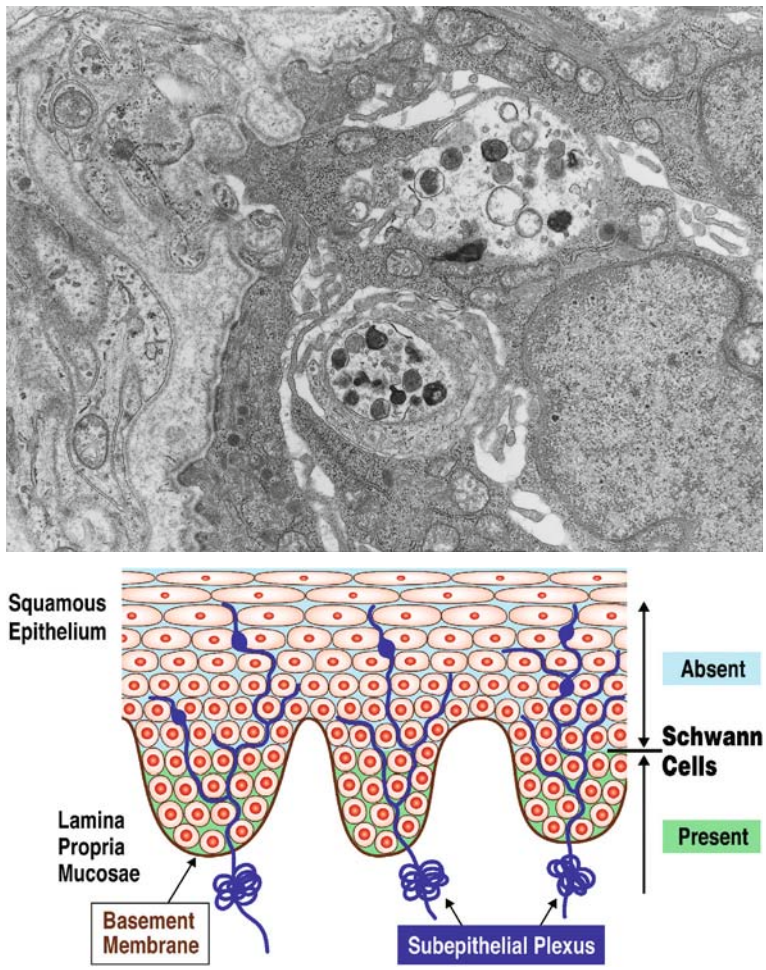


FIG. 2-13. **a** High-magnification view of Fig. 2-12. Cross sections of two axons are seen in the intercellular spaces of the prickle cells. One of them is surrounded by Schwann cells. **b** Schema of free ending nerves. The fibers reaching the subepithelial plexus emanate from the submucosal plexus. The axons are surrounded by Schwann cell processes for a short distance through the basement membrane and then leave the Schwann cells among the epithelial cells. The axons are very circuitous

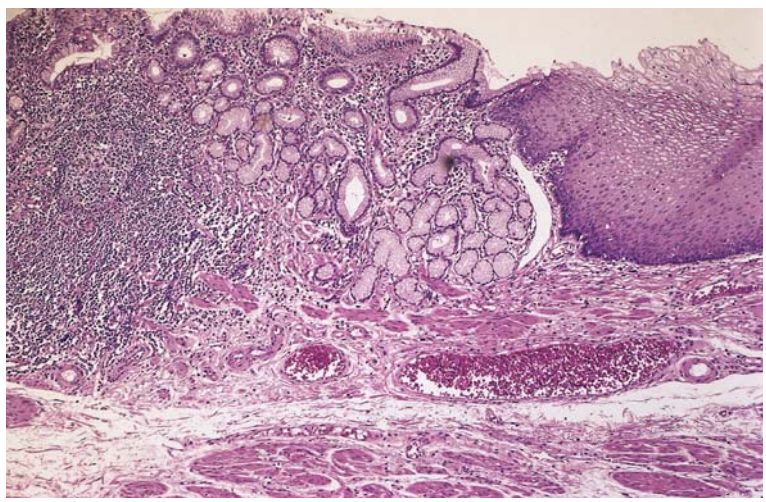


FIG. 2-14. Esophagogastric junction of the clear-cut demarcation type. Cardiac glands are seen in the gastric mucosa but there are none in the lamina propria beneath the flat stratified squamous epithelium

epithelium with flat stratified squamous epithelium (subepithelial inclusion type; Figs. 2-15 through 2-17); and Barrett's epithelium (Barrett's esophagus type). The subepithelial inclusion type, with cardiac glands of the stomach uninterruptedly extending into the lamina propria under the flat stratified squamous epithelium, is predominant, having an incidence of 74% in total gastrectomy specimens resected for carcinoma and in esophagectomy specimens resected for carcinoma or stricture. The length of the overlapping segment is no more than 12 mm (Takubo). Goblet cells, pancreatic metaplasia, and squamous metaplasia-like change may be seen in the glands beneath the squamous epithelium.

Electron microscopy reveals the presence of junctional apparatus between the stratified squamous epithelium and the columnar epithelium at the squamocolumnar junction (Fig. 2-18).

2.2.1.2.1. Squamous Metaplasia-Like Change, Multilayered Epithelium

So-called reserve cell hyperplasia-like change, squamous metaplasia-like change (Takubo 1981; Takubo et al. 1981), or multilayered epithelium (Glickman et al. 2001; Shields et al. 1993), may be found in cardiac glands beneath the stratified squamous epithelium in the vicinity of the esophagogastric junction (see Figs. 2-15 through 2-17). This

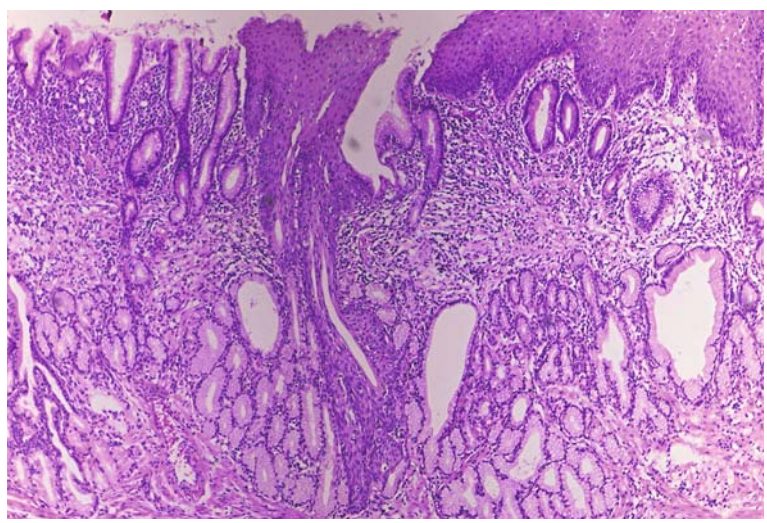


Fig. 2-15. Squamous metaplasia-like change in cardiac glands at the esophagogastric junction

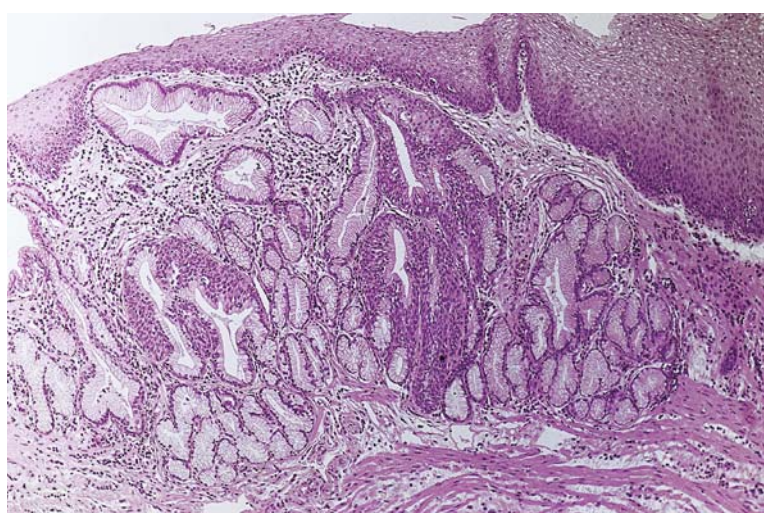


Fig. 2-16. Esophagogastric junction. There are gastric cardiac glands under the flat stratified squamous epithelium. Pseudostratified epithelium is evident in the cardiac glands

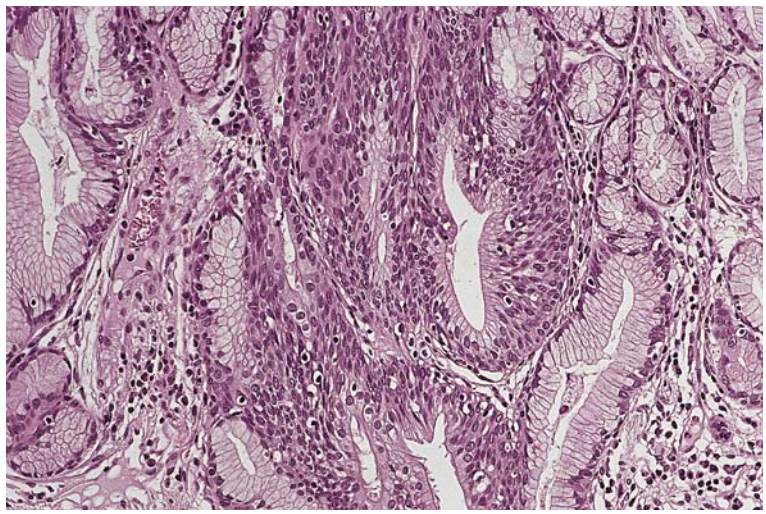


FIG. 2-17. High-magnification view of Fig. 2-16. There are cilia on the luminal surface of the pseudostratified epithelial cells

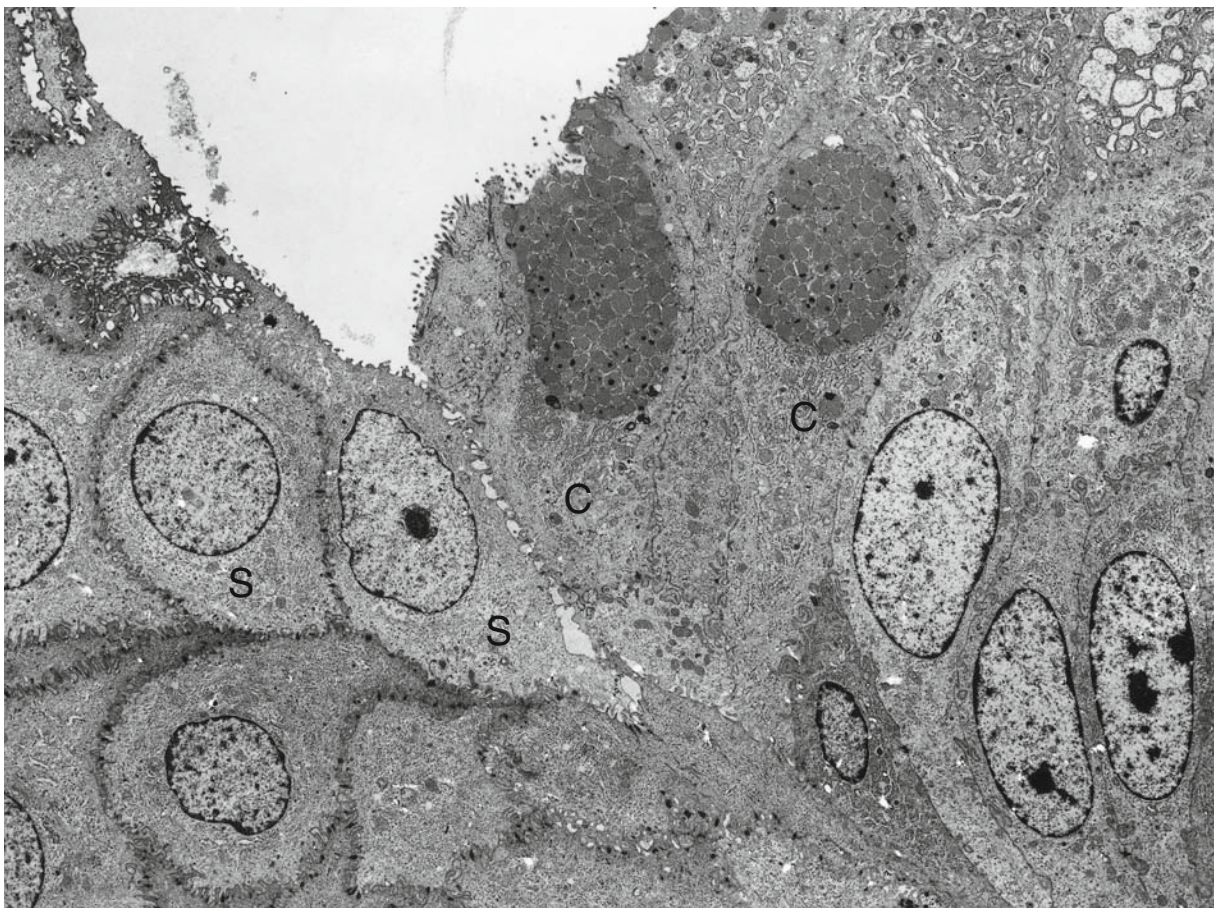


FIG. 2-18. Electron micrograph of the squamocolumnar junction in the esophagogastric junction zone. Desmosomes are evident between squamous and columnar cells. *S*, squamous cell; *C*, columnar cell

change usually has the appearance of pseudostratified epithelium (see Figs. 2-16, 2-17), but sometimes has the appearance of squamous metaplasia (see Fig. 2-15). In the present author's studies, pseudostratified epithelium was found at the esophagogastric junction in 20% of autopsy cases and in 24% to 49% of surgical resection specimens for gastric cancer (total gastrectomy) or esophageal cancer (Takubo 1981; Takubo et al. 2005). It was formerly thought that the stratified squamous epithelium changed abruptly to columnar epithelium at the esophagogastric junction and that other types or patterns of epithelium were very infrequent. However, recent detailed histopathological studies have revealed that pseudostratified epithelium frequently occurs at the esophagogastric junction (Takubo et al. 2005). This lesion has both a similar histological appearance and similar immunohistochemical profile to respiratory bronchial epithelium. By electron microscopy, many cilia are detected at the apices of the epithelial cells.

2.2.1.2.2. Squamous Metaplasia Extending into Gastric Mucosa

Mature squamous epithelium may be seen in the gastric cardiac mucosa, and this has been demonstrated in a few case reports (Takeda et al.; Fass and Sampliner 2000). Takeda et al. (2000) reported that biopsy specimens from white areas of gastric mucosa seen endoscopically showed mature squamous epithelium.

2.2.1.2.3. Pancreatic Metaplasia

Recent studies have shown that there are cells morphologically similar to acinar cells of the exocrine pancreas, and not regarded as ectopic pancreatic tissue (heterotopia), in the gastric mucosa. These cells are considered to represent a metaplastic change (Doglioni et al. 1993). In particular, such cells are frequently found in the mucosa at the esophagogastric junction, in esophageal cardiac glands in the lamina propria beneath the stratified squamous epithelium, and in columnar-lined esophagus (Krishnamurthy and Dayal 1995). These cells may also be found in Barrett's mucosa (Wang et al. 1996). It has been suggested that bile and pancreatic juice may have a role in the process of carcinogenesis in Barrett's adenocarcinoma, but it is unknown whether pancreatic metaplasia has such a role. Pancreatic acinar-like cells have been reported to be present in the stomach or esophagus in 65% of total gastrectomies and esophagectomies performed for gastric or esophageal cancer (Nokubi 1996).

These cells, which are easily seen with hematoxylin and eosin (H&E) stain, have many fine red cytoplasmic secretory granules in their apical and midregions. The cytoplasm in the basal region is basophilic. The appearance of these cells is similar to that of the acinar cells of pancreatic exocrine glands (Fig. 2-19). The red granules are slightly smaller than those seen in Paneth cells. These cells show positive staining for lipase, trypsinogen, and

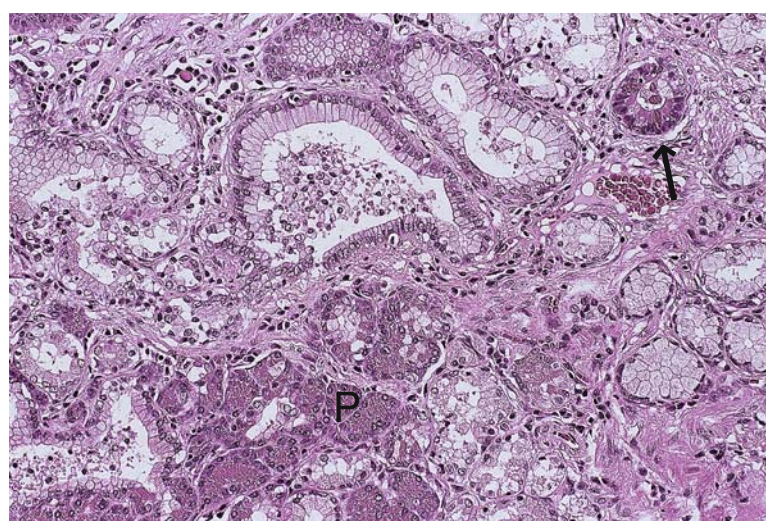


FIG. 2-19. Pancreatic acinar-like cells in the mucosa at the esophagogastric junction. Pancreatic acinar-like cells (*P*), with red cytoplasmic granules, are present in cardiac glands at the esophagogastric junction. *Arrow*, Paneth cells of intestinal metaplasia

amylase and may also be positive for chromogranin, serotonin, somatostatin, gastrin, and pancreatic polypeptide. Electron microscopy has shown that their cytoplasm is filled with almost spherical secretory granules and that there is abundant rough endoplasmic reticulum in their basal regions.

2.2.1.3. Glycogenic Acanthosis and Leukoplakia

Glycogenic acanthosis of the esophagus was studied in detail for the first time by Rywlin and Ortega (1970), who found this change in each of 27 consecutive adult autopsies. Postlethwait and Musser (1974) investigated 1000 autopsy cases and found glycogenic acanthosis in 23% of them. This term has come up frequently at recent medical meetings in Japan. In the World Health Organization (WHO) histological classification of esophageal tumors (1990), glycogenic acanthosis is classified as a tumor-like condition.

Esophagoscopic and esophagographic studies have revealed that lesions of this type may reach a size of 15 mm (Berliner et al. 1981). The relationship between this change and aging is unclear, and there have not been any reports on its morphogenesis. Glycogenic acanthosis is reported to be frequent in the lower esophagus. It is not accompanied by subepithelial inflammation and, therefore, is considered to be a variant of normal. It has no relationship to infection in the esophagus or elsewhere or to malignant disease outside the esophagus.

Macroscopically, glycogenic acanthosis is a slightly elevated, mild acanthotic change of the mucosal epithelium, with a transparency similar to that of the surrounding epithelium (Fig. 2-20).

Histologically, it is a localized acanthotic lesion showing enlargement of epithelial cells with clearing of their cytoplasm (Fig. 2-21). The clear appearance is due to abundant intracytoplasmic glycogen. Glycogenic acanthosis is not usually accompanied by hyperkeratosis or cellular atypia, and it has only a minimal relationship to squamous cell carcinoma of the esophagus.

2.2.1.3.1. Leukoplakia

Leukoplakia is a lesion totally different from glycogenic acanthosis. Acanthosis of the epithelium is only occasionally seen in esophageal leukoplakia. Leukoplakia caused by hyperkeratosis, a well-known condition in the oral mucosa, rarely occurs in the esophagus, only being found in noncancerous regions of resected esophagi in 2 (0.7%) of this author's series of 287 consecutive cases of esophageal squamous cell carcinoma. According to Postlethwait and Musser, hyperkeratosis, parakeratosis, or leukoplakia was found in a total of 1% of the cases they examined. Although some leukoplakia of the oral mucosa is known to be precancerous, the relationship between leukoplakia and cancer of the esophagus remains unclear because the incidence of esophageal leukoplakia is so low. Leukoplakia with atypia is frequently seen in patients with achalasia. Nakanishi et al. reported epidermization of the esophageal epithelium in association with squamous cell carcinoma. Hyperorthokeratosis and a granular layer were observed in the epidermization (1997).

FIG. 2-20. Macroscopic appearance of esophageal mucosa showing glycogenic acanthosis (*arrow*). The lesion is localized and slightly elevated

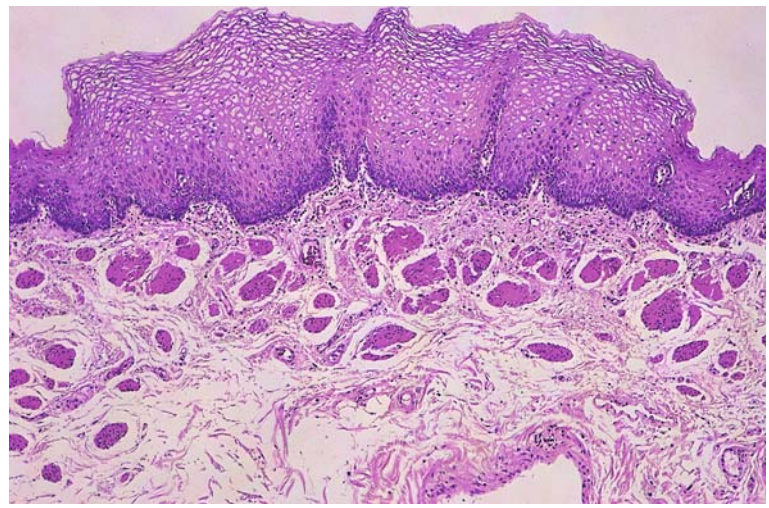


Fig. 2-21. Glycogenic acanthosis composed of prickle cells having clear and abundant cytoplasm. There is no cellular atypia in the acanthotic focus

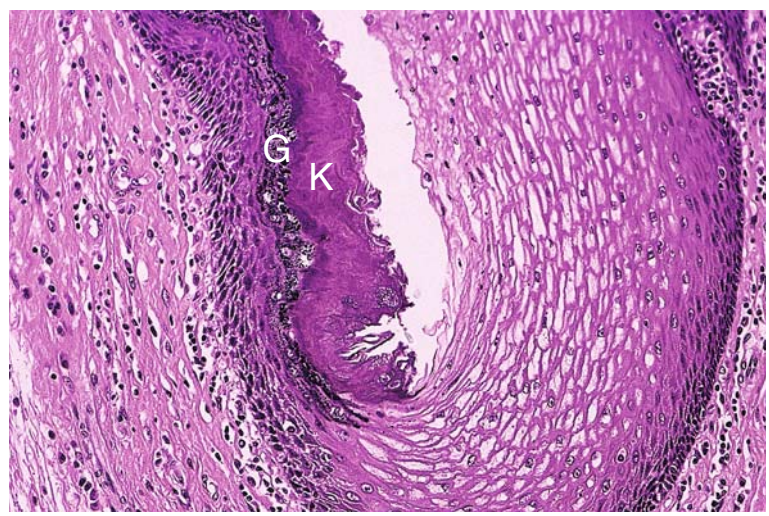


Fig. 2-22. Leukoplakia of the esophageal mucosa. The keratin layer (*K*) is devoid of nuclei. There is a granular layer (*G*), showing atypia

Macroscopically, leukoplakia usually appears as a very small, nearly opaque lesion (measuring about 5 mm) with a white pearl-like luster. The macroscopic appearance resembles that of well-differentiated squamous cell carcinoma in situ.

Histologically, there is hyperkeratosis, and a granular layer appears in the superficial epithelium, giving an appearance similar to that of oral leukoplakia (Fig. 2-22). Cell nuclei may be present (parakeratosis) or absent (orthokeratosis) in the keratin layer. Foci of mild dysplasia are sometimes seen.

2.2.1.4. Esophageal Manifestations of Cowden's Disease (Multiple Hamartoma Syndrome)

Cowden's disease is a congenital disorder, first described in detail by Lloyd and Dennis. It was named after the first reported patient (a 20-year-old female), but examples of this syndrome had been known as early as 1941 (Haggitt and Reid; Honma et al.). Cowden's disease is inherited as an autosomal dominant trait. More than 50 patients in Japan and 140 patients in Europe and

America have been reported on (Miyakawa et al. 1993).

Affected patients have hamartomatous lesions in many organs including the skin, oral mucosa, gastrointestinal tract, thyroid, breast, uterus, and ovary. Polyps are seen in the gastrointestinal tract. Malignant tumors tend to arise after middle age in Cowden's disease, so it is important to establish the diagnosis before this time. Esophageal lesions are seen in 86% of patients with Cowden's disease, this incidence being similar to the incidence of gastric involvement and higher than that of large or small intestinal involvement.

In this condition, the esophageal mucosa is covered by multiple small acanthotic lesions, measuring up to 3 mm in size. They are difficult to distinguish histologically from glycogenic acanthosis (Fig. 2-23).

2.2.1.5. Ectopic Gastric Mucosa (Inlet Patch)

According to a report by Rector and Connerley (1941), islets of ectopic gastric mucosa were first described in the esophagus by Schmidt in 1805. Rector and Connerley reported that islets of gastric mucosa without parietal cells were found in 6.3% of children younger than 15 years and islets with parietal cells in 2.6% of children under 15. In a study of 500 autopsy cases by de la Pava et al., the incidence of islets of ectopic gastric mucosa was 12%. The figures in these two reports have been cited frequently in subsequent papers. A recent endoscopic study (Borhan-Manesh and Farnum 1991) found an incidence of 10%; in this study the islets measured 0.2–5 cm, and almost half the subjects had two or more islets. A recent endoscopic study found ectopic gastric mucosa in 13.8% of 2398 consecutive endoscopic examinations (Kumagai 2005).

In this author's study of subserial 5-mm-thick sections of whole esophageal specimens from 246 autopsies, islets of ectopic gastric mucosa were found in 20% of cases; they were most frequently located at the hypopharyngoesophageal junction, at the level of the cricoid cartilage.

The previous WHO histological classification of esophageal tumors (1990) deals with ectopic gastric mucosa as gastric heterotopia, within the category of tumor-like lesions.

Esophagitis may surround islets of ectopic gastric mucosa in the cervical esophagus, and this condition has been documented as a cause of dysphagia. In addition, islets of ectopic gastric mucosa have been known to be associated with stenosis caused by esophagitis and ulcers (Steadman et al.), fistulae (Kohler et al.), esophageal rings, hyperplastic polyps (see Chapter 9, p. 114), adenomas, and adenocarcinomas of the cervical esophagus (see Section 12.2. Primary Adenocarcinoma of the Esophagus, p. 202).

Colonization of heterotopic gastric mucosa in the upper esophagus by *Helicobacter pylori* (HP)

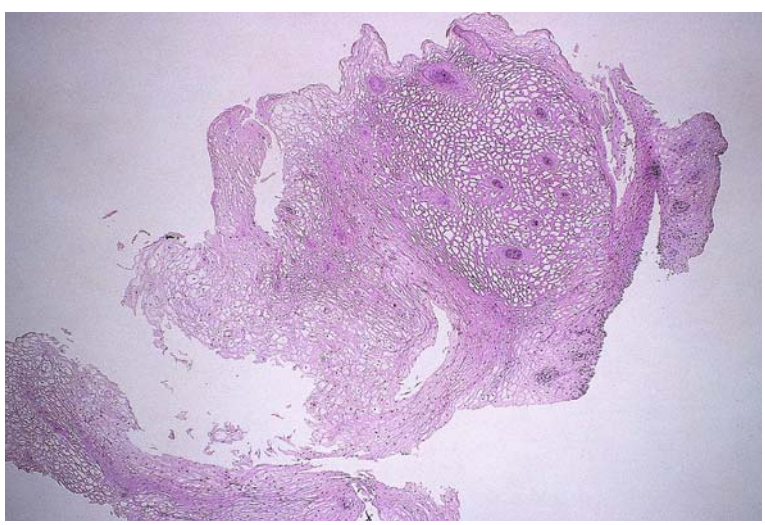


Fig. 2-23. Biopsy specimen of esophageal mucosa from a patient with Cowden's disease. The squamous epithelium is markedly acanthotic but shows no cellular atypia

has been reported (Borhan-Manesh and Farnum 1993; Tang et al. 2004); this occurred in association with HP gastritis. Independent colonization of heterotopic gastric mucosa by HP, without gastric infection, does not occur.

Islets of ectopic gastric mucosa are considered to be rests of embryonic mucosa, but the columnar epithelium of embryonal esophageal mucosa has a different histological appearance from that seen in ectopic gastric mucosa. Also, there have been very few reports of embryonal epithelium forming glands similar to the cardiac or pyloric glands of ectopic gastric mucosa. In fixed specimens, islets of ectopic gastric mucosa are brown, as is gastric mucosa, and are often oval in shape (Figs. 2-24, 2-25).

The histological features of ectopic gastric mucosa are similar to those of the cardiac mucosa of the stomach (Fig. 2-26) but in at least 50% of cases there are also glands resembling fundic glands. The glands of ectopic gastric mucosa are frequently difficult to distinguish from cardiac glands of the esophagus, and so some authors have concluded that ectopic gastric mucosa and

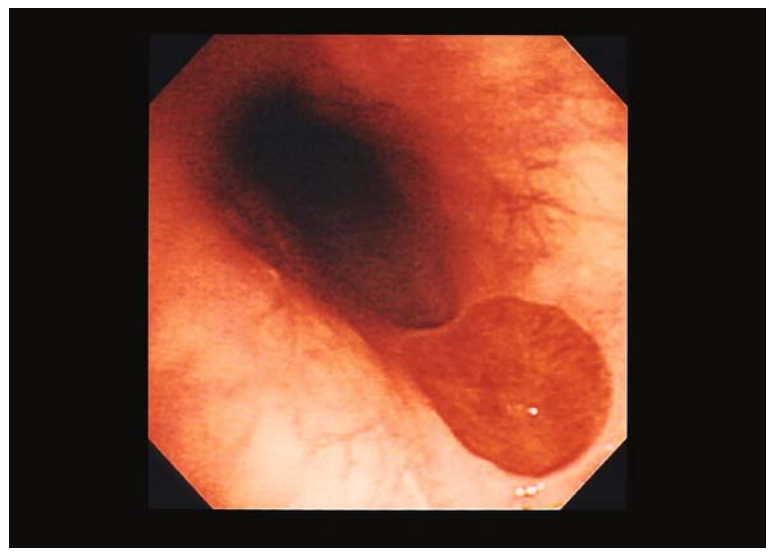


Fig. 2-24. Endoscopic appearance of an islet of ectopic gastric mucosa. A round red mucosa is seen surrounded with white squamous epithelium

Fig. 2-25. Macroscopic appearance of an islet of ectopic gastric mucosa in the upper esophagus (formalin-fixed)

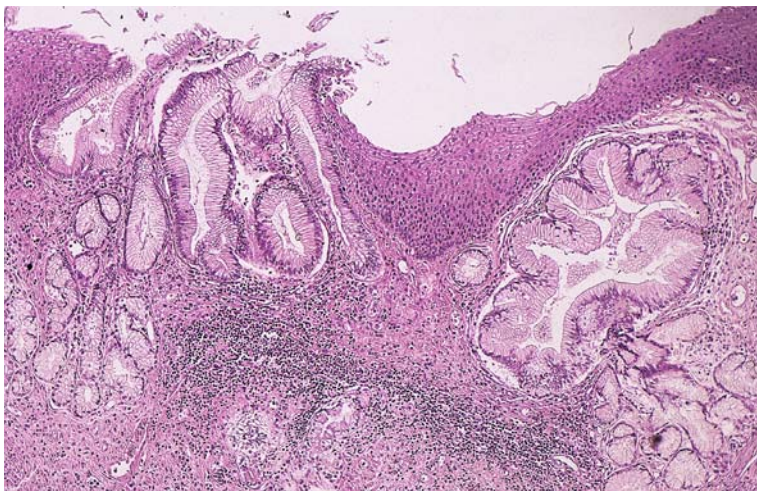


FIG. 2-26. Islet of ectopic gastric mucosa resembles the structure of cardiac glands

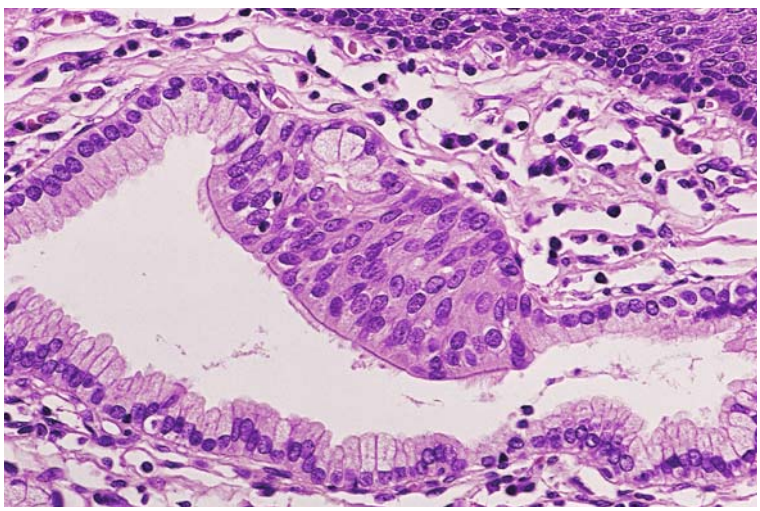


FIG. 2-27. Pseudostratified epithelium in an esophageal cardiac gland. The pseudostratified epithelial cells are ciliated

esophageal cardiac glands have the same histogenesis. This author, however, regards mucosal islets as ectopic gastric mucosa only when the superficial layer is not formed by flat stratified squamous epithelium. In this author's series, goblet cells were seen in 1 case but no Paneth cells were found in 246 consecutive autopsy cases. There are many cardiac glands in the lamina propria of the esophageal mucosa at the level of the cricoid cartilage, suggesting a close relationship between these and islets of ectopic gastric mucosa. Pseudostratified epithelium and squamous metaplasia-like change are occasionally seen in islets of ectopic gastric mucosa; in this author's study of 246 autopsy cases, these features were observed in 11 cases (4.2%).

2.2.1.6. Pseudostratified Epithelium

Pseudostratified epithelium may be found in the esophageal cardiac glands, at the esophagogastric junction, and in islets of ectopic gastric mucosa, but not in the esophageal glands proper. There are ciliated cells in pseudostratified epithelium (Fig.

2-27), making it easy to distinguish from epithelium of other types. It is currently unclear whether pseudostratified epithelium is an embryonic rest or is the result of metaplasia, but its histological features seem to be different from those of embryonal epithelium.

2.2.1.7. Melanosis, Argyrophil Cells, Argentaffin Cells, Langerhans' Cells, and Merkel Cells

2.2.1.7.1. Melanosis and Melanocytosis

In one report, melanosis was observed prospectively at endoscopy in 14 (0.1%) of 13013 endoscopic examinations (Makuuchi and Mitomi 1986), and retrospectively in 1685 (4.8%) of 35112 examinations (Makuuchi 2003). The foci of melanosis measured from a few millimeters to 4 cm in size and were brown and flat. Melanosis is a paler brown color than early malignant melanoma (Fig. 2-28).

Melanosis of the esophagus is characterized by an increase in the amount of melanin in mucosal epithelial cells, with or without an increase in the number of melanocytes (Figs. 2-29, 2-30). Melanocytosis is a condition of abnormal melanocyte proliferation; this resembles mild dysplasia histologically, but with experience can be easily recognized in H&E sections. In some cases, the basal layer of the mucosal epithelium is expanded and appears as though it is forming droplets in the lamina propria. At high magnification, melanocytes sometimes have brownish cytoplasm and sometimes clear cytoplasm. Although melanocytosis and melanosis are different entities, they are often not distinguished.

Melanocytosis can be easily detected by the Fontana–Masson method or by S-100 protein immunostaining. The melanocytes are chiefly located in or near the basal layer (Fig. 2-31), and they extend their dendritic processes among neighboring epithelial cells. Melanocytes are often

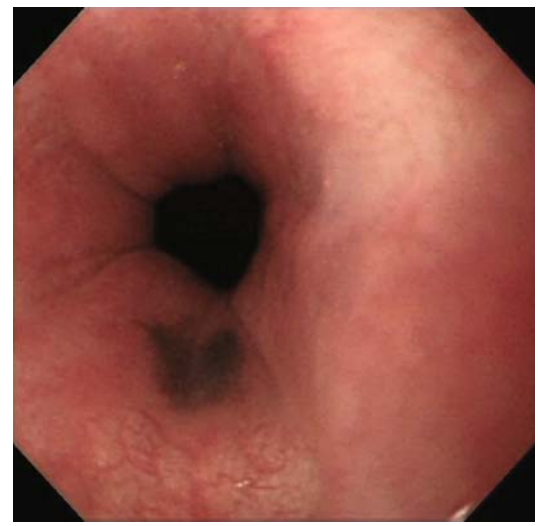


Fig. 2-28. Endoscopic appearance of esophageal melanosis. A flat, brown area of melanosis in the esophageal mucosa. Melanosis is a paler brown color than the early lesion of malignant melanoma

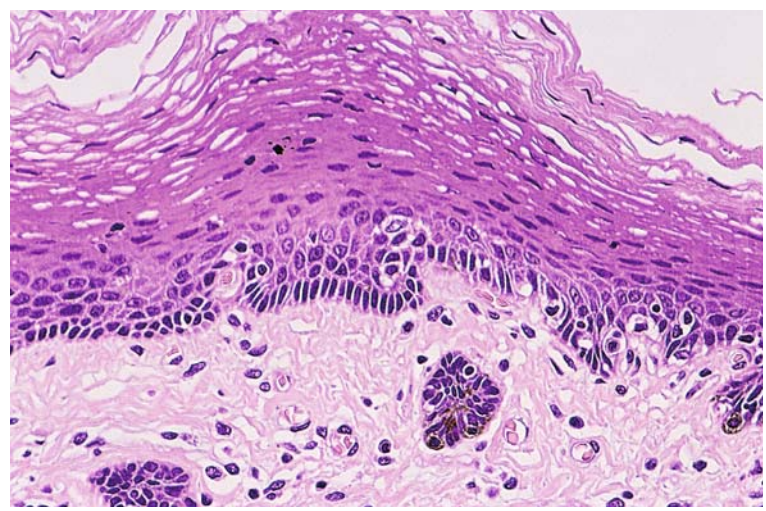


Fig. 2-29. Esophageal melanosis. Brown melanin granules are evident. There are droplet-like epithelial islets in the lamina propria

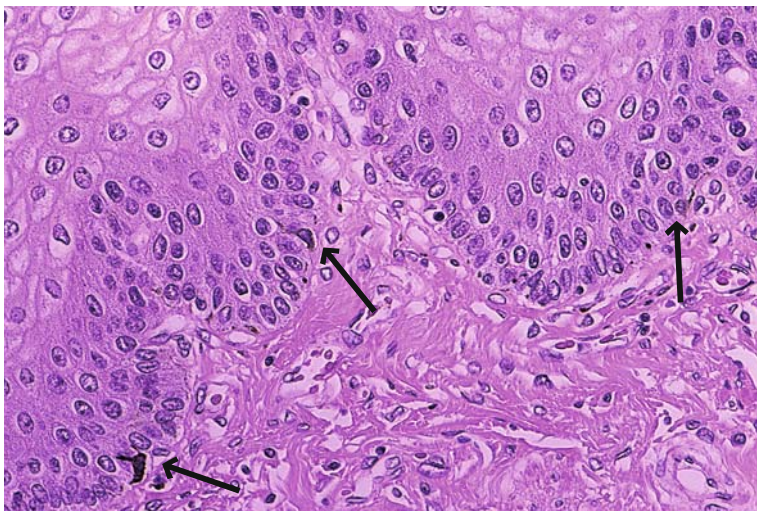


FIG. 2-30. Melanocytes in esophageal epithelium. Sporadic melanocytes (*arrows*) are evident in the basal layer of the esophageal epithelium

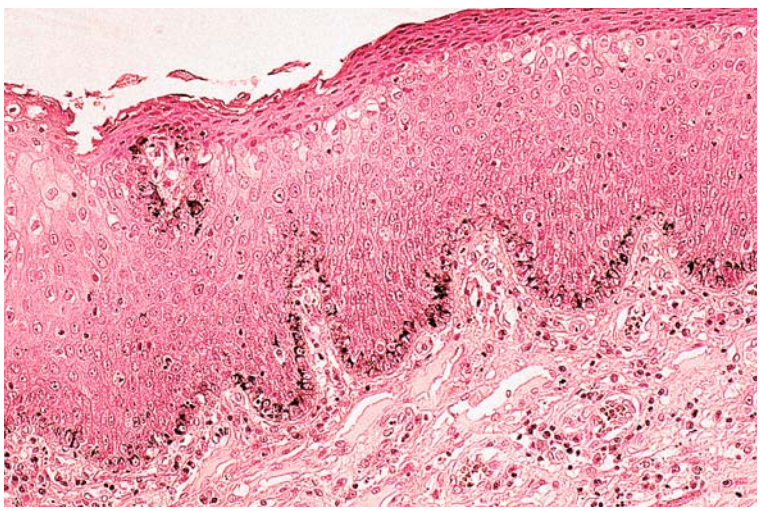


FIG. 2-31. Esophageal melanosis (Fontana–Masson method). Esophageal melanosis showing positively stained cells in the basal layer of the epithelium

found in the mucosal epithelium following irradiation or in cases of esophageal cancer (Ohashi et al.) and reflux esophagitis.

Studies on the occurrence of melanocytes in the esophageal mucosa have been carried out by de la Pava et al., Tateishi et al., and Shibata. These three studies have been cited in many subsequent reports published from Japan and elsewhere. The incidence of melanocytes in the esophageal mucosa was 4% according to de la Pava et al., who used Fontana's method, and 8% according to Tateishi et al., who used the Fontana–Masson method. According to Shibata, it was 11.5% by the dihydroxyphenylalanine (DOPA) reaction and 2.5% by Fontana's method. A recent study by Ohashi et al. found that the incidence of melanocytosis was 7.7% in autopsy cases without distinct abnormalities of the esophagus, 34% in noncancerous regions of esophagi resected for cancer following preoperative radiation therapy, and 27.0% in esophagi resected for cancer without preoperative radiation therapy.

Anthracosis of the esophagus is described in Section 16.3, p. 278.

2.2.1.7.2. Argyrophil Cells and Argentaffin Cells

Argyrophil cells may also be seen in the esophageal epithelium; the incidence of cells staining

positively with the Grimelius technique in the esophagus was 28% in a study by Tateishi et al. Argyrophil cells are located mostly in the basal layer of the mucosal epithelium (Fig. 2-32) and are not found in the esophageal glands proper, but both argyrophil and argentaffin cells may be found in esophageal cardiac glands (Fig. 2-33).

2.2.1.7.3. Langerhans' Cells

In addition to the skin, oral mucosa, and vagina, there is a small number of Langerhans' cells in the esophagus (Al Yassin and Toner). Although Langerhans' cells were formerly considered to be melanocytes that had lost the ability to produce melanin, they are now regarded as belonging to the histiocyte series and are bone marrow-derived dendritic cells. They stain positively for S-100 protein and this stain also stains their processes. However anti-CD1a immunolabeling (Fig. 2-34) is considered to be the most reliable way to identify human Langerhans' cells in epithelium (Terris and Potet 1995). In contrast to melanocytes, Langerhans' cells are distributed predominantly in the midzone of the epithelium. They are negative with both the Grimelius and Fontana–Masson methods. They are thought to increase in number during reflux esophagitis (Geboes et al. 1983; Takubo et al. 2005). Although Langerhans' cells in the skin

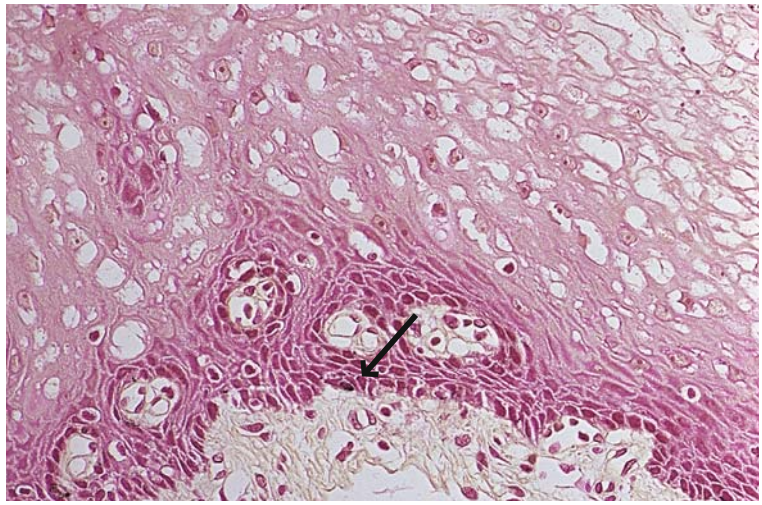


Fig. 2-32. Argyrophil cells in esophageal epithelium (Grimelius method). Argyrophil cells (*arrow*) in the basal layer of the esophageal mucosal epithelium

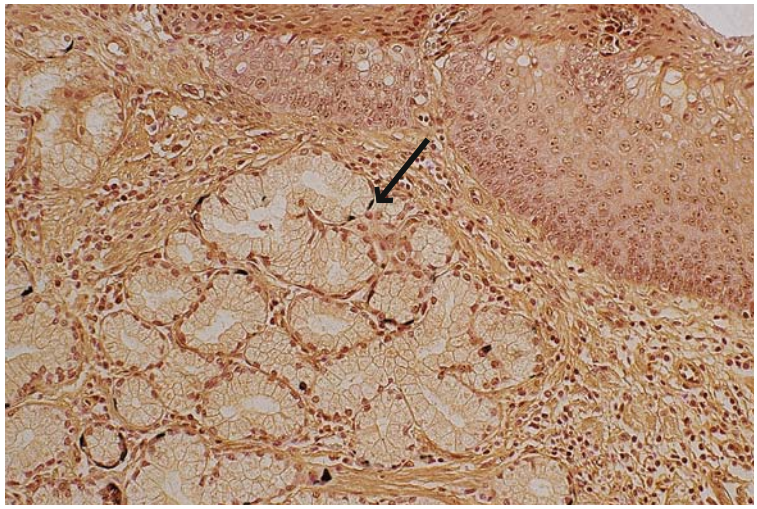


Fig. 2-33. Argyrophil cells in esophageal cardiac glands (Grimelius method). Argyrophil cells (*arrow*) are evident on the basement membrane

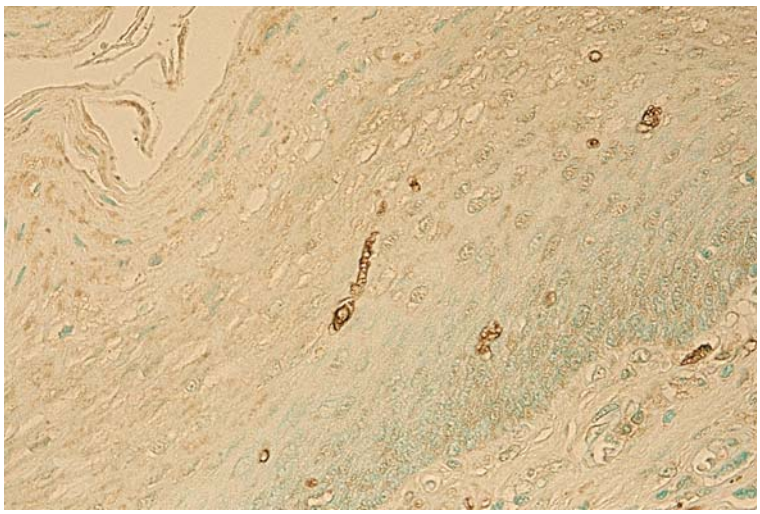


FIG. 2-34. Langerhans' cells (S-100 protein immunostain). Langerhans' cells, with long dendrites, in the middle layer of the esophageal mucosal epithelium

have been shown to be mainly involved in antigen presentation to lymphocytes, their role in the esophagus has not yet been fully elucidated.

Ultrastructurally, Langerhans' cells can be distinguished from other cells by the presence of Langerhans' granules (Birbeck's granules) in their cytoplasm. Langerhans' granules have a long, narrow, rod-shaped profile and are about 460 nm long. One end of the granule is sometimes expanded to a width of 160 nm, giving a shape similar to that of a tennis racket.

2.2.1.7.4. Merkel Cells

Harmse et al. (1999) reported the presence of Merkel cells in the human esophageal epithelium. Their function is not clear. Merkel cells are also found in the skin and oral mucosa.

2.2.1.8. Esophageal Glands

There are two types of secretory gland in the esophagus, the esophageal cardiac glands, located in the lamina propria, and the esophageal glands proper, located in the submucosa. These two gland types can be easily distinguished by their location. Sebaceous glands are also occasionally found in the esophagus.

2.2.1.8.1. Esophageal Cardiac Glands

The esophageal cardiac glands are small mucous glands located in the lamina propria and are occasionally observed endoscopically through squamous epithelium. They are also called superficial glands or mucosal glands, having a structure similar to that of gastric cardiac glands. Most are branched simple tubuloalveolar glands, but this author has observed that some are unbranched. They are located mainly in the lower and upper esophagus but there are also some in the mid-esophagus, although one report has stated that esophageal cardiac glands can be seen to be distributed evenly along the esophagus when islets of ectopic gastric mucosa and Barrett's epithelium are carefully excluded. The columnar or cuboidal epithelial cells of the cardiac glands extend almost up to the surface of the mucosal squamous epithelium (Fig. 2-35). The cardiac glands stain positively with PAS, Alcian blue, and high-iron diamine (HID).

2.2.1.8.2. Esophageal Glands Proper

The esophageal glands proper are compound tubuloalveolar glands, with branchings in both the excretory ducts and the terminal portions (acini). The terminal portions are located in the submucosa (Fig. 2-36), and these glands are also called submucosal or deep glands. The terminal portion (acinus) connects with the mucosal epithelium via the excretory duct. The number of glands varies between individuals. According to this author's observations of esophagi subserially sectioned at a thickness of 5 mm, the number of esophageal glands proper in the esophagus ranges from 6 to

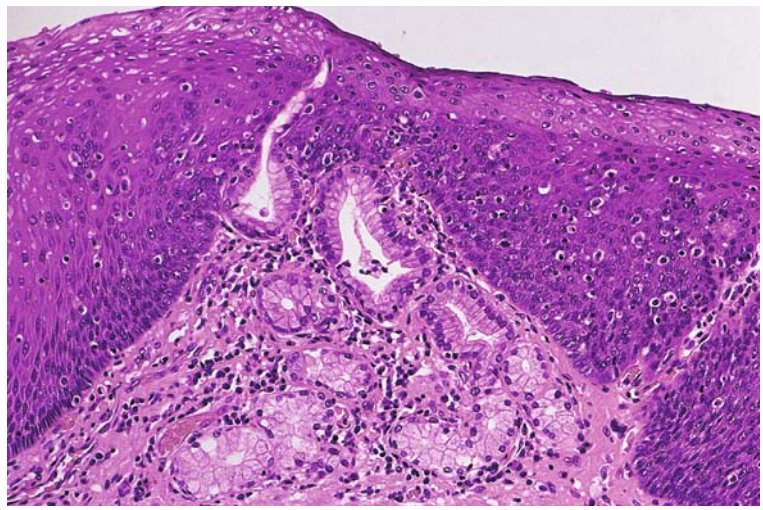


FIG. 2-35. Esophageal cardiac glands. These glands, closely resembling gastric cardiac glands, are located in the lamina propria. A gland lumen is apparent in the flat stratified squamous epithelium. This gland is composed of mucous cells

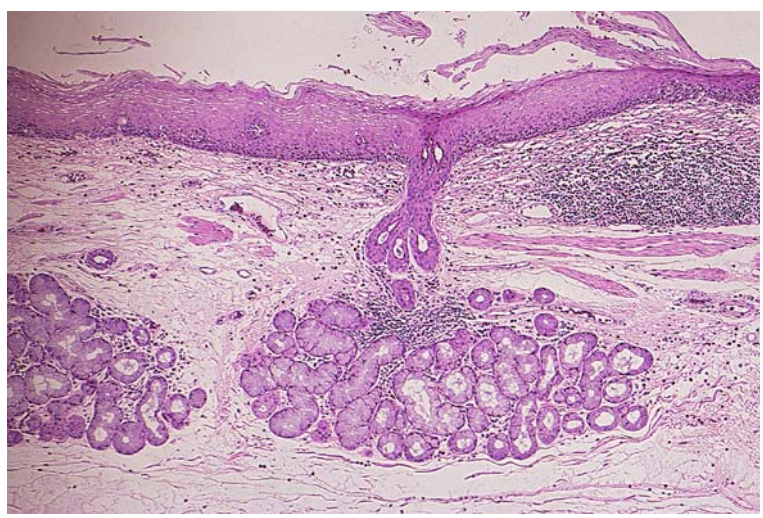


FIG. 2-36. Esophageal gland proper. The gland has a branched excretory duct (compound gland), and its terminal portion is located in the submucosa

620, with a mean count of 227 (1981). The number of esophageal glands proper has also been discussed in detail in another report (Goetsch 1910). Goetsch examined the distribution of esophageal glands proper in two esophageal specimens, and found 741 and 62 glands, respectively. A diagram given in his paper suggests that there is no specific pattern to their distribution. Mucous cells are predominant among the cells constituting the terminal portion. Although many textbooks of histology and pathology describe the esophageal glands proper as mucous glands, serous cells have been reported to be present in the glands (Johns 1952). This author has also found that quite a number are actually mixed, containing both mucous and serous cells (Fig. 2-37). Also, a monograph, published about 50 years ago, reported that the esophageal glands proper are mixed glands that contain serous cells (Yokochi et al. 1954), but they are still described as mucous glands in most current textbooks.

There are also oncocytes and myoepithelial cells in the terminal portions of these glands. Infiltrating plasma cells and lymphocytes can often be seen in the stroma and around excretory ducts in the terminal portions.

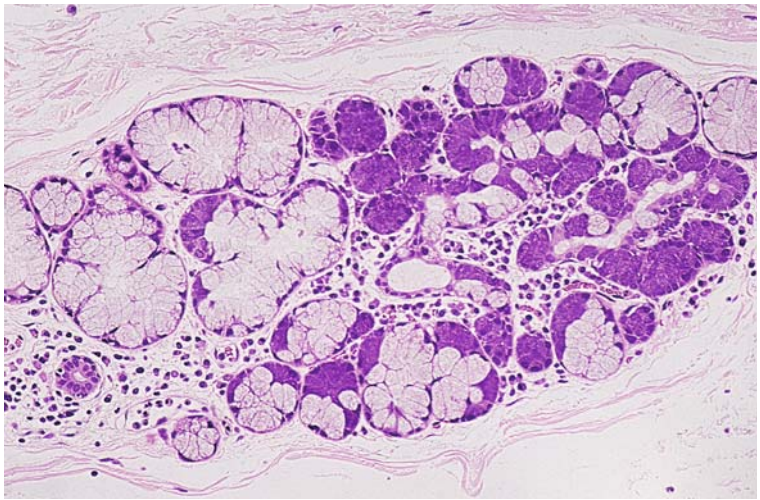


FIG. 2-37. Terminal portion of an esophageal gland proper. Clear mucous cells and dark serous cells form demilunes

TABLE 2-1. Summary of the results of various staining procedures of components of the esophageal glands proper

	SC	CEA	LF	S-100	Actin	Alcian blue/ PAS/Mucicarmine	HID
Mucous cells	–	–	–	–	–	+	+/–
Serous cells	–	–	+	+	–	–	–
Oncocytes	–	–	–	–	–	–	–
Myoepithelial cells	–	–	–	+	+	–	–
Peripheral ductal epithelium in the submucosa	+	–	+	–	–	–	–
Ductal stratified cuboidal epithelium in the lamina propria	–	–	–	–	–	–	–

SC, secretory component; CEA, carcinoembryonic antigen; LF, lactoferrin; S-100, S-100 protein; PAS, periodic acid–Schiff; HID, high-iron diamine; +, positive; –, negative

The glands are thought to secrete bicarbonate and epidermal growth factor (EGF) and, similar to the secretions of major and minor salivary glands, these have a role in supporting the mucosal squamous epithelium. Although the presence of esophageal glands proper confirms that a tissue specimen is of esophageal origin, these glands can only rarely be used as markers of esophageal tissue in biopsy specimens because they are so sparsely distributed (about 2–3 glands/cm^2 of mucosa), but they can provide an important indicator when examining resection specimens of Barrett's esophagus (see Section 12.1. Barrett's Esophagus). The reactions of the glandular tissue to various stains are summarized in Table 2-1.

Only a few cases of primary adenocarcinoma that were thought to have arisen from esophageal glands proper have been reported (see p. 211).

2.2.1.8.2.1. Mucous Cells. Mucous cells in the terminal portions of the esophageal glands proper have small, flat nuclei that almost touch the cell membrane at the base of the cell and clear cytoplasm filled with mucus. The cytoplasm stains positively with Alcian blue and mucicarmine. Most mucous cells give a positive reaction with HID, but some are negative (Fig. 2-38).

Electron microscopy reveals that the cytoplasm is filled with mucous granules (Fig. 2-39). Desmosomes are occasionally found between mucous cells and myoepithelial cells, which lie between the mucous cells and the basement membrane. In areas devoid of myoepithelial cells, mucous cells make direct contact with the basement membrane via hemides-mosomes.

2.2.1.8.2.2. Serous Cells. Serous cells do not stain with the aforementioned mucin stains but stain deeply with hematoxylin, because of their high cytoplasmic RNA content, in endoplasmic reticulum. They are also S-100 protein positive. Serous cells in the terminal portions of the

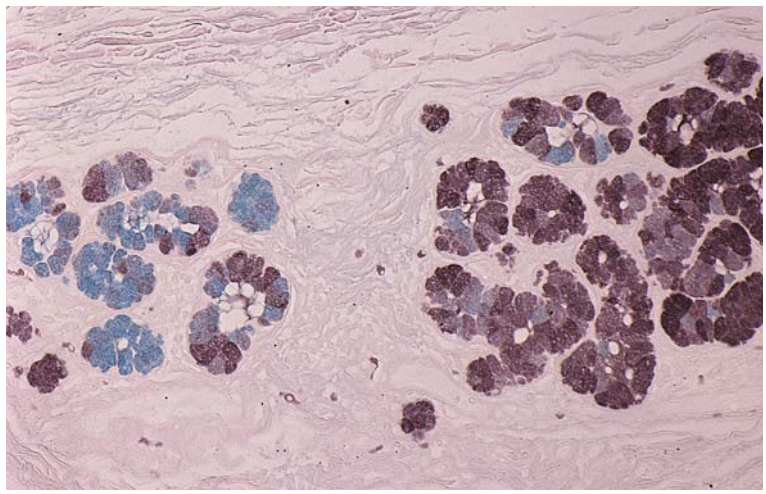


FIG. 2-38. Terminal portion of an esophageal gland proper (high-iron diamine Alcian blue stain). Sialomucin and sulfomucin are present

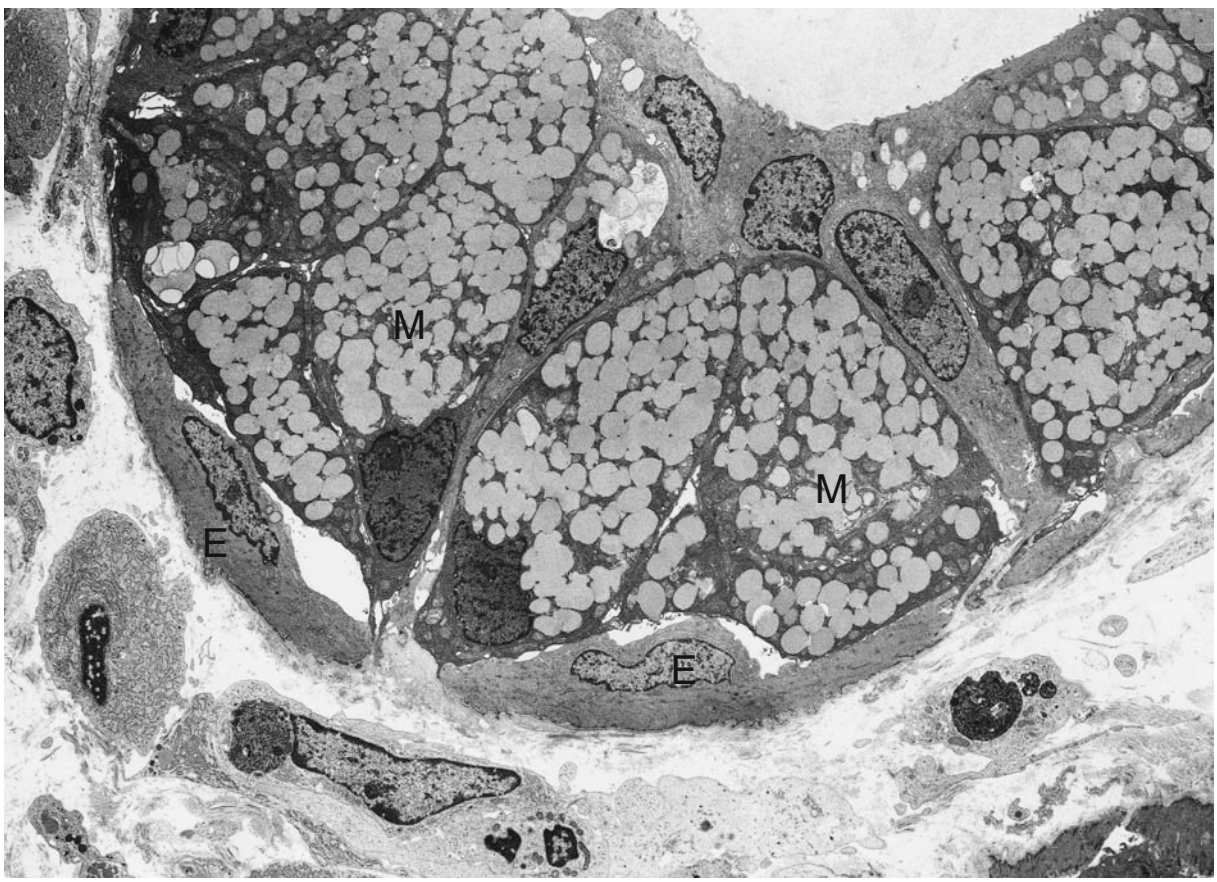


FIG. 2-39. Electron micrograph of the terminal portion of an esophageal gland. There are secretory granules in the mucous cells (*M*) and actin filaments in the myoepithelial cells (*E*)

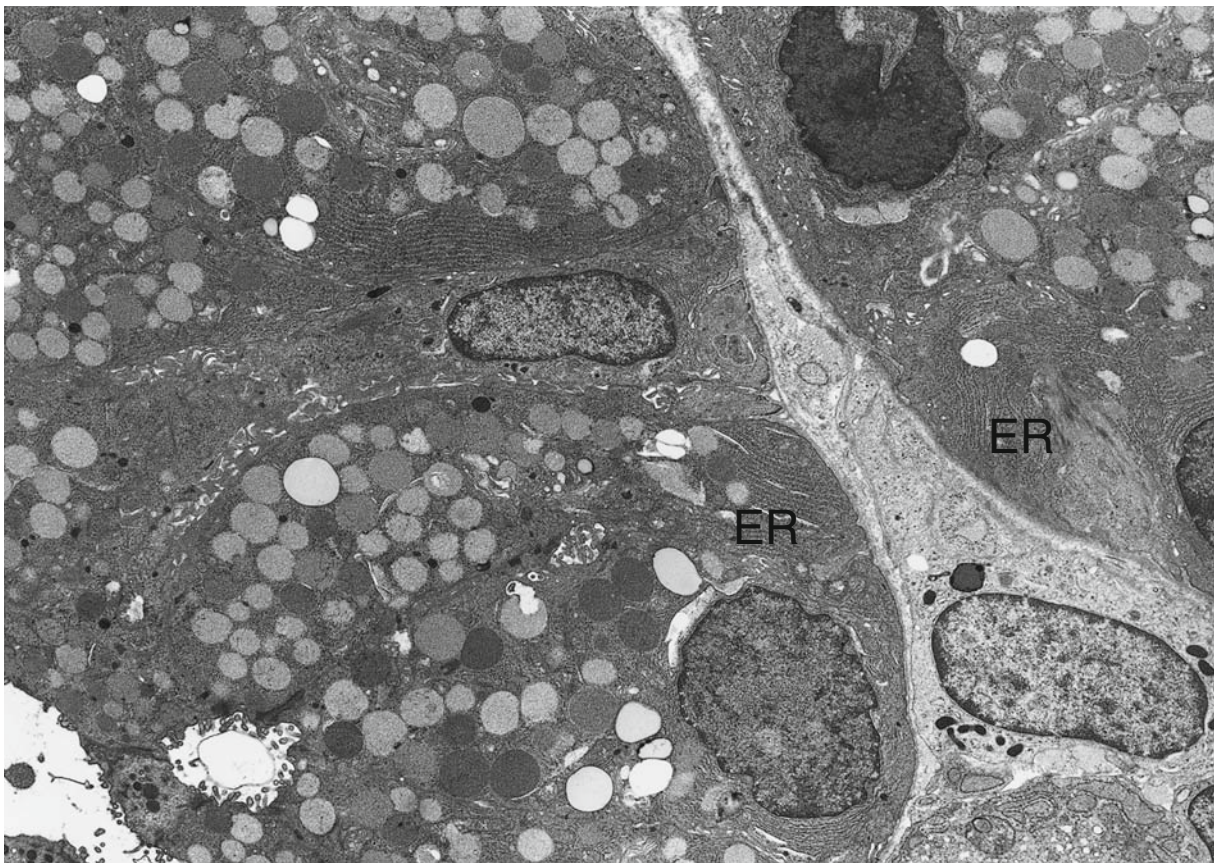


FIG. 2-40. Electron micrograph of serous cells in an esophageal gland proper. There are many secretory granules toward the luminal aspect, and there is abundant rough endoplasmic reticulum (*ER*) at the base of the serous cells

esophageal glands may form demilunes because mucous cells tend to be aggregated toward the excretory duct (Fig. 2-40).

It is apparent by electron microscopy that serous cells have round basal nuclei and, near the basement membrane, abundant endoplasmic reticulum. They have secretory granules in their cytoplasm, most numerous near the luminal aspect. Serous cells make direct contact with the basement membrane in areas where there are no myoepithelial cells.

2.2.1.8.2.3. Oncocytes. Oncocytes were named Onkocyten by Hamperl in 1931 because of their large size. The existence of these cells, however, had been known since 1897 (citation of report by Yabuki et al. 1967) and they have also been called eosinophilic granular cells.

According to Hamperl, oncocytes increase in number with age, particularly after age 70, in various organs and tissues. It has been reported that they also increase rapidly in number in the esophagus after age 60 (Yabuki et al.).

Oncocytes in the esophagus are morphologically similar to those seen in salivary glands; they have small, irregularly shaped nuclei and fine granular cytoplasm that stains pink on H&E (Fig. 2-41). Oncocytes are present not only in the terminal portions but also in the excretory ducts of the esophageal glands proper. In contrast to mucous cells, the nuclei of oncocytes are located in the center of the cell. Cells in the terminal portions of the esophageal glands proper become replaced by oncocytes relatively frequently. This phenomenon is known as oncocytic hyperplasia (Fig. 2-42). Although more commonly seen in adults, this change has also been found in some pediatric autopsy cases.

Electron microscopy shows that oncocytes have short villi on their luminal surfaces and that their

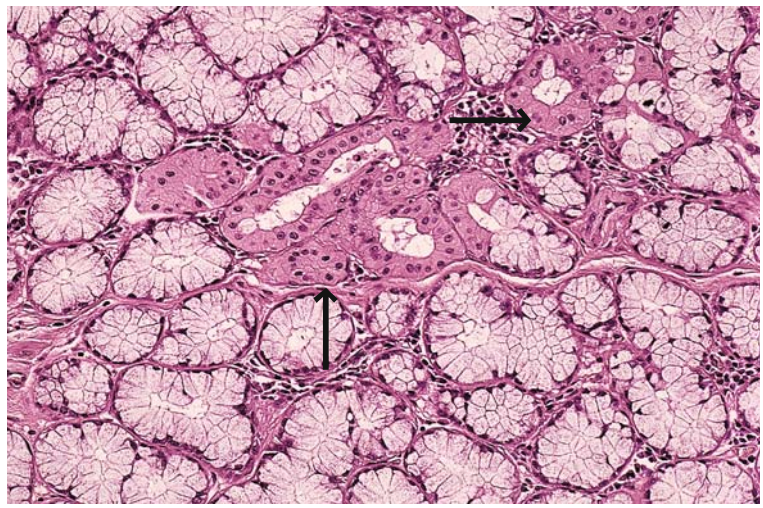


FIG. 2-41. Oncocytes in an esophageal gland proper. Oncocytes (*arrows*), located in the terminal portion, have pink, finely granular cytoplasm

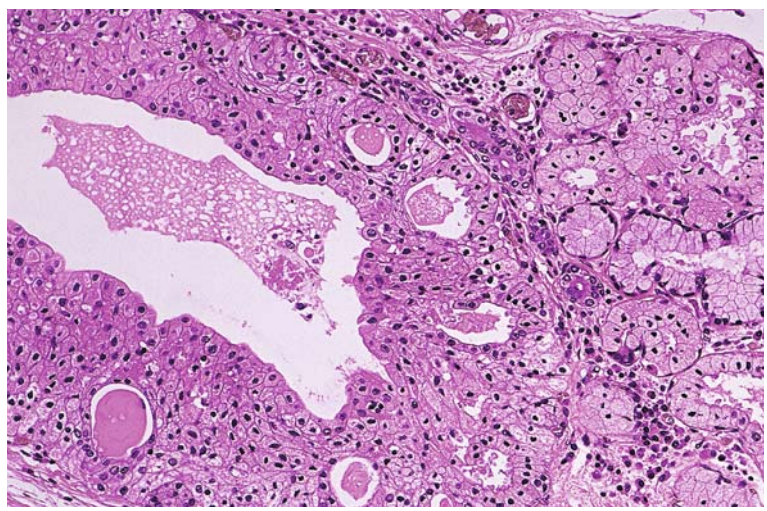


FIG. 2-42. Oncocytic hyperplasia. The terminal portion of the gland, and the excretory duct, have been replaced by oncocytes

cytoplasm is filled with many mitochondria (Fig. 2-43). Oncocytes are located on the basement membrane and make contact with each other via hemidesmosomes.

2.2.1.8.2.4. Myoepithelial Cells. Forming a basket with their netlike processes, myoepithelial cells (basket cells) lie between the basement membrane and the mucous cells, serous cells, or oncocytes that constitute the terminal portions of the esophageal glands proper. Myoepithelial cells may also be seen beneath the terminal ductal cells. They are thought to be responsible for the discharge of secretions by contracting when food passes down the esophagus. However, much remains to be learned about their role.

Although these cells are hardly visible in H&E-stained sections, they can be stained with immunohistochemical stains for actin (Fig. 2-44) and S-100 protein, similar to the myoepithelial cells of salivary and mammary glands. They also stain positively for keratin.

Electron microscopy shows that myoepithelial cells, thin and long in shape, are arranged on the basement membrane (see Fig. 2-39). They contain many fine filaments, consistent with actin, and focal densities are present in the filaments, suggesting an ability to contract. Myoepithelial cells are sparsely bound to one another, to mucous cells and to oncocytes, by desmosomes.

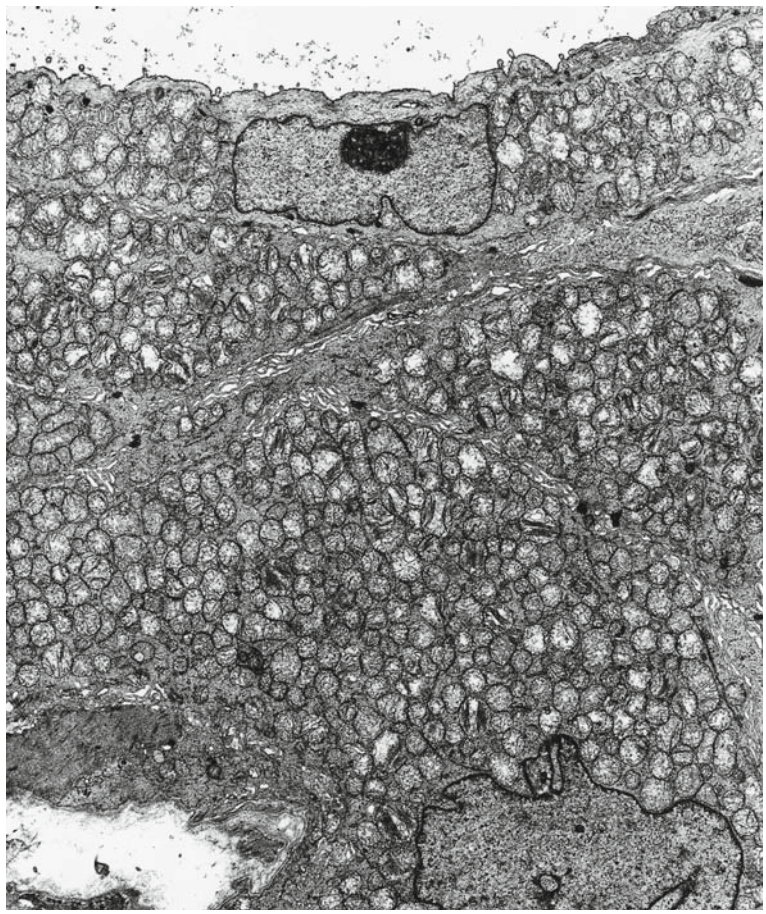


FIG. 2-43. Electron micrograph of oncocytes. Oncocytes have small nuclei and many mitochondria

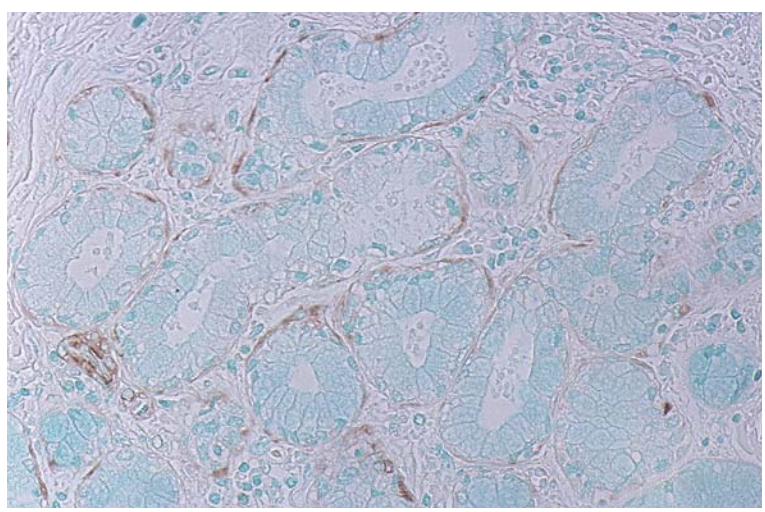


FIG. 2-44. Myoepithelial cells of an esophageal gland proper (actin immunostain). Myoepithelial cells, staining positively for actin, are located on the basement membrane

2.2.1.8.2.5. Ductal Epithelium. The ductal epithelium in the lamina propria is a thick, stratified cuboidal type. It becomes thinner as the duct approaches the terminal portions of the esophageal glands proper in the submucosa. In the vicinity of the terminal portions, the ductal epithelium consists of one or two layers of cuboidal or columnar cells. Epithelial cells on the luminal side have clear cytoplasm, whereas those on the basement membrane side have dark cytoplasm. The peripheral ductal epithelium in the submucosa stains positively for secretory component (SC) and lactoferrin (LF).

Electron microscopy shows that ductal epithelial cells have microvilli on their luminal surface and that these are shorter than those of mucous epithelial cells. The stratified cuboidal epithelium in the lamina propria contains lymphocytes (Fig. 2-45). In the vicinity of the terminal portions of the glands the epithelium becomes columnar, showing a two-layered structure of clear cells and dark cells (Fig. 2-46a).

In this author's study of subserial sections of esophageal specimens obtained from 246 autopsy cases, the incidence of ductal hyperplasia was 34%. In hyperplastic ducts, there is marked stratification of ductal cells in the submucosa (Fig. 2-46b). Ductal dysplasia was also found in some cases (3%). Ductal dysplasia suggests the possibility that cancer may arise in the ductal epithelium.

2.2.1.8.3. Sebaceous Glands

A system of glands similar to the sebaceous glands of the skin can be found in the lamina propria of the esophagus, although rarely. The presence of sebaceous glands in the oral or vulvar mucosa is characteristic of Fordyce's syndrome. In the esophagus these glands, called ectopic sebaceous glands, were first reported by de la Pava and Pickren (1962). Apart from autopsy cases, 17 patients (9 male and 8 female) with ectopic sebaceous glands of the esophagus have been reported (Bertoni et al. 1994). No change in the endoscopic appearance of the glands was seen over a few years of follow-up.

Details of the histogenesis remain unclear, and some studies have attributed these glands to metaplasia. In this author's studies of subserial sections of resected esophagi from patients with esophageal cancer, ectopic sebaceous glands were found in noncancerous regions in 0.6% of specimens. However an incidence of 2% (4 of 200 adults) (de la Pava and Pickren), and the occurrence of

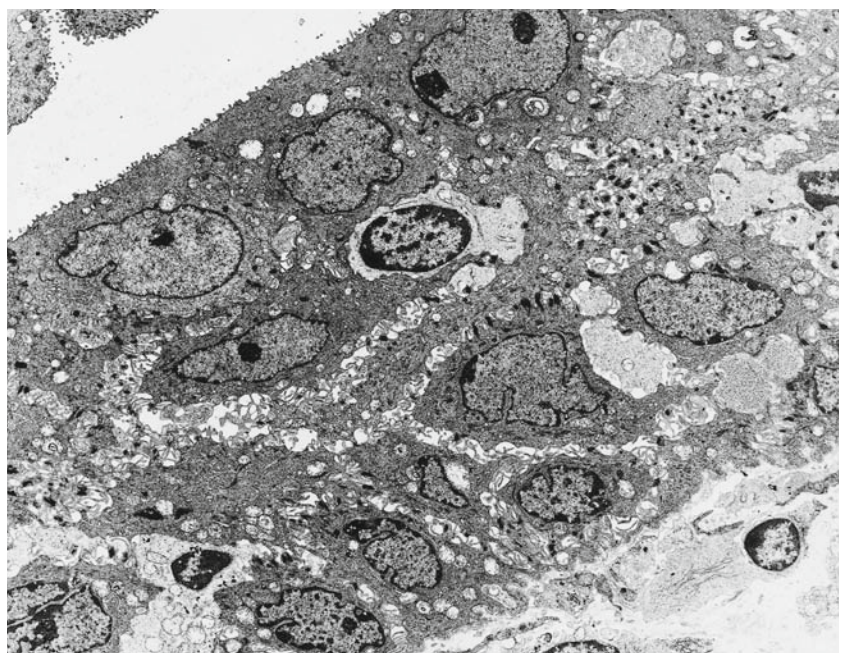


FIG. 2-45. Electron micrograph of the epithelium of an excretory duct. The epithelial cells on the luminal side are cuboidal

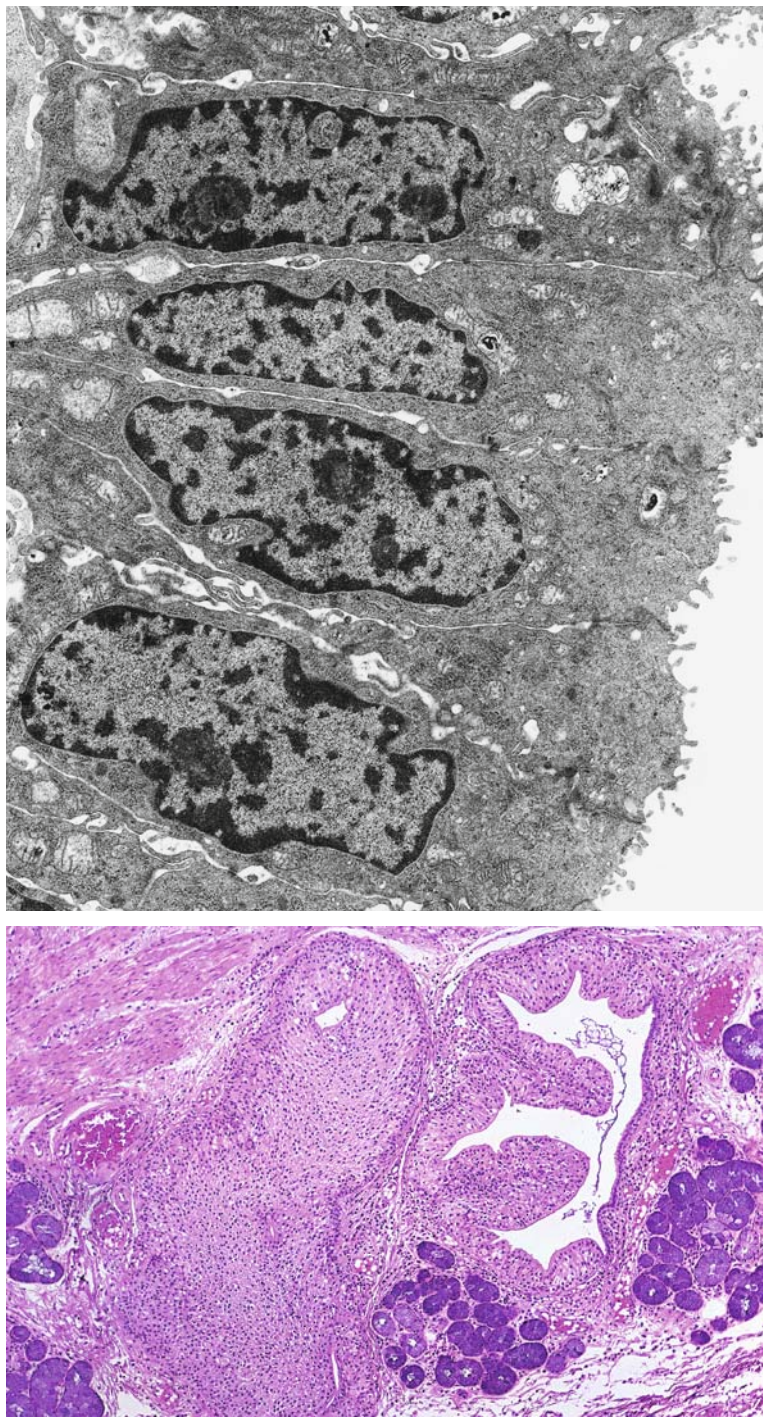


FIG. 2-46. **a** Electron micrograph of ductal epithelium in the submucosa. The ductal epithelium consists of columnar cells. **b** Ductal hyperplasia in an esophageal gland proper. Marked thickening of the ductal epithelium is evident

multiple ectopic sebaceous glands in women with esophagitis, have also been reported. de la Pava and Pickren did not rule out the possibility that this lesion is a metaplastic change, and in fact cited a previous study which indicated that no sebaceous glands were found in the esophagi of 1000 pediatric autopsy cases (Rector and Connerley 1941); however, they stressed that there were differences in methodology between their study and that of Rector and Connerley.

Endoscopically, ectopic sebaceous glands show whitish yellow and slight elevation with a protrud-

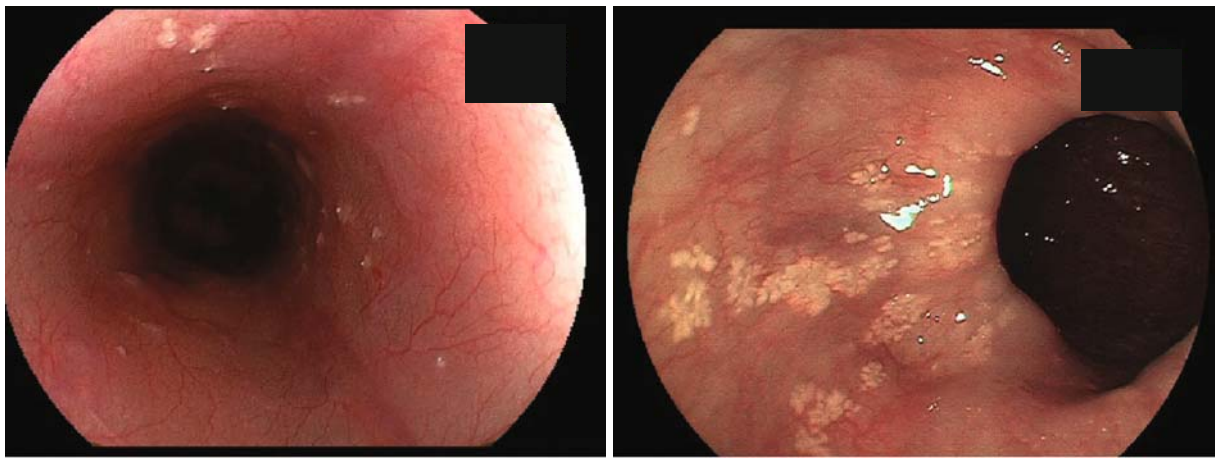


FIG. 2-47. **a** Endoscopic appearance of multiple ectopic sebaceous glands. Ectopic sebaceous glands show whitish yellow and slight elevation with a protruding sebaceous gland duct. Multiple lesions can be recognized. **b** Endoscopic appearance of multiple ectopic sebaceous glands. Multiple whitish-yellow lesions can be recognized. Gland ducts are not prominent

ing sebaceous gland duct. Small vessels are observed through the epithelium above the whitish-yellow sebaceous glands (personal communication; Miwako Arima, Saitama Cancer Center, Ina-machi, Saitama-ken, Japan). Multiple lesions can be recognized on endoscopy (Fig. 2-47a,b).

There are reports describing ectopic sebaceous glands in the esophageal mucosa as forming macroscopic small, yellow, slightly elevated lesions (Zak and Lawson 1976; Nakanishi et al. 1999). The elevation could also be seen endoscopically (Hoshika et al. 1995). This author, however, has observed the mucosa to be flat, with yellow sebaceous glandular tissue evident through the surface epithelium.

Histologically, sebaceous gland cells are located in the lamina propria and have clear granular cytoplasm and small central nuclei (Fig. 2-48). Cells lying on the basement membrane have no fat droplets, but the cytoplasm of other cells is filled with fine foam-like fat droplets. Ectopic sebaceous glands in the esophagus exist independently, without associated hair follicles. Sebaceous cells stain positively for acid phosphatase.

2.2.1.9. Lamina Propria Mucosae, Lamina Propria

The lamina propria consists of delicate connective tissue, including elastic fibers, and forms small papillae (rete ridges) that project into the epithelium. Under normal conditions, the papillae in the upper and middle portions of the esophagus are said to have a height of less than two-thirds the thickness of the epithelium. Elastic fibers in the lamina propria connect with those in the muscularis mucosae. Smooth muscle fibers are occasionally seen, and esophageal cardiac glands are also situated in the lamina propria. Well-developed lymphoid follicles are often seen around the excretory ducts of the esophageal glands proper. In contrast to other parts of the digestive tract, the lamina propria of the esophagus has a dense vasculature and extremely abundant lymphatic vessels.

2.2.1.9.1. Intrapapillary Vessels, Intrapapillary Capillary Loops

The papillae of the lamina propria contain capillary loops measuring about 0.01 mm diameter. They are dilated in gastroesophageal reflux disease and in squamous cell carcinoma in situ, when their diameter may be about 0.1 mm. The different capillary sizes seen on magnifying endoscopy is the basis for distinguishing between benign epithelium and malignancy.

2.2.1.10. Lamina Muscularis Mucosae, Muscularis Mucosae

The muscularis mucosae of the esophagus is composed of smooth muscle fibers that mainly run longitudinally. Unlike the muscularis propria, the muscularis mucosae consists entirely of smooth

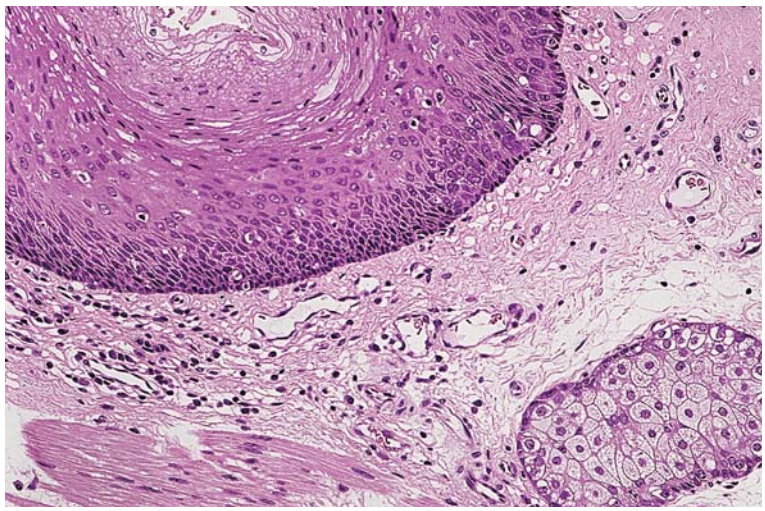


FIG. 2-48. Ectopic sebaceous gland. There is a sebaceous gland in the lamina propria

muscle. In the upper esophagus, the muscularis mucosae merges with the fibrous membrane of the hypopharynx, whereas in the lower esophagus it is linked to the muscularis mucosae of the stomach. The muscularis mucosae is thicker in the lower than in the upper esophagus, and the esophageal muscularis mucosae is thicker than that of the stomach, measuring up to 300 µm in thickness.

Although it has been reported that the difference in thickness of the muscularis mucosae between the lower esophagus and the stomach near the esophagogastric junction is a good clue to the site of the junction, in this author's experience this distinction is not very clear. However, the muscle fibers of the esophageal muscularis mucosae usually run longitudinally in a more orderly manner than those of the stomach.

Irregular thickening of the muscularis mucosae, or formation of a double lamina in very small, limited areas, may occur in esophagitis or in response to irradiation or cancer infiltration. Therefore, irregular arrangement of a few smooth muscle fibers is also often found in the lamina propria.

Defects of the muscularis mucosae have also been noted, although rarely (Kuwano et al.; Groote et al.). The double lamina muscularis mucosae is described in detail in the section on Barrett's esophagus (p. 199).

2.2.1.10.1. Biopsy Sites

Thick collections of fine smooth muscle fibers are seen at previous biopsy sites in esophageal resection specimens; this is the histological appearance of regeneration of the muscularis mucosae.

2.2.2. Tunica Submucosa

The submucosa consists of connective tissue that is coarser than that in the lamina propria and which contains abundant elastic fibers. Also, similar to the lamina propria, the submucosa has numerous lymphatic and blood vessels and has well-developed venous plexuses. The terminal portions of the esophageal glands proper are located in this layer. The submucosa also contains the submucosal plexus (Meissner's plexus), which is composed of a network of several ganglion cells and nerve fibers (Fig. 2-49) and is reportedly involved in the movement of the muscularis mucosae and in the function of secretory glands. Meissner's plexus is far less prominent than Auerbach's plexus in the esophagus.

2.2.3. Tunica Muscularis Propria

The muscularis propria is broadly divided into inner circular and outer longitudinal layers. It is composed of striated muscle in the upper esophagus and of smooth muscle in the lower esophagus. A recent study has shown that the portion composed of striated muscle alone is much shorter than formerly thought (Meyer et al. 1986). The portion composed of smooth muscle alone accounts for more than 50% of the total length of the esophagus, whereas the portion composed of

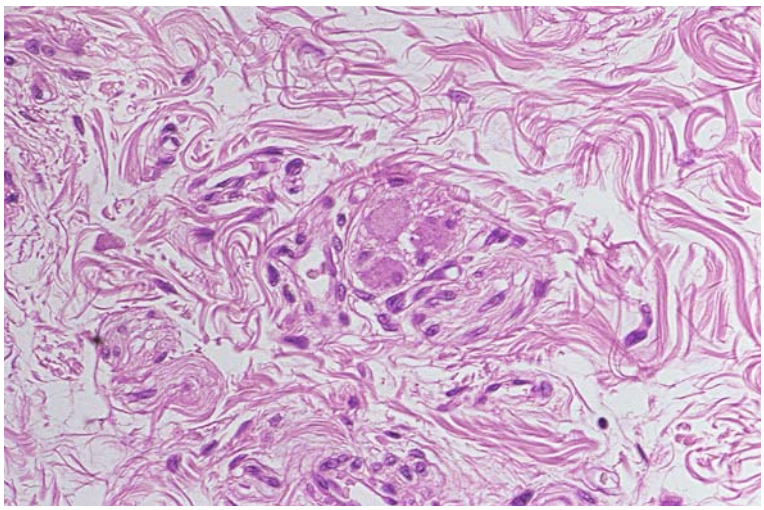


Fig. 2-49. Meissner's plexus in the submucosa. The plexus contains several ganglion cells

striated muscle alone accounts for only about the proximal 5%. In the remaining esophagus, the muscularis propria consists of a mixture of striated and smooth muscle. It has been reported that the amount of striated and smooth muscle becomes equal at a point 5 cm below the esophagopharyngeal junction.

After fixation, the striated muscle of the upper esophagus appears macroscopically brown, similar to skeletal muscle, whereas the smooth muscle in the lower portion appears whitish ivory, the two being clearly distinguishable.

Between the inner circular and outer longitudinal muscle layers there is a well-developed myenteric plexus, Auerbach's plexus, composed of ganglion cells and nerve fibers (Fig. 2-50). In the upper esophagus, with only striated muscle, Auerbach's plexus is poorly developed. The number of ganglion cells and nerve fibers in Auerbach's plexus decreases with age (see Section 4.6. Aging and Changes in the Nerve Plexus and Smooth Muscle).

The inner circular muscle at the lower end of the esophagus is called the lower esophageal sphincter, and this muscle tenses and relaxes in the presence of gastrin or secretin. However, no clear thickening of the muscularis propria, corresponding to the lower esophageal sphincter, can be seen in histological sections.

2.2.4. Tunica Adventitia

The tunica adventitia is a thick layer of coarse connective tissue linking the esophagus to surrounding structures. This layer corresponds to part of the mediastinum, and contains thick nerves, lymphatic vessels, and blood vessels. Although not an established view, it is common practice in Japan for nerves running in the adventitial connective tissue to be regarded as part of the esophageal wall when judging the depth of invasion of esophageal cancer. In a similar way, the thoracic duct, recurrent laryngeal nerve, and azygos vein are also regarded as parts of the esophageal wall.

2.2.5. Organs Neighboring the Esophagus That May Be Seen on Examination of Biopsy and Surgical Specimens

The stomach, spleen, pharynx, and larynx (Fig. 2-51) are occasionally resected with the esophagus during surgery for esophageal carcinoma. In addition, this author has had the opportunity to carry out microscopic studies of other structures including the trachea, bronchus, lung (Figs. 2-52, 2-53), heart (Fig. 2-54), pericardium (Fig. 2-55), diaphragm (Fig. 2-56), pleura (Figs. 2-57 through 2-59), azygos vein, thoracic duct (Figs. 2-60, 2-61), aorta (Fig. 2-62), thymus (Fig. 2-63), and pancreas, in association with the examination of esophageal

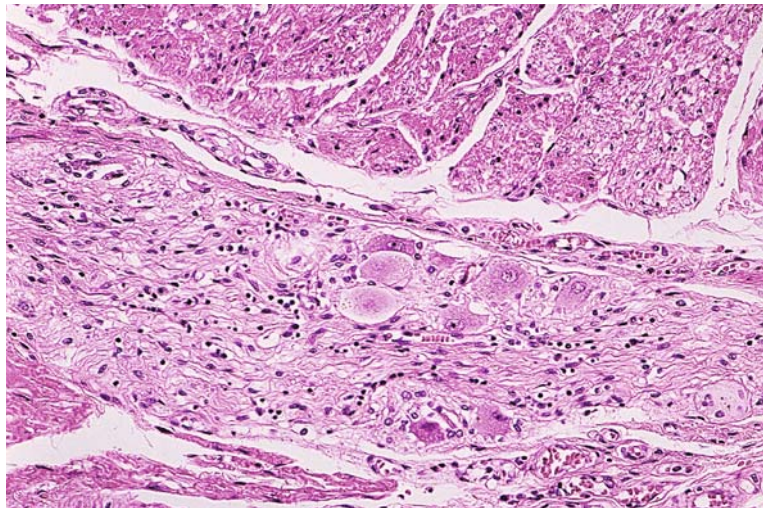


FIG. 2-50. Auerbach's plexus in the muscularis propria. The plexus is located between the inner circular and outer longitudinal muscle layers

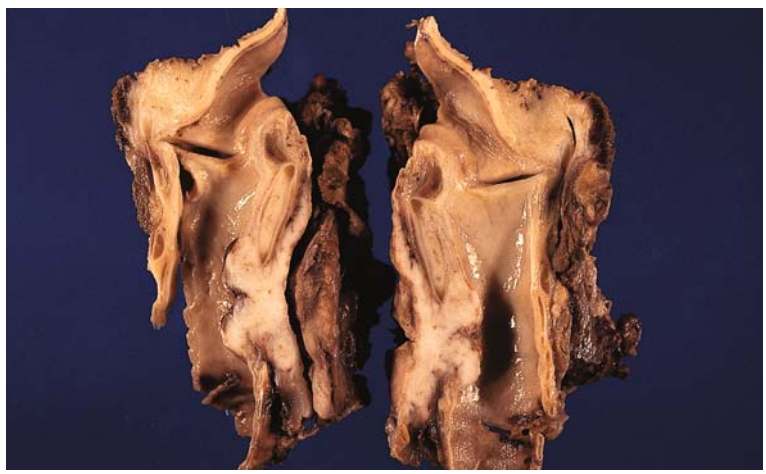


FIG. 2-51. Macroscopic appearance of direct invasion of esophageal cancer into upper respiratory organs

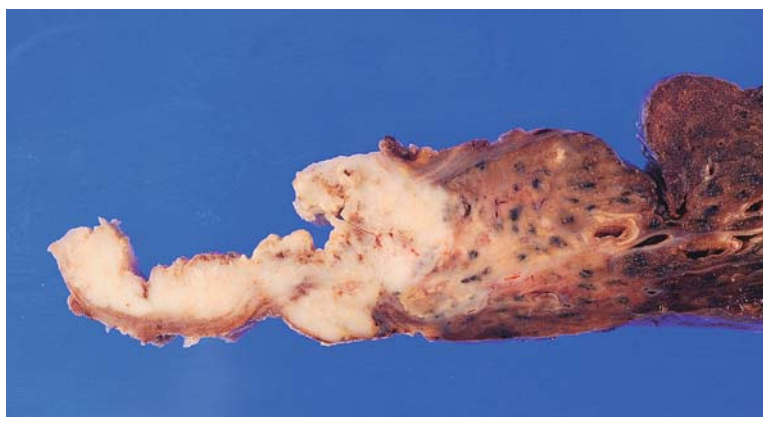


FIG. 2-52. Macroscopic appearance of direct invasion of esophageal cancer into lung. The lung is yellowish white as a result of fibrosis

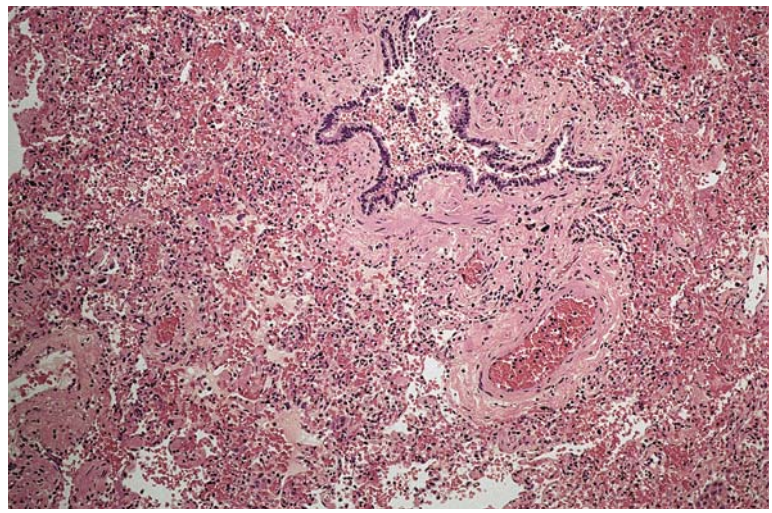


Fig. 2-53. Lung tissue near the invading esophageal cancer. Alveolar spaces are unclear because of hemorrhage, infiltrating inflammatory cells and progressive fibrosis, but bronchial epithelium is identifiable

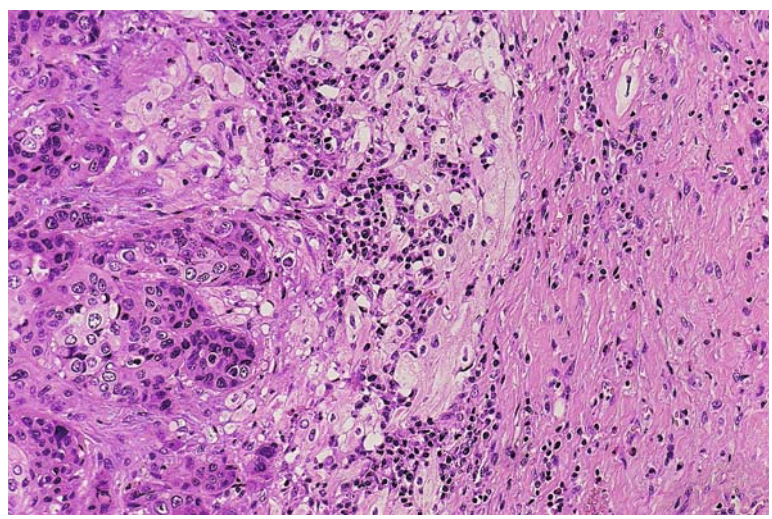


Fig. 2-54. Invasion of esophageal cancer into the left atrium of the heart. Cancer tissue invades the myocardium

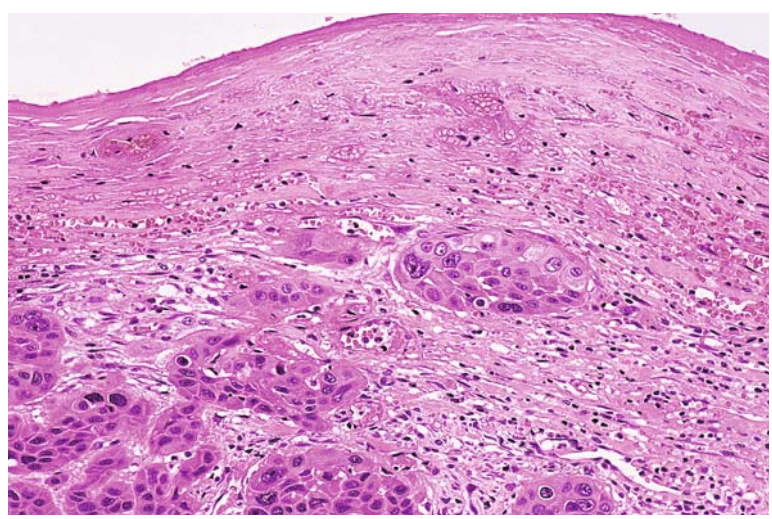


Fig. 2-55. Invasion of esophageal cancer into pericardium. Mesothelial cells have disappeared

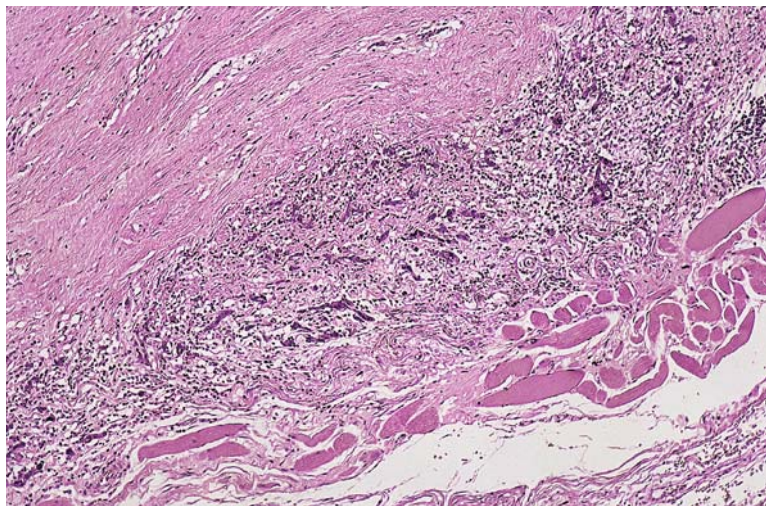


Fig. 2-56. Direct invasion of esophageal cancer into the diaphragm. Cancer cells are infiltrating into the striated muscle

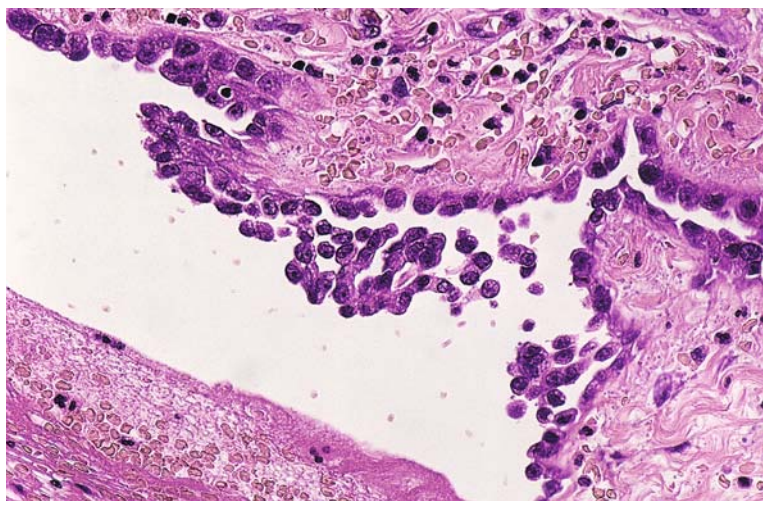


Fig. 2-57. Reactive mesothelial cells in pleura. The mesothelial cells are enlarged and cuboidal in shape

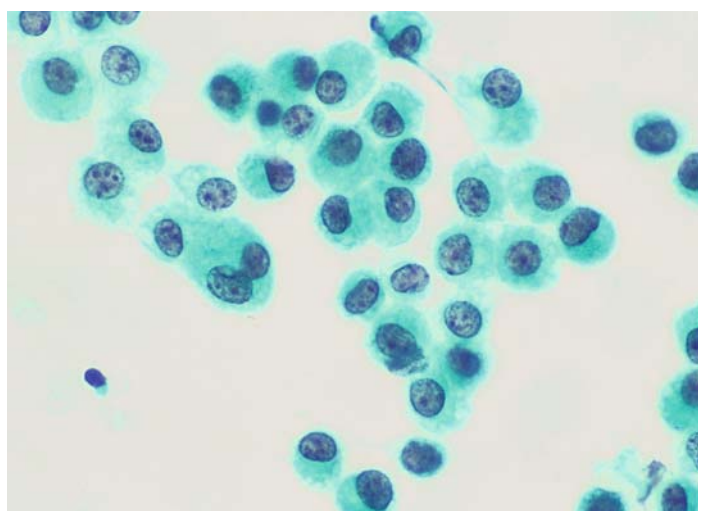


Fig. 2-58. Reactive mesothelial cells in pleural fluid (Papanicolaou stain)

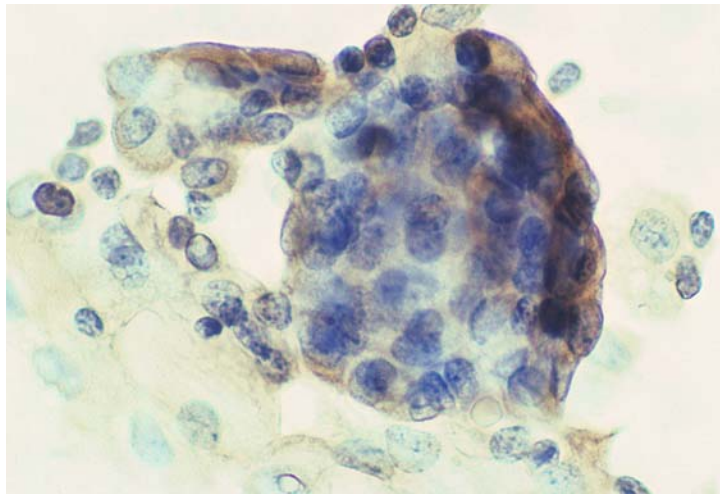


Fig. 2-59. Reactive mesothelial cells in pleural fluid (vimentin immunostain). Reactive mesothelial cells are occasionally aggregated and show positive staining for vimentin

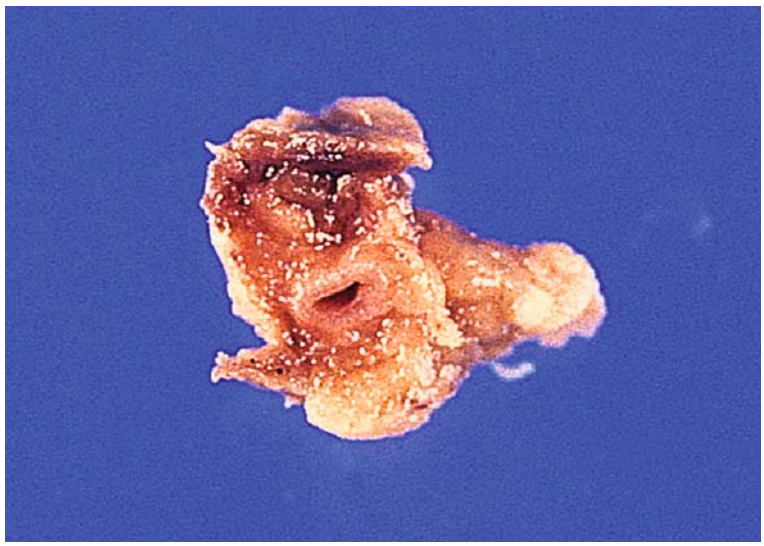


Fig. 2-60. Macroscopic appearance of the thoracic duct. The thoracic duct, 2–3 mm in diameter in cross section, is seen in connective tissue

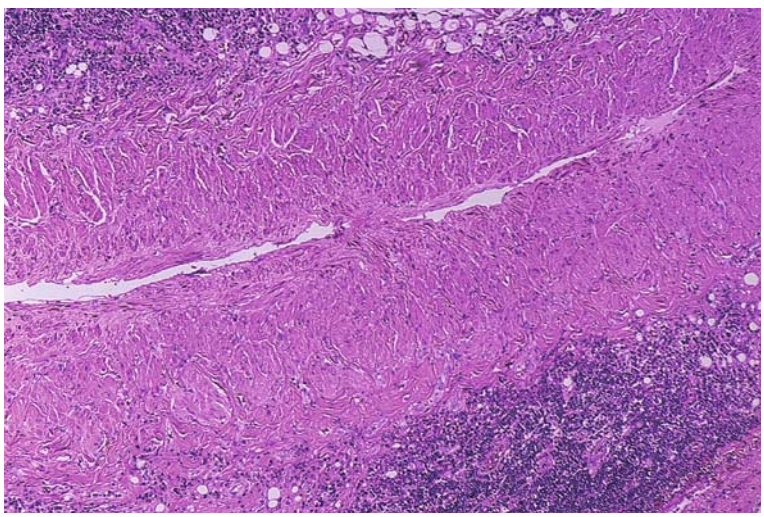


Fig. 2-61. Longitudinal section of the thoracic duct. The thoracic duct has a thick media

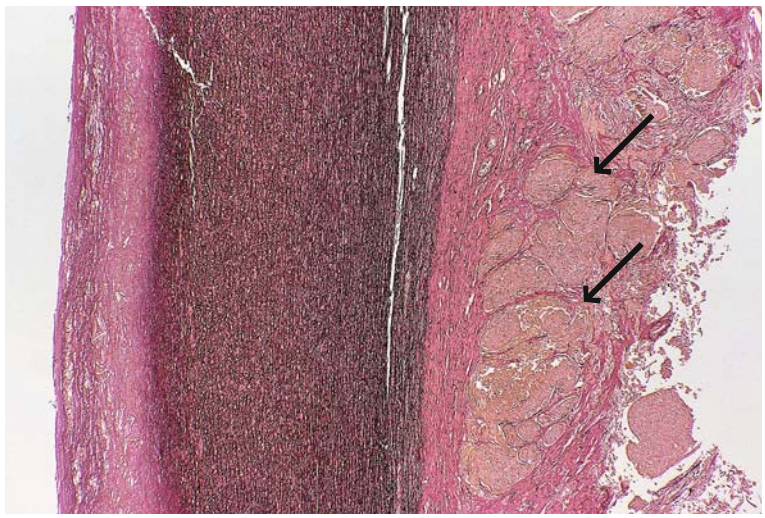


FIG. 2-62. Direct cancer invasion of the aorta (elastica van Gieson stain). Cancer invasion (*arrows*) is seen in the aortic adventitia

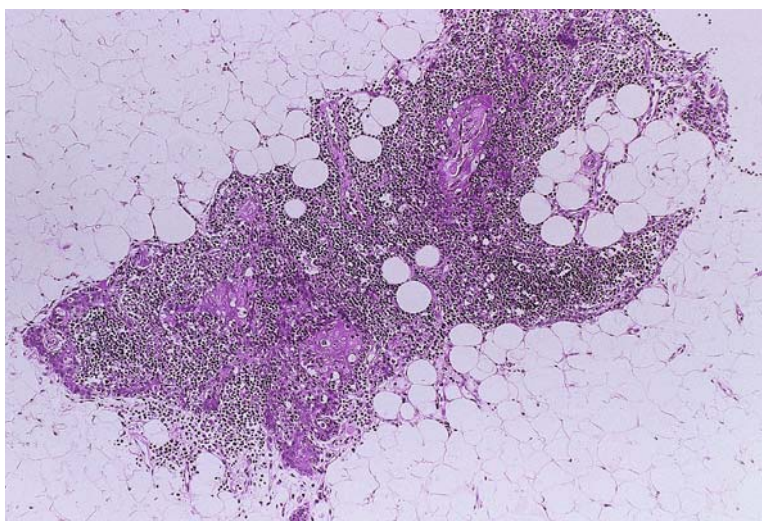


FIG. 2-63. Markedly atrophic thymus in an adult with esophageal cancer. An aggregate of thymic epithelial cells and lymphocytes is seen in adipose tissue

specimens obtained at surgery. These structures may be examined clinically by endoscopic ultrasound sonography to detect direct cancer invasion.

The lung tends to show dense infiltration by inflammatory cells, often with loss of alveolar spaces, when invaded by esophageal cancer. Consequently, it is common for the lung to be only recognizable by the presence of bronchial spaces and bronchial cartilage (see Fig. 2-53).

When striated muscle fibers are seen deep to the muscularis propria of the gastric cardia or lower esophagus, these represent the diaphragm (see Fig. 2-56). These muscle fibers are seen in the esophagogastric junction zone, less than 24 mm distal to the squamocolumnar junction. Invasion of individual muscle fibers may be seen when cancer invades the diaphragm; this can also be seen with invasion by cancers of other organs such as the breast.

The pericardium consists of two layers, the fibrous pericardium, composed of thick collagen fibers, and the serosal pericardium. Absence of mesothelial cells or enlarged, reactive mesothelial cells may be noted when there is cancer invasion (see Fig. 2-55). Reactive mesothelial cells may also be found in the pleura and on the serosa of the esophagus and stomach. They are enlarged, cuboidal in shape, and have enlarged nuclei (see Fig. 2-

57). Reactive mesothelial cells sometimes appear in aggregates in cytological specimens of coelomic fluid, making them difficult to distinguish from adenocarcinoma (see Figs. 2-58, 2-59). Mesothelial cells are negative with B72.3 and carcinoembryonic antigen (CEA) immunostains, and at most show only focal positivity for Ber EP4 (Gaffey et al.). They are almost always negative for neutral mucin (PAS negative after diastase digestion) but are positive for vimentin (see Fig. 2-59). Activated, benign mesothelial cells often show patchy epithelial membrane antigen (EMA) positivity, whereas malignant mesothelial cells are often strongly EMA positive. Mesothelial cells can usually be distinguished from adenocarcinoma in cytology specimens by a combination of neutral mucin and immunohistochemical stains for CEA, B72.3, and Ber EP4.

Macroscopically, the thoracic duct is slightly thicker than a pencil lead (see Fig. 2-60) and has a thick media (see Fig. 2-61).

The aorta may also occasionally be resected along with the esophagus in cases of carcinoma. Invasion by carcinoma is usually only observed in the aortic adventitia (see Fig. 2-62), rarely in the media and intima. Histological findings in autopsy cases after aortic rupture caused by invasion by esophageal cancer suggest that rupture occurs because of either bacterial infection from the cancerous ulcer base or obstruction of the vasa vasora. The intimal surface may be covered by infected thrombus.

The thymus is white in color in young infants, allowing relatively clear distinction from surrounding tissues, but at the usual age of presentation of esophageal cancer it is very atrophic, grossly resembling adipose tissue. Thymic tissue may be surgically removed with dissected lymph nodes. Histologically, atrophic thymus consists mainly of adipose tissue, with thymic epithelial cells and thymic lymphocytes gathered in the form of islets (see Fig. 2-63).

Depending on the extent of lymph node dissection during surgery, thyroid and/or parathyroid tissues, and neuroganglia, may also be included with dissected lymph nodes.

2.2.6. Other Ectopic Tissues

Ectopic thyroid, hepatic tissue, pancreatic tissue, and parathyroid glands have all been reported in the esophagus, but this author has never seen these tissues in surgically resected esophagi.

2.2.6.1. Ectopic Thyroid Gland

It has been reported that ectopic thyroid tissue in the esophagus may appear macroscopically as a submucosal tumor, appearing brown and transparent on cut surface. Only three case reports have been published (Postlethwait and Detmer 1975).

2.2.6.2. Ectopic Hepatic Tissue and Ectopic Pancreatic Tissue

Ectopic hepatic tissue (a 70-year-old man; Jimenez and Hayward 1971) and ectopic pancreatic tissue (a 51-year-old man; Razi 1966) are also known to very occasionally occur in the esophagus. Severe esophageal stenosis caused by ectopic hepatic tissue and bleeding from ectopic pancreatic tissue have been reported, but these situations are extremely rare and are not generally discussed in currently available textbooks of gastroenterology.

2.2.6.3. Ectopic Parathyroid Gland

Ectopic parathyroid glands have been reported in the esophagus of a 35-year-old woman (Sloane and Moody 1978).

Chapter 3
Vascular Disorders of the Esophagus

3.1. Esophageal Varices

Although a number of disorders can cause portal hypertension with esophageal varices, this author has seen only cirrhosis of the liver and constrictive pericarditis as actual autopsy cases.

Usual autopsy techniques may allow blood to flow out from the vessels of the esophagus. This practice interferes with the macroscopic observation of dilated veins from the mucosal aspect, often making it difficult to confirm the presence of mild varices in cases of liver cirrhosis. In the normal situation, however, there are generally very few blood vessels visible through the esophageal epithelium at autopsy, so, in practice, the identification of many blood vessels from the mucosal aspect is evidence of varices. If the esophagus is removed without allowing the blood in intramural vessels to flow out, thick veins can be easily observed from the mucosal aspect and in cut sections (Fig. 3-1). Therefore, although esophageal varices are rather common at autopsy, most books on surgical pathology do not show photographs of them. On rare occasions, esophageal varices can be observed histologically in surgical specimens of transaction rings.

Four layers of veins can be identified in the esophageal wall in both normal individuals and in patients with portal hypertension (Kitano et al.). These layers comprise veins in the papillae of the lamina propria protruding into the epithelium, a venous plexus in the superficial layer of the submucosa, thick veins in the deep layer of the submucosa, and veins in the adventitia, all of which communicate with each other. These veins are enlarged threefold to fivefold in cases of portal hypertension. A report by Kitano et al. documented that typical large varices develop from large veins in the deep layer of the submucosa.

The histological appearance of esophageal varices includes enlarged veins and capillaries in the lamina propria (Fig. 3-2) and submucosa

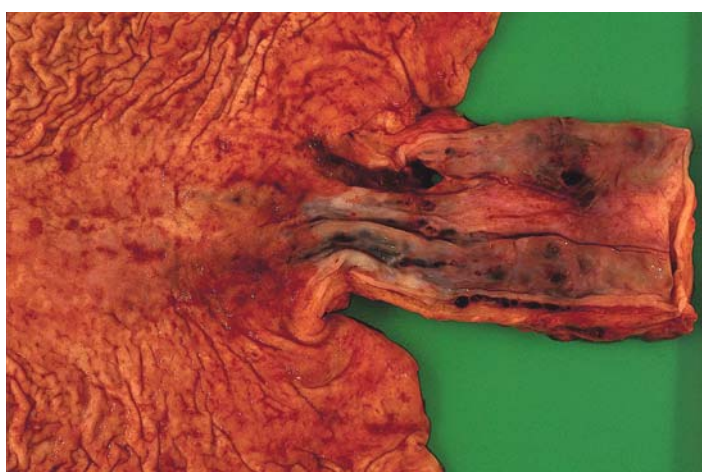


Fig. 3-1. Macroscopic appearance of esophageal varices (autopsy specimen). Blood vessels are seen through the mucosa, running longitudinally, and on the cut surface

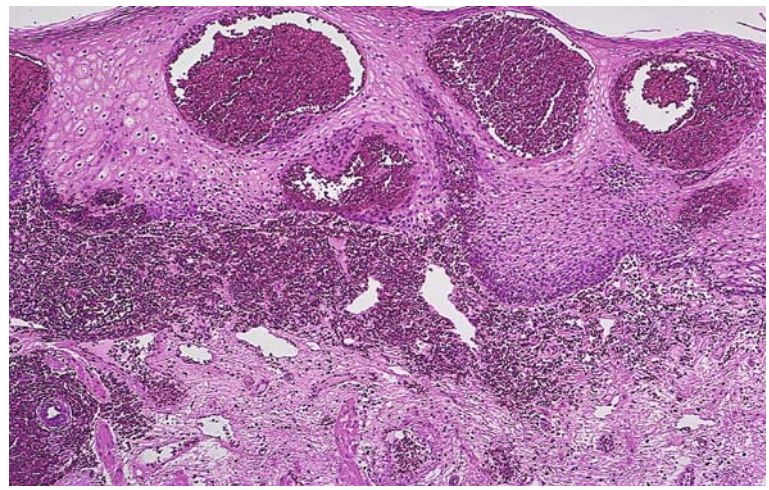


FIG. 3-2. Esophageal varices (surgical specimen). Enlarged channels are seen in the epithelium

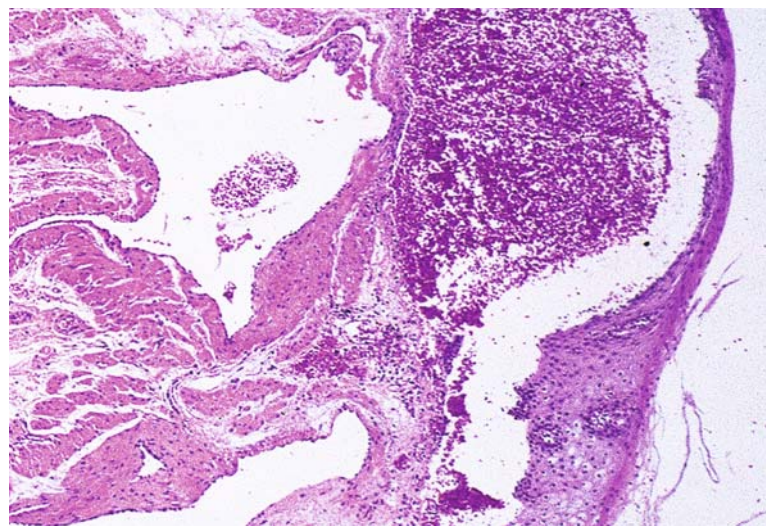


FIG. 3-3. Esophageal varices (surgical specimen). There are enlarged veins in the lamina propria and submucosa

(Fig. 3-3). Enlargement of capillaries in the papillae of the lamina propria that project into the mucosal epithelium is particularly conspicuous, but these vascular changes are also observed in the muscularis propria and adventitia. The enlarged capillaries in the papillae are called intraepithelial channels (Spence et al.) or vascular ducts.

Electron microscopy has shown that these channels are not lined by endothelial cells or a basement membrane, suggesting that they are closely related to variceal bleeding, but it has been reported that the flat cells around the channels react with immunohistochemical stains for Factor VIII (Spence et al.). Cherry-red spots observed on the mucosal surface at endoscopy are thought to represent these channels. The dilated veins in the submucosa have hardened walls, are enlarged into irregular shapes, and sometimes contain thrombi. Although it is reported that esophagitis plays no important role in the pathogenesis of bleeding from esophageal varices (Heil et al.), this is still controversial.

Extensive venous thrombosis is seen in the esophageal wall, particularly the superficial layers, after sclerotherapy. The thrombosis occurs not only in the lower but also in the upper esophagus. Ulcers and necrotic foci are sometimes seen, and fibrosis of the submucosa gradually becomes more conspicuous. Loss of the muscularis mucosae is occasionally observed (Fig. 3-4). After 4 months of sclerotherapy, there is diffuse fibrosis in the mucosa and submucosa (Harada et al.).

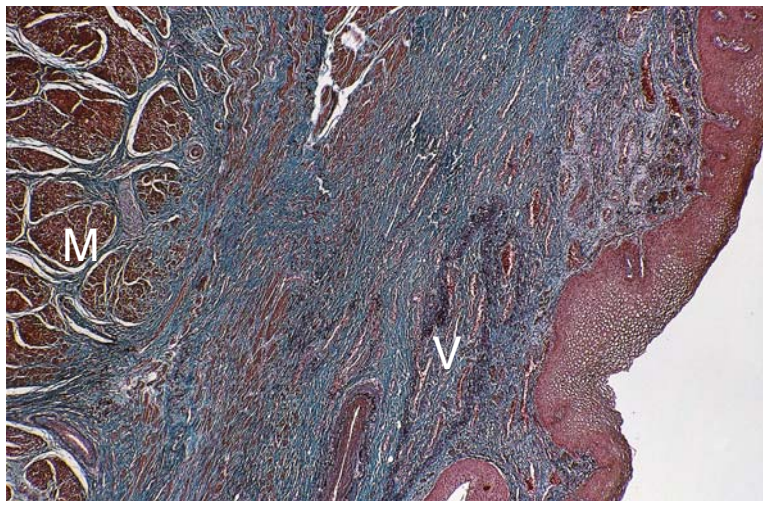


FIG. 3-4. Esophageal varices after sclerotherapy (elastica–Masson stain). Elastic fibers of occluded veins (*V*) are seen in the fibrous connective tissue of the esophageal wall. The muscularis mucosae are not recognizable. *M*, muscularis propria

Condensed elastic fibers from thrombosed veins can be seen in the fibrous tissue (Fujioka).

3.1.1. Sclerotherapy and Carcinogenesis

It is known that intramural hematomas, mucosal bridges, ulcers, stenosis, and papillomas (Yamada et al.) may occur following sclerotherapy for esophageal varices.

The occurrence of esophageal cancer following sclerotherapy has also been increasingly reported in recent years (Tanoue et al.). Although there is no clear etiological relationship between sclerotherapy and cancer, it has been stated that the possibility of cancer should be considered when dysphagia occurs after sclerotherapy (Jalan et al.; Giorcelli and Rodi). No data are available on the incidence of esophageal malignancy in patients with cirrhosis. The incidence of esophageal squamous cell carcinoma in patients who had undergone sclerotherapy was 0.042% in Japan, which was higher than the incidence in the general population (Kokudo et al. 1990). There have not been any reports that have fully described the histopathology of sclerotherapy-related cancer, including a description of the surrounding mucosa.

3.2. Dieulafoy's Lesion of the Esophagus

Dieulafoy's lesion is described as an arterial malformation in the submucosal layer that can cause massive gastrointestinal hemorrhage. The lesion is frequently found in the proximal stomach, whereas it is rare in the esophagus and colon (Lee et al. 2003).

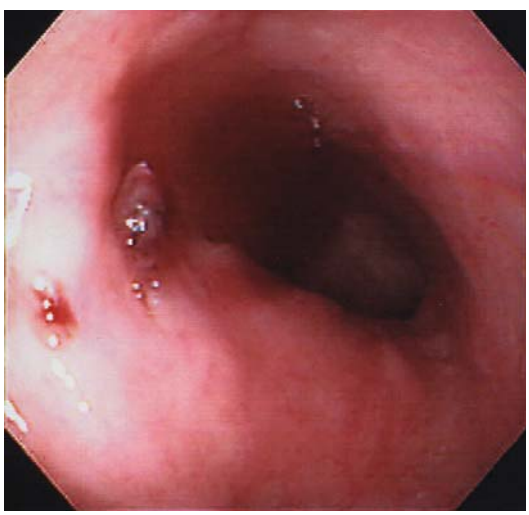


FIG. 3-5. Endoscopic appearance of Dieulafoy's lesion. The lesion shows a small protruding reddish lesion accompanied by oozing hemorrhage. (From Yoshida T with permission)

Although esophageal Dieulafoy's lesion is uncommon, the most common site is the distal esophagus and Dieulafoy's lesion has been found to be an alternative source of bleeding despite the presence of esophageal varices. Endoscopically, it showed a small protruding reddish lesion accompanied by oozing hemorrhage (Fig. 3-5) (Yoshida et al. 2004).

Chapter 4
Achalasia and Esophageal Motor Dysfunction

4.1. Achalasia

Esophageal achalasia has been known for a long time, being first described by Willis in 1674 (Vantrappen and Hellemans 1974). Its etiology is still controversial, however, and much remains to be clarified about its pathophysiology. Measurements of esophageal pressure have revealed a lack of both esophageal peristalsis and reflex relaxation of the lower esophageal sphincter at the time of swallowing.

It is rare in Japan for resected esophagi with achalasia to be referred for pathological examination, apart from those cases complicated by carcinoma. No description of the histopathological findings is given in the *Descriptive Rules for Achalasia of the Esophagus*, edited by the Japanese Society for Esophageal Diseases (3rd edition, 1983).

Histologically the esophageal wall in the distal, nondilated segment is almost normal in thickness, but the wall in the dilated segment is often thickened because of hypertrophy of the inner circular muscle layer of the muscularis propria (Fig. 4-1). However, in some cases, the wall is thinned, and the muscularis mucosae and muscularis propria show extensive fibrosis.

The histological and electron microscopic appearance of Auerbach's plexus of the esophagus in achalasia is described in detail in a report by Cassella et al. (1964). In their study of 34 cases, they found a loss of ganglion cells in Auerbach's plexus in the muscularis propria and degeneration of nerve fibers in the esophageal wall (Figs. 4-2, 4-3). Lymphocyte infiltration and fibrosis (Fig. 4-4) were also noted in Auerbach's plexus. In another study, many of the lymphocytes infiltrating Auerbach's plexus were found to be resting and activated cytotoxic T cells (Clark et al. 2000). These changes occur in the dilated esophageal segment, in contrast to the situation in Hirschsprung's disease. Ganglion cells may be reduced in number distal to the dilated segment

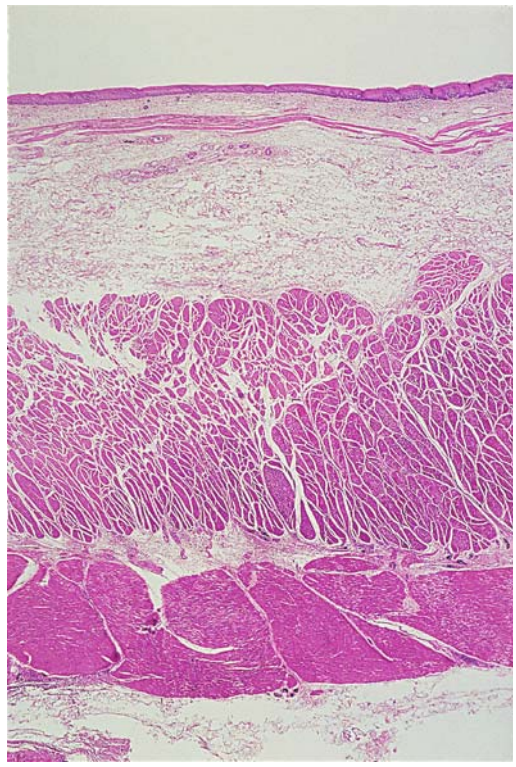


FIG. 4-1. Achalasia. The inner circular layer of the muscularis propria is markedly thickened. There is fibrosis in the lamina propria and submucosa, and no esophageal glands proper are seen

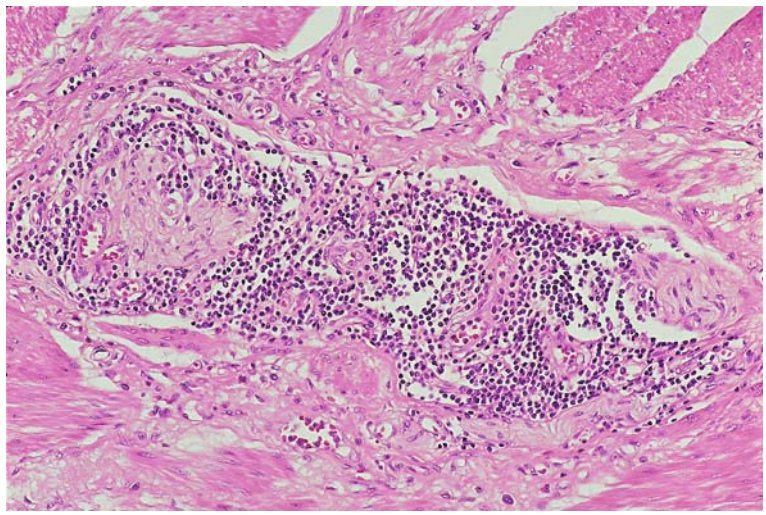


FIG. 4-2. Achalasia. Auerbach's plexus is infiltrated by many lymphocytes and plasma cells

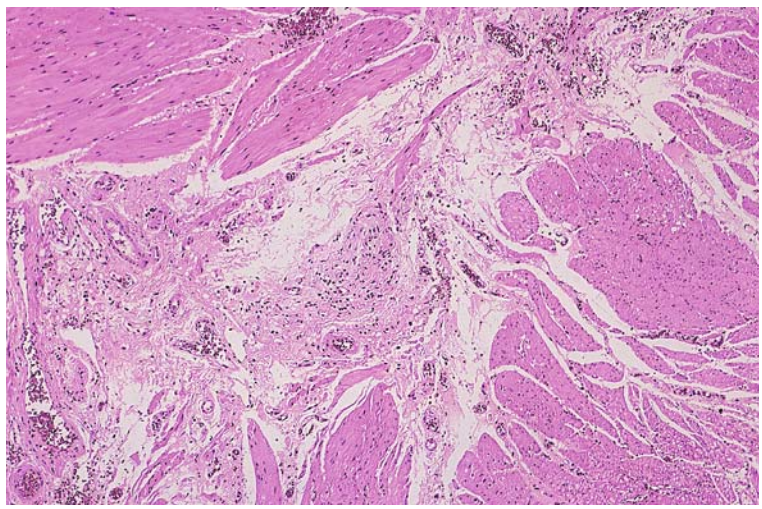


FIG. 4-3. Achalasia. Auerbach's plexus is seen between the hypertrophic inner circular and outer longitudinal muscle layers of the muscularis propria

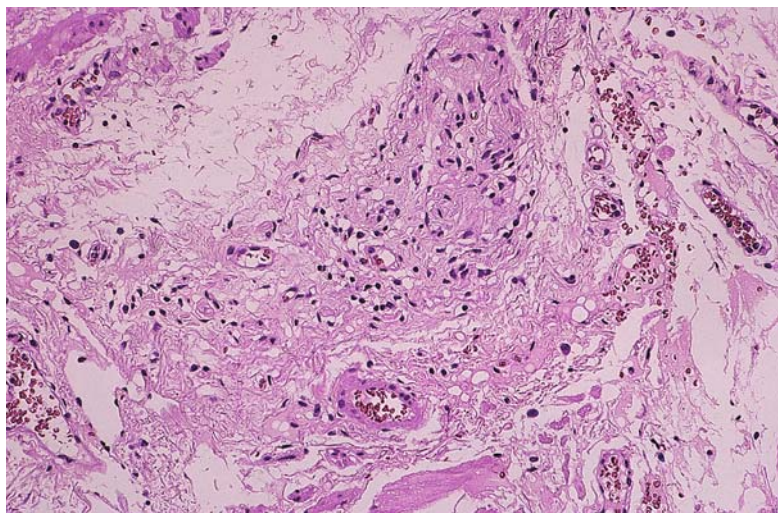


FIG. 4-4. Achalasia. Disappearance of ganglion cells, and fibrosis of Auerbach's plexus, are evident

but are never absent. Complete loss of Auerbach's plexus and of ganglion cells has also been reported in subserial sections of the dilated segment by Fujii et al. It is not yet known whether these changes in the plexus are the cause or the result of the achalasia. A similar decrease in the number of ganglion cells has also been described in the stomach (Csendes et al.). Besides these findings, Lewy bodies (see Figs. 6-15, 6-16; Chapter 6), which characteristically occur in the locus ceruleus and substantia nigra of the brain in Parkinson's disease (see Chapter 6, p. 78), have been reported in the ganglion cells of Auerbach's plexus in some patients with achalasia (Qualman et al.). In the latter report, Lewy bodies were present in ganglion cells in the esophagi of 2 of 8 patients with achalasia.

The esophageal mucosa in achalasia shows hyperplasia of the squamous epithelium, similar to that seen in glycogenic acanthosis. In addition there is papillomatosis and basal cell hyperplasia, similar to the appearances seen in chronic esophagitis. Atrophy of the terminal portions of the esophageal glands proper is often found in the dilated segment. In a report by Goldblum et al. (1994) of 42 cases of esophageal achalasia treated by resection, there were no terminal portions of esophageal glands proper in 21 (50%) of the 42 cases, and cystic dilatation of the excretory ducts of the esophageal glands proper was seen in 27 cases. Lymphocytic infiltration of the mucosa and/or submucosa is another characteristic finding in achalasia. In addition, there is fibrosis of the adventitia. No obvious changes in the vagus nerve are evident by light microscopy.

Electron microscopy reveals necrosis, atrophy, and hypertrophy of smooth muscle cells in the muscularis propria.

4.1.1. Achalasia, Atypical Epithelium, and Carcinoma

According to a report by Meijssen et al. (1992), an association between achalasia and esophageal carcinoma was reported as early as 1872 by Fagge. More than 20 articles have been published discussing this association. Esophageal carcinoma is reported to develop in 2% to 17% of cases of achalasia. Recently, a review of 195 cases was reported in which the risk of esophageal carcinoma was more than 33 times greater in patients with achalasia than in those without (Meijssen et al. 1992). Concomitant carcinoma is more frequent in men than in women, with a male : female ratio of 3 : 1 to 12 : 1.

Carcinoma arising in association with achalasia occurs more than 10 years earlier than the average age of patients usually affected by esophageal carcinoma; there is one report of a squamous cell carcinoma that occurred in a 33-year-old patient with achalasia (Hankins and McLaughlin). Hayashi et al. (1989), who studied 43 Japanese patients with achalasia accompanied by carcinoma (none of whom had received previous surgical therapy for achalasia), stated that there was a greater percentage of female patients (male : female ratio, 6 : 4) compared to the percentage of women with esophageal carcinoma not associated with achalasia. Also, the age of onset was about 5 years earlier than in patients with esophageal carcinoma not associated with achalasia.

Tanaka reported the results of a survey of 125 Japanese medical facilities at the 46th meeting of the Japanese Society for Esophageal Diseases (Tokyo, June 1992); a total of 2419 patients with achalasia were found, of whom 1151 had suffered from the disorder during the preceding 10 years. Forty-five patients (1.9%) had had a concomitant esophageal carcinoma, and 33 of the 45 carcinomas had occurred after surgery for the achalasia. Arima et al. (2000) reviewed 486 Japanese cases of achalasia and found 21 associated squamous cell carcinomas and 3 adenocarcinomas with associated Barrett's esophagus.

Concomitant carcinomas usually occur in the dilated segment of the esophagus, away from the narrowed portion. The middle third of the esophagus has been the predominant site in the cases reported (Fig. 4-5). In contrast, corrosive carcinomas (see Chapter 7, p. 91) occur in the mucosa just proximal to the narrowed segment. There have also been some reports of multiple carcinomas of the esophagus occurring in association with achalasia.

Figure 4-5 shows the macroscopic appearance of the specimen from a case reported by Fujii et al. The maximum diameter of the esophagus was 8 cm, and the carcinoma was located in the upper thoracic region.

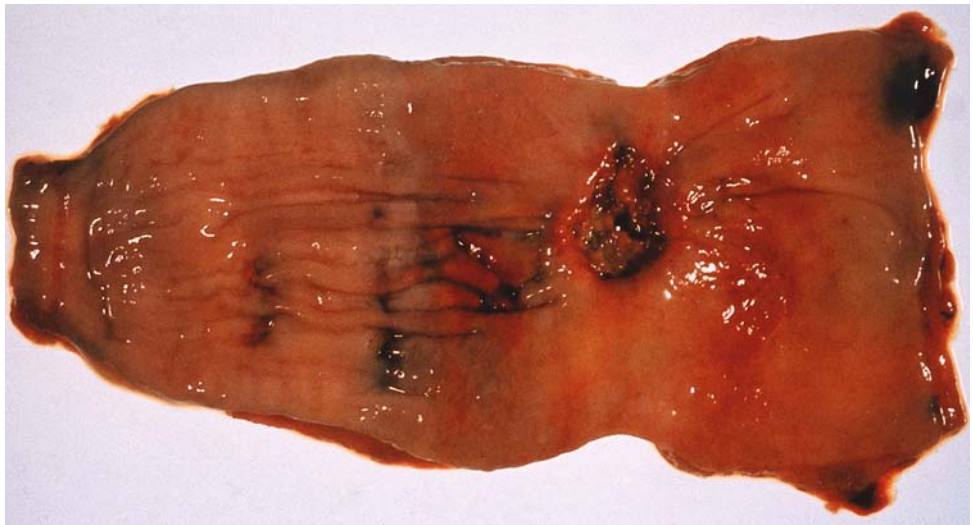


FIG. 4-5. Macroscopic appearance of an esophageal carcinoma that occurred in association with achalasia. An advanced ulcerative and infiltrative type of carcinoma is seen in the markedly dilated esophagus away from the narrowed distal segment

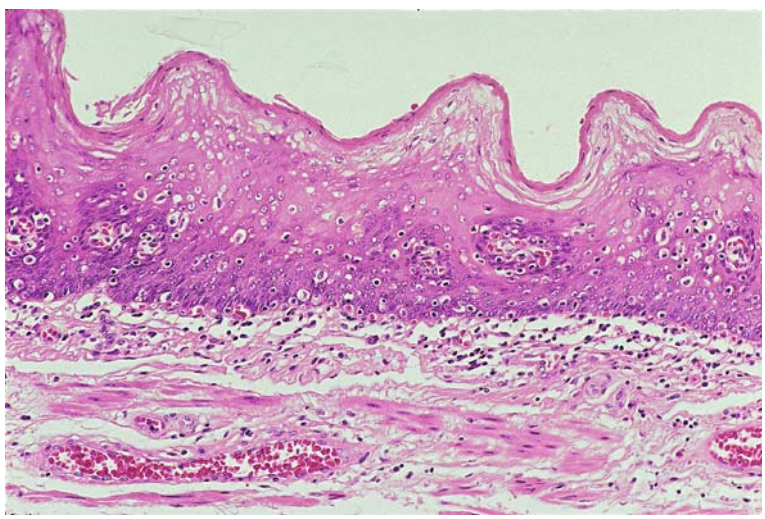


FIG. 4-6. Achalasia. Atypical squamous epithelium with hyperkeratosis, from a patient with achalasia

A histological analysis of carcinomas occurring in association with achalasia, by Just-Viera and Haight, showed that squamous cell carcinomas were predominant, accounting for 68 (88%) of 77 cases, with only 8 cases of adenocarcinoma. Two cases of verrucous carcinoma (Wychulis et al. 1971; Roach and Barr 1993), 2 cases of undifferentiated carcinoma (citation of report by Bolivar and Herendeen; Proctor et al.), and 2 cases of carcinosarcoma have also been reported (citation of report by Just-Viera and Haight; Iwaya et al.). Also a case of choriocarcinoma associated with adenocarcinoma arising in Barrett's esophagus, in a patient with achalasia, has been reported from Japan (Aonuma et al.).

Keratinization and dysplasia (Fig. 4-6) have been reported in the nonneoplastic esophageal mucosa in resected esophagi from patients with achalasia and associated carcinoma (Uchiyama et al.); hyperkeratosis, parakeratosis, and orthokeratosis were described in this study. However, most papers reporting concomitant achalasia and carcinoma have not described the histology of the nonneoplastic esophageal epithelium.

4.1.2. Reflux Esophagitis and Barrett's Esophagus Associated with Achalasia

Esophagitis resulting from food retention, and spontaneous rupture of the esophagus, have been known to occur in patients with esophageal achalasia who have not had surgical treatment, while reflux esophagitis is an important postoperative complication.

Barrett's epithelium has been reported to occur after surgery for achalasia. In one report of two cases, Barrett's esophagus was found endoscopically 4 years 7 months and 10 years 9 months after surgery (Taniguchi et al.). In another report, Barrett's esophagus was found in three patients 8 to 30 years after surgery for achalasia. One of these was a 74-year-old man who had developed an adenocarcinoma in the metaplastic mucosa of Barrett's esophagus 30 years after surgery. In other reports, 4 of 46 patients (9%) and 4 of 34 patients (12%) with achalasia treated by surgical myotomy were found subsequently to have Barrett's esophagus (Jaakkola et al. 1994; Goldblum et al. 1994). Also, as noted in the previous section, a case of choriocarcinoma associated with adenocarcinoma in Barrett's esophagus has been reported (Aonuma et al.).

4.2. Secondary Achalasia

Apart from the primary type already described, it is known that achalasia may occur following irradiation or as a result of amyloidosis, sarcoidosis, trypanosomiasis (Chagas' disease), benign tumors (lymphangioma, leiomyomatosis), and malignant tumors. Malignant tumors causing achalasia have included gastric adenocarcinoma, pulmonary adenocarcinoma, pulmonary oat cell carcinoma, hepatocellular carcinoma, pancreatic adenocarcinoma, prostatic carcinoma, and renal cell carcinoma (Manela et al.). Malignancy-induced achalasia has been attributed to esophageal stenosis caused by direct infiltration or pressure from the primary tumor or lymph node metastases, neoplastic destruction of the nerve plexus of the lower esophageal sphincter, metastatic disease in the brainstem affecting the dorsal nucleus of the vagus nerve, and paraneoplastic syndromes (Parkman and Cohen). There have been very few detailed reports on the pathology of secondary achalasia except for Chagas' disease.

4.2.1. Chagas' Disease (American Trypanosomiasis)

Chagas' disease was initially described in 1909 by Carlos Chagas. Chagas' disease, found endemically in Central and South America, is caused by *Trypanosoma cruzi*. No case of Chagas' disease has been reported in Japan, and only a few cases of Chagas' disease have been identified in the United States (Navin et al.; Galel and Kirchhoff 1996). Chagas' disease has a predilection to affect the heart and gastrointestinal tract. The cardiac involvement is related to the prognosis. Gastrointestinal involvement is more frequent in South America than Central America, probably because of different strains of *Trypanosoma cruzi*. Megaesophagus is not always present in patients of Chagas' disease. However, esophageal achalasia is one of the major digestive disorders in patients in the chronic stage of Chagas' disease. *Trypanosoma cruzi* destroys the myenteric plexus of the esophagus, which is thought to be the cause of altered motor dysfunction and relaxation of the lower esophageal sphincter.

Esophagographically, endoscopically, and macroscopically, the esophagus demonstrates dilation (Figs. 4-7 through 4-10). It is known that in cases of Chagas' disease hypertrophic muscularis propria (Fig. 4-11) and marked decreased number of ganglion cells in the myenteric plexus (Fig. 4-12) were observed (Köberle 1968). Focal myositis with accumulation of chronic inflammatory cells is also evident in the muscularis propria. The basal layer of the squamous epithelium becomes hypertrophic, having a similar appearance to that seen in chronic esophagitis. Figures 4-7 through 4-12 were offered by Ivan Cecconello, M.D. and Kiyoshi Iria, M.D., Departments of Surgery and Pathology, University of São Paulo School of Medicine.

Squamous cell carcinoma is frequently associated with Chagas' disease with achalasia (see Fig. 4-10) and was observed in 2.8% of patients with Chagas's disease with achalasia at the Departments of Surgery and Pathology, University of São Paulo School of Medicine.

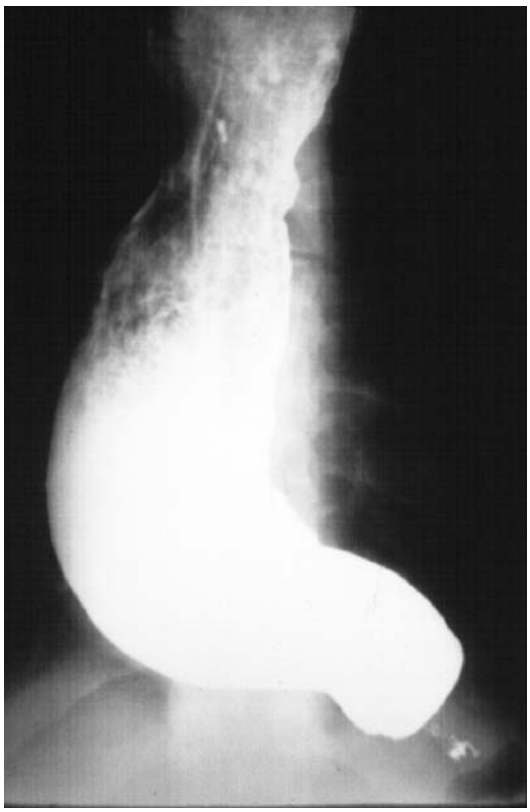


FIG. 4-7. Esophagogram from a patient with Chagas' disease with achalasia. A dilated esophagus and narrowed esophagogastric junction are evident

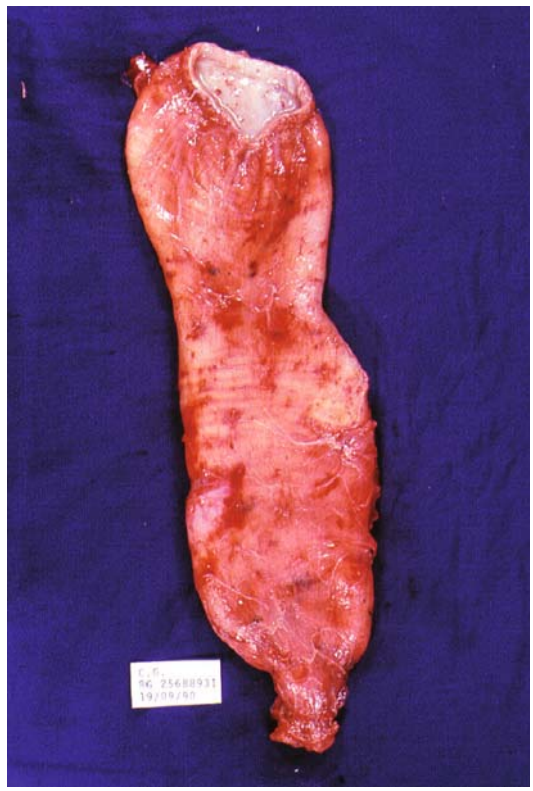


FIG. 4-8. Macroscopic appearance of the esophagus in a patient with Chagas' disease

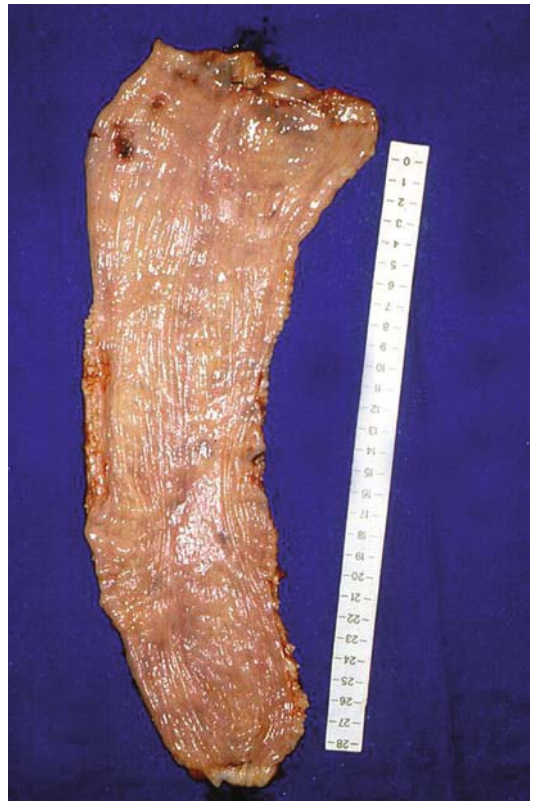


FIG. 4-9. Macroscopic appearance of the opened esophagus in a patient with Chagas' disease. This is the same esophagus as in Fig. 4-8. A markedly dilated and thickened esophagus is observed

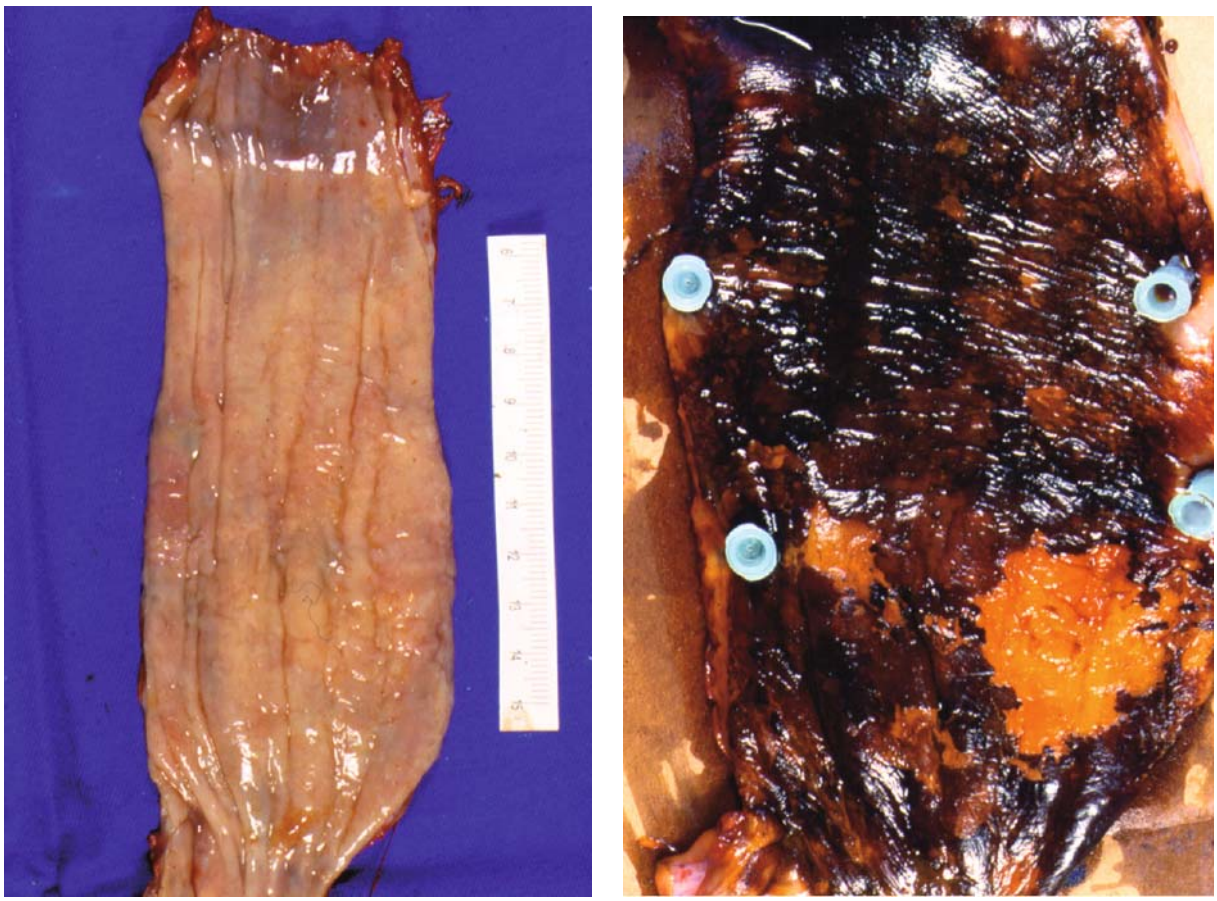


Fig. 4-10. Macroscopic appearance of the esophagus in a patient with Chagas' disease associated with early squamous cell carcinoma. *Left:* Markedly dilated and thickened esophagus is observed. *Right:* After Lugol's iodine staining, flat but clearly demarcated squamous cell carcinoma is evident

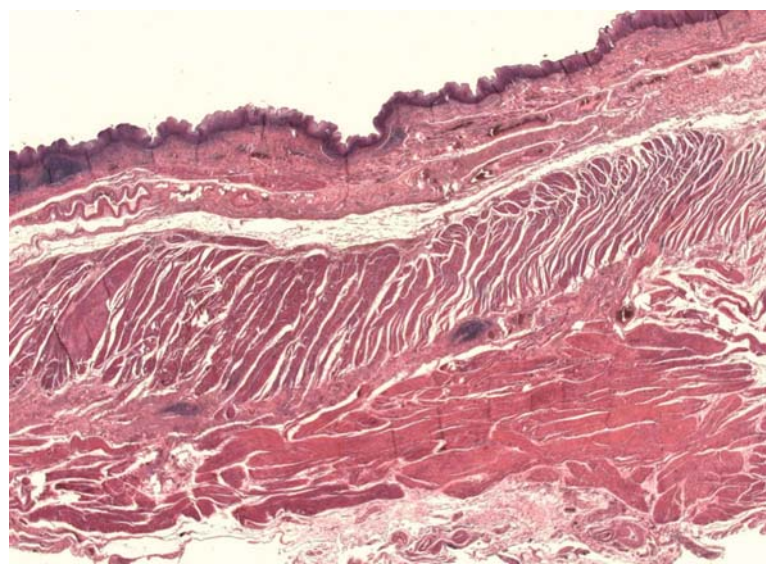


Fig. 4-11. Chagas' disease. Hypertrophic muscularis propria and two foci of inflammatory cell accumulation in the myenteric plexus are observed

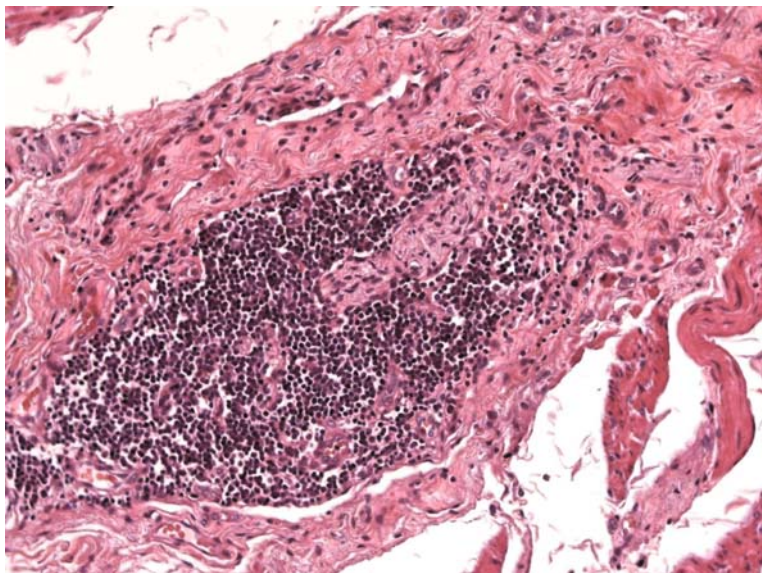


FIG. 4-12. Chagas' disease. No or marked decreased number of ganglion cells were observed in the myenteric plexus with accumulation of chronic inflammatory cells

4.2.2. Paraneoplastic Syndromes and Gastrointestinal Motor Dysfunction

Some cases of malignancy-induced achalasia have been attributed to esophageal stenosis caused by paraneoplastic syndromes (Parkman and Cohen). In one reported group of seven patients with lung carcinomas who developed visceral neuropathies, several showed esophageal dysmotility (Chinn and Schuffler). Six of the seven lung carcinomas were small cell carcinomas. In these cases the gastrointestinal tract pathology was confined to Auerbach's plexuses; these were infiltrated by lymphocytes, plasma cells, and eosinophils, and showed a marked loss of ganglion cells.

4.3. Diffuse Esophageal Spasm, Nutcracker Esophagus, and Hypertensive Lower Esophageal Sphincter

Esophageal motility disorders are comparatively rare and present with two major symptoms, chest pain and dysphagia. These disorders are divided into achalasia, diffuse esophageal spasm, hypercontracting (nutcracker) esophagus, hypocontracting esophagus, and secondary motility disorders. They are generally diagnosed by esophageal manometry (Richter 2001; Kahrilas et al. 1994). There have not been any published descriptions of the histopathological findings in these disorders, apart from achalasia.

4.4. Alcoholic Neuropathy and Deterioration of Esophageal Peristalsis

Esophageal motor dysfunction has been described in a patient who had peripheral neuropathy secondary to chronic alcoholism (Winship et al.).

4.5. Allgrove's Syndrome

Achalasia sometimes occurs as part of an autosomal recessive disorder termed Allgrove's syndrome that features achalasia, Addison's syndrome (ACTH insensitivity), and alacrima (lack of tears). Khelif et al. reviewed ten such cases.

4.6. Aging and Changes in the Nerve Plexus and Smooth Muscle

Abnormal motility of the esophagus is occasionally seen in the elderly (Soergel et al.) from various known causes such as achalasia and collagen vascular diseases. However, the cause of presbyesophagus (abnormal esophageal mobility in older individuals without achalasia or collagen

vascular disease) is unknown (Meshkinpour et al.).

It is known that the number of ganglion cells in Auerbach's plexus of the esophagus decreases with age (Eckardt and LeCompte 1978). Lymphocyte infiltration of Auerbach's plexus is often prominent in the elderly but may also be seen in the young. It has been reported that there is no significant change in the thickness of the esophageal wall in the elderly, leading to speculation that presbyesophagus is attributable to a decrease in the number of ganglion cells in Auerbach's plexus rather than to a change in the smooth muscle layer.

Chapter 5
Infective Esophagitis

5.1. Viral Esophagitis

5.1.1. Herpetic Esophagitis

5.1.1.1. Herpes Simplex Virus Esophagitis

The commonest cause of viral esophagitis is herpes simplex virus type 1, and most cases not caused by this are attributable to cytomegalovirus.

According to Cronstedt et al. (1992), herpetic esophagitis was first reported by Johnson in 1940. Of all visceral organs, the esophagus is the most common site of infection by herpes simplex virus. The incidence of herpetic esophagitis in different autopsy series has varied from 1.4% to 6%. Herpetic esophagitis is most often found at autopsy in cases of malignant disease, particularly malignant lymphoma and leukemia, and in immunodeficiency disorders. In an autopsy study by Matsumoto and Sumiyoshi, eight of nine patients with herpetic esophagitis had malignant disease, and in all eight cases the causative strain was herpesvirus type 1. Kawasaki and Masuda, however, reported the case of a 66-year-old woman with renal failure who had esophagitis caused by herpes simplex virus type 2.

Bleeding (Fishbein et al.), fistula (Cirillo et al.), and perforation (Cronstedt et al.; Shintaku et al.) have all been reported as rare complications of herpetic esophagitis.

The lesions of herpetic esophagitis mostly consist of erosions of the esophageal mucosa, measuring 3–5 mm in diameter and having slightly elevated margins. Mucosa adjacent to the erosions appears relatively normal (Figs. 5-1 through 5-3).

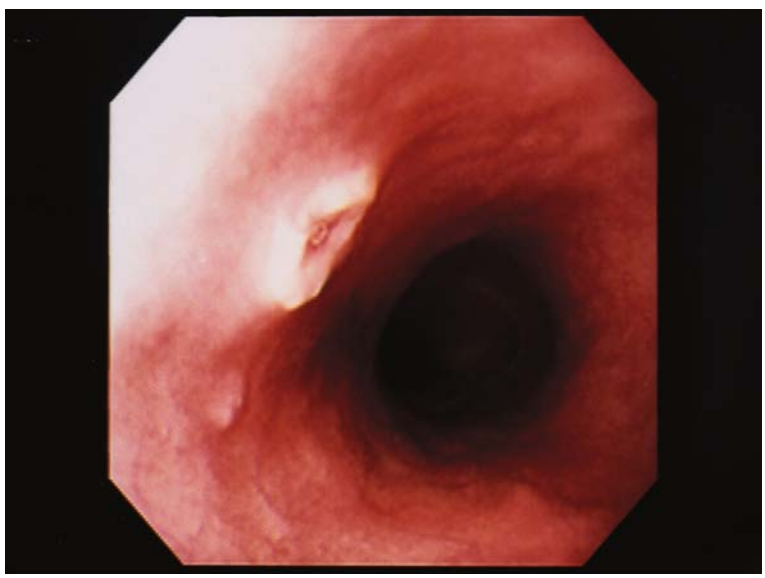


FIG. 5-1. Esophagoscopic features of herpetic esophagitis. Small erosive lesions with elevated margins are seen in the esophageal mucosa

FIG. 5-2. Macroscopic appearance of herpetic esophagitis (unfixed specimen). Many small erosions are present in the lower to midesophagus. From an autopsy case after chemotherapy for gastric cancer

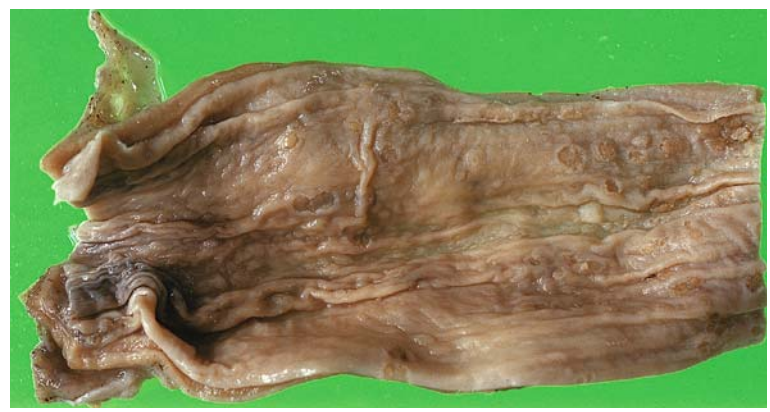


FIG. 5-3. Macroscopic appearance of herpetic esophagitis (fixed specimen). There are multiple small round mucosal erosions, up to 3 mm in diameter

Vesicles similar to those seen in the skin are usually not found in the esophageal mucosa because the esophageal epithelium lacks a keratin layer. The erosions may become extensive.

Histologically the erosions show exfoliation of either the surface layer alone or the whole thickness of the squamous epithelium, and there is infiltration by granulocytes and lymphocytes. Epithelial cells with inclusion bodies occupying the entire nucleus (full type), or with spherical or oval intranuclear inclusion bodies larger than nucleoli and staining pink on hematoxylin and eosin (H&E) (Cowdry A type), are seen around the erosive lesions. Halos surround the intranuclear inclusion bodies. Giant cells with many small nuclei and ground glass-like chromatin are also found, as are epithelial cells with either edematous cytoplasm, very weakly staining on H&E, or strongly eosinophilic cytoplasm (Fig. 5-4). These morphological findings suggest herpetic esophagitis. Positive immunohistochemical staining of nuclei with commercially available antibodies against herpesviruses (anti-HSV-1, -2) helps confirm the diagnosis (Fig. 5-5).

Herpes esophagitis is easily diagnosed cytologically, being characterized by large multinucleate cells with ground glass-like nuclei, in a necrotic background (Fig. 5-6). These findings are similar to those seen in cervical smears in cases of herpesvirus infection.

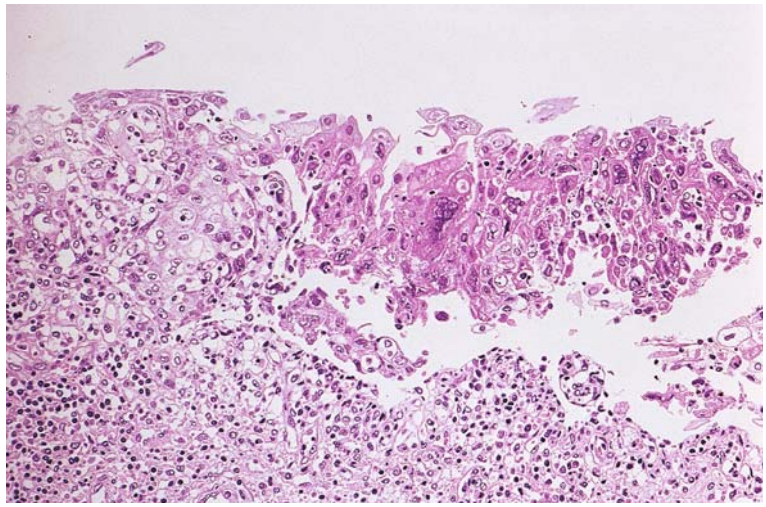


FIG. 5-4. Herpetic esophagitis. There are multinucleate giant cells in the epithelium

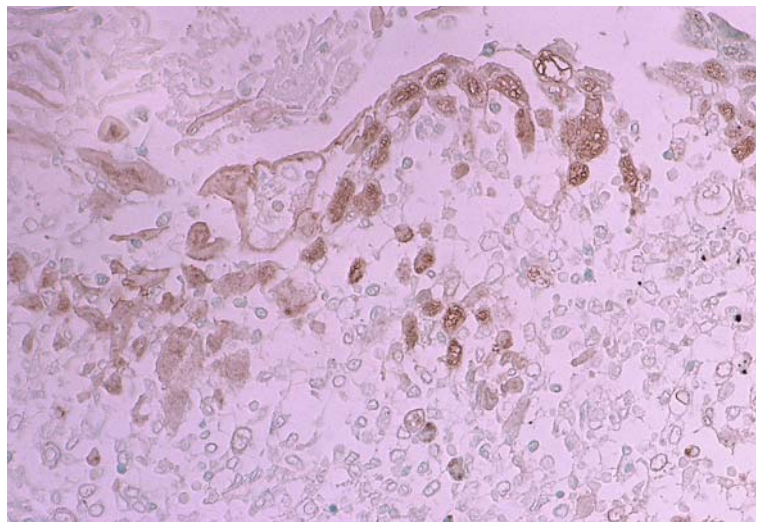


FIG. 5-5. Herpetic esophagitis [anti-herpes simplex virus (anti-HSV-1) antibody immunostain]. The epithelial cells stain positively for HSV-1

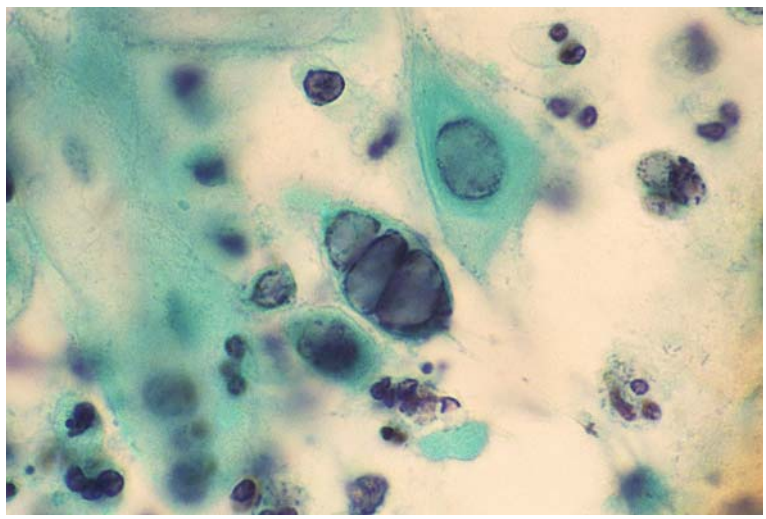


FIG. 5-6. Cytological appearance of herpetic esophagitis (Papanicolaou stain). The cells have ground glass-like nuclei

5.1.1.2. Varicella Zoster Virus Esophagitis

Esophageal lesions due to infection by varicella zoster virus are rare, but one such autopsy case, of a 19-year-old man, has been reported (Meigh et al.). This patient had been receiving steroid and cyclosporin A therapy after a renal transplant. Another report documented foci of esophageal viral infection in 25 of a series of 59 autopsies performed on bone marrow transplant patients (McDonald et al.); varicella zoster virus infection was seen in 1 of the 25 cases. Moretti et al. reported the case of an esophageal varicella zoster virus infection associated with an esophagobronchial fistula that occurred in a 31-year-old man with acquired immunodeficiency syndrome (AIDS). The present author has encountered one autopsy case of systemic varicella zoster virus infection associated with steroid therapy. The esophageal histology in this case was very similar to that seen in herpes simplex infection, except that full type and Cowdry A type inclusion bodies were often found in stromal cells in the lamina propria, as well as in epithelial cells. The inclusion bodies in the stromal cells were smaller than those in the epithelial cells (Fig. 5-7).

5.1.2. Cytomegalovirus Esophagitis

Although cytomegalovirus (CMV) infection has been long known in the field of pediatric pathology, the virus itself was not isolated until 1956.

In a study by Takayama (1969), cytomegalovirus infection of at least one organ was found in 2.7% of 3020 autopsies, the corresponding rate being 0.4% when only adult cases (age 16 years or older) were included. Takayama found that 4% of cases of cytomegalovirus infection had cytomegalovirus-related inclusion bodies in the esophagus, and that the inclusion bodies were all in stromal, not epithelial, cells. Rosen and Hajdu (1971) found cytomegalovirus (CMV) infection of organs other than the esophagus in 19 (0.3%) of 5788 patients with carcinoma who came to autopsy. There was also herpetic esophagitis in 1 of these cases. In their series, lymphoma and leukemia accounted for about 80% of the CMV-positive cases, with only a low proportion caused by other solid cancers; there were no cases of esophageal involvement by CMV in this series.

Cytomegalovirus esophagitis often occurs in combination with cytomegalovirus infection of the lung. Many cases of cytomegalovirus esophagitis have recently been reported in immunocompromised patients.

The endoscopic and esophagographic appearance of cytomegalovirus esophagitis is of mucosal redness or ulceration (Fig. 5-8), or, rarely, a nodular mass (Fig. 5-9) or polyp (Laguna et al.). The ulcerative lesions have no distinctive macroscopic features (Fig. 5-10). They are occasionally punched out.

The ulcer base in cytomegalovirus esophagitis consists of granulation tissue and necrotic debris.

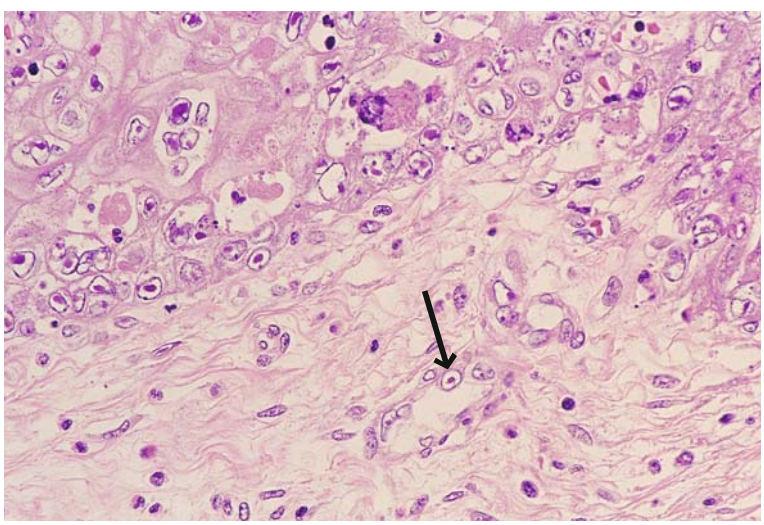


Fig. 5-7. Varicella zoster infection of the esophagus. Cowdry A type inclusion bodies are seen in stromal cells (*arrow*)

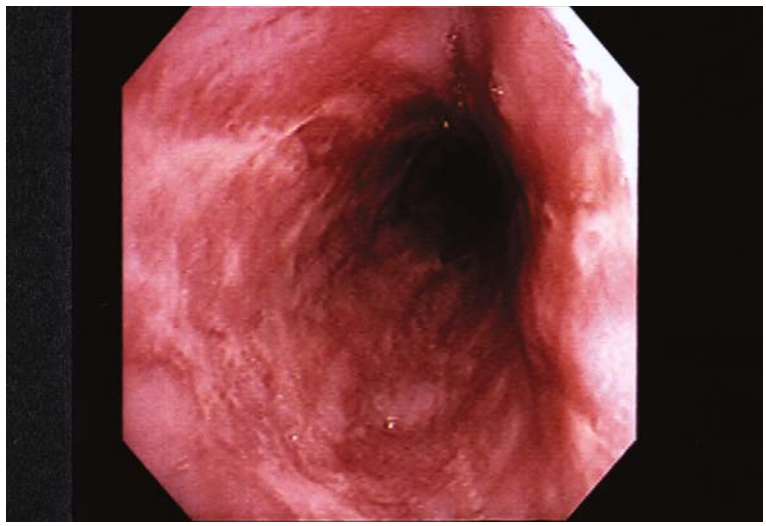


FIG. 5-8. Esophagoscopic features of cytomegalovirus esophagitis. There is extensive erosion of the mucosa

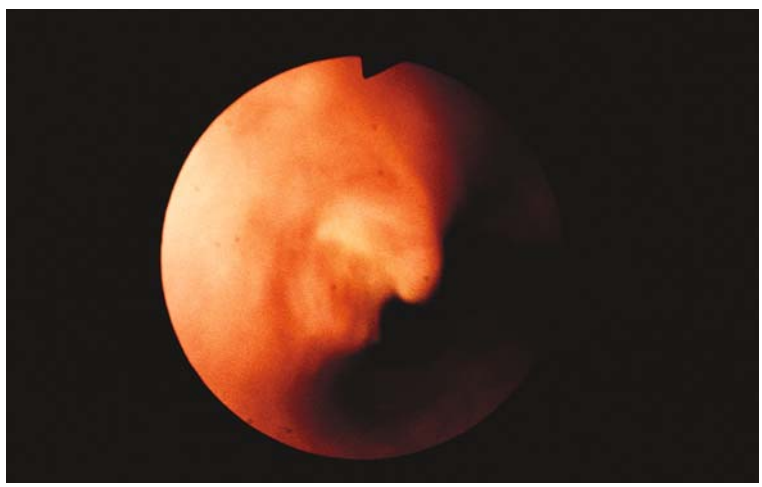


FIG. 5-9. Esophagoscopic appearance of cytomegalovirus esophagitis. There is a tumor-like appearance, with ulceration

FIG. 5-10. Macroscopic appearance of cytomegalovirus esophagitis shows extensive erosions. From a patient with acute myeloid leukemia who died after bone marrow transplantation

The inclusion bodies are large, basophilic, and intranuclear (Cowdry A type), with halos; they are mainly seen in nonepithelial cells such as vascular endothelial cells and fibroblasts (Figs. 5-11, 5-12). There may be exfoliation of vascular endothelial cells, most of which contain inclusion bodies. This change is often only seen in endothelial cells in the lamina propria and submucosa.

Biopsy specimens from the ulcer base are best for histological diagnosis because inclusions are most often found in the endothelial cells of granulation tissue in this region. Antibodies for the immunohistochemical detection of cytomegalovirus are available commercially from various manufacturers (Fig. 5-13). It is probable that cytomegalovirus infection now occurs more frequently than at the incidence reported by Takayama as a result of the increasing use of aggressive antineoplastic chemotherapy. Cytomegalovirus infection of the esophagus and of other organs is, however, often overlooked at autopsy.

The present author has only twice seen cytomegalovirus inclusion bodies in esophageal biopsy material. The first case was of a 65-year-old undernourished man who had undergone a gastrectomy 23 years earlier. Endoscopy revealed an ulcerated

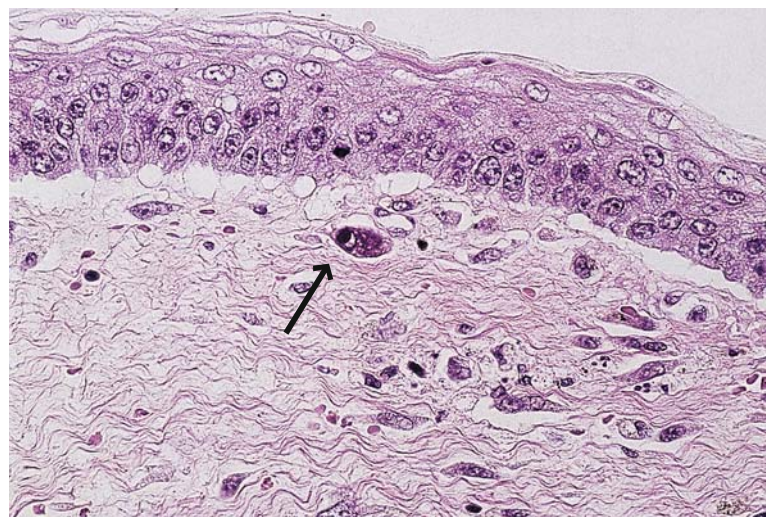


FIG. 5-11. Cytomegalovirus esophagitis. An inclusion body (*arrow*) is seen in a fibroblast in the lamina propria

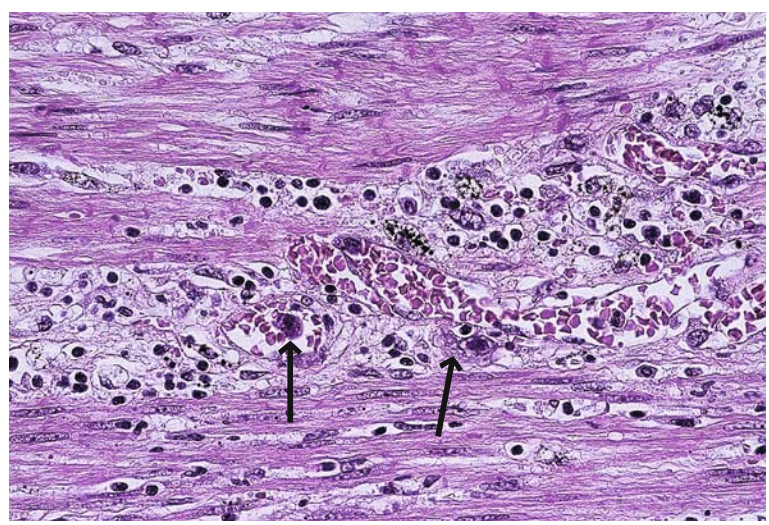


FIG. 5-12. Cytomegalovirus esophagitis. Inclusion bodies (*arrows*) are found in vascular endothelial cells

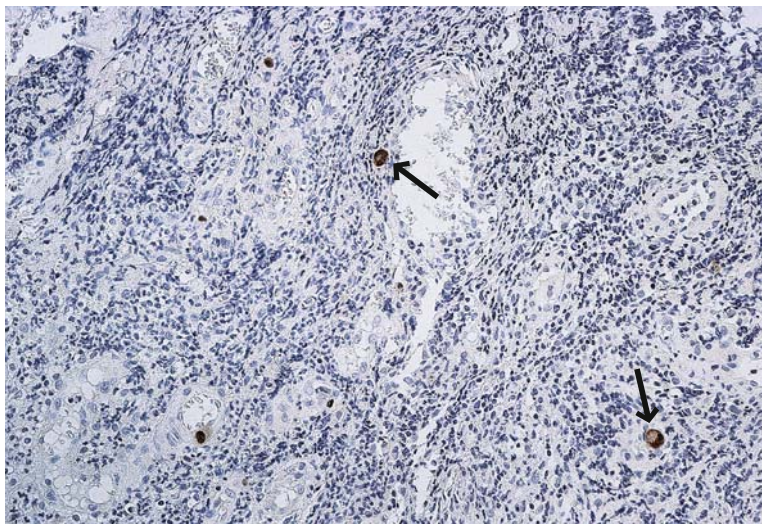


FIG. 5-13. Cytomegalovirus esophagitis (anti-cytomegalovirus antibody immunostain). Positively stained cells (*arrows*), corresponding to cells with inclusion bodies, are seen

protruding lesion (see Fig. 5-9), and the biopsy showed a few fibroblasts with inclusion bodies in the granulation tissue. The esophageal lesion disappeared in about 3 weeks with improvement of the patient's nutritional state, and no further inclusions were seen on repeated biopsy. Similar spontaneous healing of a cytomegalovirus esophageal ulcer has been previously reported (Wilcox and Schwartz 1993). The second case was of a 72-year-old man who was suffering from cerebrovascular disease and malnutrition. An endoscopic picture from this patient is shown in Fig. 5-8.

The author has occasionally seen cytomegalovirus esophagitis at autopsy. Figure 5-10 shows the macroscopic appearance of an esophageal specimen from a patient with acute myeloid leukemia (AML) who had undergone bone marrow transplantation. Figure 5-11 shows the histological appearance of esophageal mucosal lesions from another bone marrow transplant patient, and Fig. 5-12 shows inclusions in the base of an ulcer at the esophagogastric junction of an 80-year-old man who had died (of other causes) 3 years after surgery for a carcinoma of the thoracic esophagus.

The cytological findings of cytomegalovirus esophagitis have been reported in AIDS patients (Teot et al. 1993). Acute inflammatory cells, mainly neutrophils, and cells containing intranuclear inclusion bodies with halos are seen, very similar to the cells seen in histology.

5.1.3. Human Papillomavirus Infection

Infection with human papillomavirus (HPV) has been found in apparently normal esophageal mucosa, in squamous papillomas (Odze et al.), and in squamous cell carcinomas of the esophagus. It has been suggested that HPV has a role in the pathogenesis of squamous cell carcinoma of the esophagus. It has been demonstrated by in situ hybridization that 23% of all cases of esophageal cancer contain HPV DNA. The detection rate is particularly high for types 16 and 18 (Chang et al. 1993). HPV DNA has also been found in 15% of nonmalignant esophageal biopsies, however (Williamson et al.). Also, the rate of HPV DNA detection in esophageal cancer is much lower than that reported in squamous cell carcinomas of the uterine cervix.

In addition, several reports have indicated that HPV DNA is often not detectable in esophageal squamous cell papillomas (Chang et al. 1991; Poljak et al. 1998), and an inability to detect HPV DNA by polymerase chain reaction (PCR) has been reported in both French and Japanese patients with esophageal carcinomas (Benamouzig et al. 1995; Akutsu et al. 1995). It therefore seems that the detection rate of HPV in

esophageal carcinoma varies in different countries. In our experience, no HPV DNA was detected by PCR in the esophageal epithelium of 60 consecutive autopsy cases (unpublished data).

5.1.4. Acute HIV-1 Infection

Patients who are infected with human immunodeficiency virus type 1 (HIV-1) often have odynophagia and dysphagia, usually attributable to esophageal infection by various fungi, viruses other than HIV-1, and bacteria (Yamada et al.). Multiple small erosive lesions with surrounding hyperemia, attributable to HIV-1 itself, have also, however, been found in HIV-1 carriers.

Endoscopy has shown multiple small ulcers with an appearance very similar to those of simple herpetic esophagitis (Bartelsman et al. 1990).

Histological findings in biopsy tissues are nonspecific, comprising desquamation of the mucosal epithelium and infiltration by numerous neutrophils. It has been reported that there are no giant cells or intranuclear inclusion bodies in these ulcers (Rabeneck et al.).

Virus particles showing the features of a retrovirus have been observed in the esophageal epithelium by electron microscopy.

Giant ulcers (Sor et al. 1995) and inflammatory fibroid polyps (Simmons et al. 1995) have also been reported in patients with AIDS.

5.1.5. Other Viral Infections

Esophageal lesions caused by infection by rubella, variola (smallpox), Epstein–Barr virus (Kitchen et al. 1990), and papovavirus have been reported, but these are all very rare. Foot-and-mouth disease virus was detected in esophagopharyngeal samples from experimentally infected steers (House and Meyer 1993).

5.2. Fungal Esophagitis

Fungal esophagitis, found at autopsy, usually occurs in disorders associated with immune compromise such as leukemia or malignant lymphoma. This trend was already evident in a study reported 20 to 30 years ago. Fungal infection of the esophagus was found in 5% of a series of autopsy cases of carcinoma (Jensen et al.) and in 6%–16% of a series of cases of leukemia. The esophagus is the commonest site for fungal infection in the alimentary tract.

5.2.1. Candida Esophagitis

Fungal infection of the esophagus is most commonly caused by *Candida albicans*. A few cases of esophageal candidiasis have been reported in association with esophageal perforation.

Endoscopically, a slightly elevated white thrush is seen (Fig. 5-14). Macroscopically, fungal esophagitis appears as thick elevated lesions having a white or greenish-white color (Fig. 5-15). Granulation tissue is seen when the elevated part is removed. The lesions occasionally form small nodules, which may coalesce to cause mild esophageal stenosis. The entire esophageal mucosa may be affected in some severe cases (Fig. 5-16). Diagnosis is easy, as pseudohyphae stain positively with periodic acid–Schiff (PAS) or Grocott's method (Fig. 5-17).

Cytologically, esophageal candidiasis shows regenerating epithelial cells in a heavily inflamed background. Fungal hyphae are brown with the Papanicolaou stain (Fig. 5-18) and are also easily seen with PAS (Fig. 5-19).

5.2.2. Esophageal Histoplasmosis

Numerous cases of esophageal histoplasmosis have been reported. This condition occurs because of spread from involved mediastinal lymph nodes and from mediastinitis caused by *Histoplasma* (Dines et al.). Complications including fistula (Coss et al.), tumor formation, and abscess (Jenkins et al.) have been reported.

Histoplasma capsulatum can be demonstrated in histological specimens by the methenamine silver stain, and culture is also helpful for diagnosis.

5.2.3. Other Fungal Infections

Esophagitis caused by various other fungi has also been reported, including *Aspergillus* (Young et al. 1970), *Phycomycetes* (Lyon et al. 1979), *Blastomyces* (Khandekar et al. 1980), *Sporotrichum*, *Paracoccidioides* (Ziliotto et al. 1980), and *Torulopsis glabrata* (Bentlif and Wiedermann 1979).

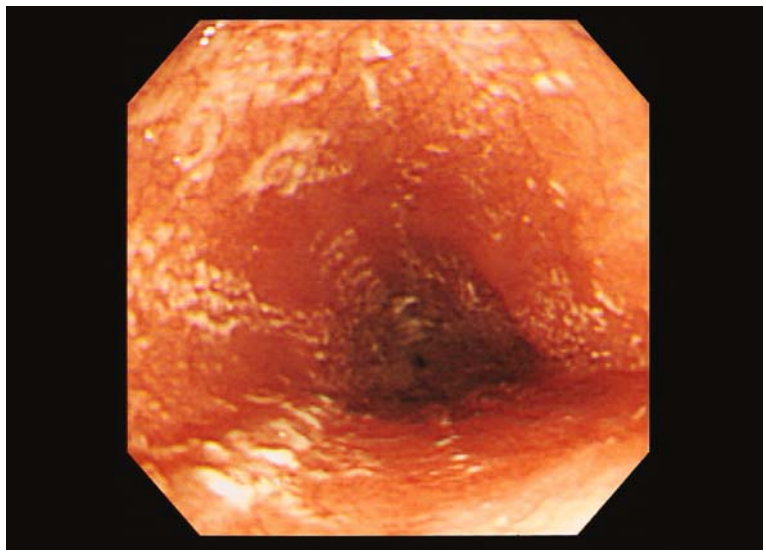


FIG. 5-14. Esophagoscopic appearance of fungal esophagitis. There is a slightly elevated white thrush on the mucosa

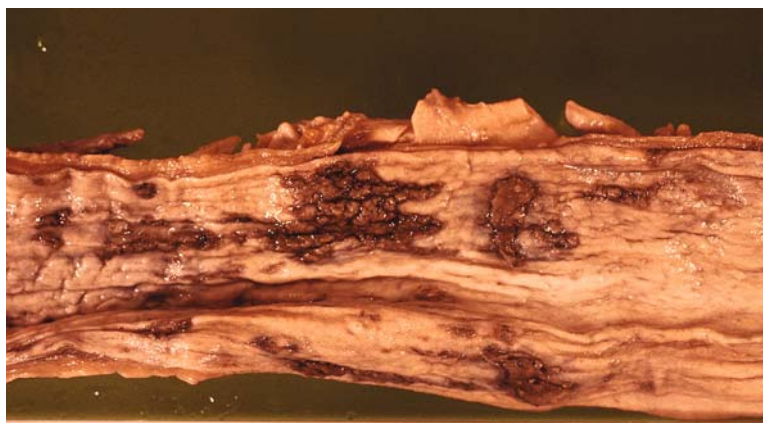


FIG. 5-15. Macroscopic appearance of fungal esophagitis accompanied by bleeding. Several foci of thrush are seen on the mucosa. From a patient with acute myeloid leukemia who died after chemotherapy

FIG. 5-16. Macroscopic appearance of fungal esophagitis. The esophageal mucosa is completely covered by thrush. From a patient who died of recurrent colon cancer

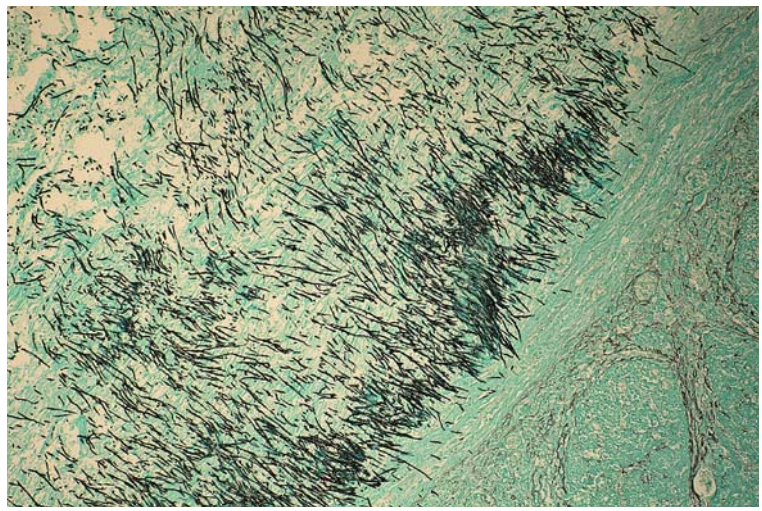


FIG. 5-17. Fungal esophagitis (Grocott's method)

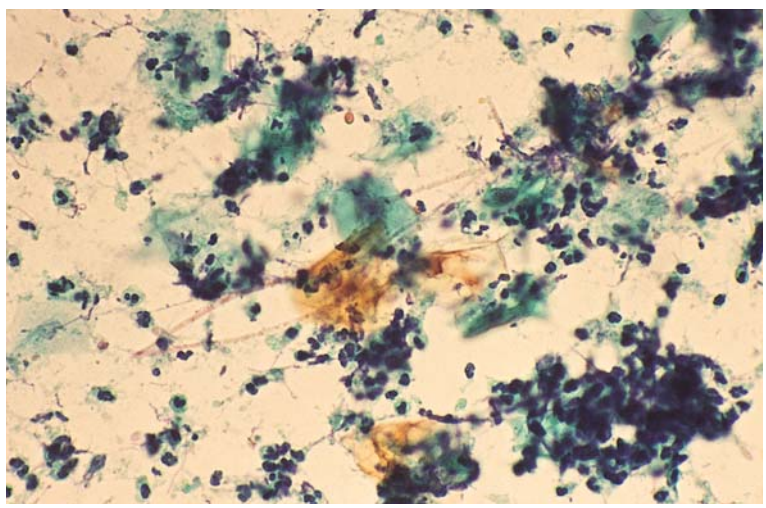


FIG. 5-18. Cytological appearance of fungal esophagitis (Papanicolaou stain)

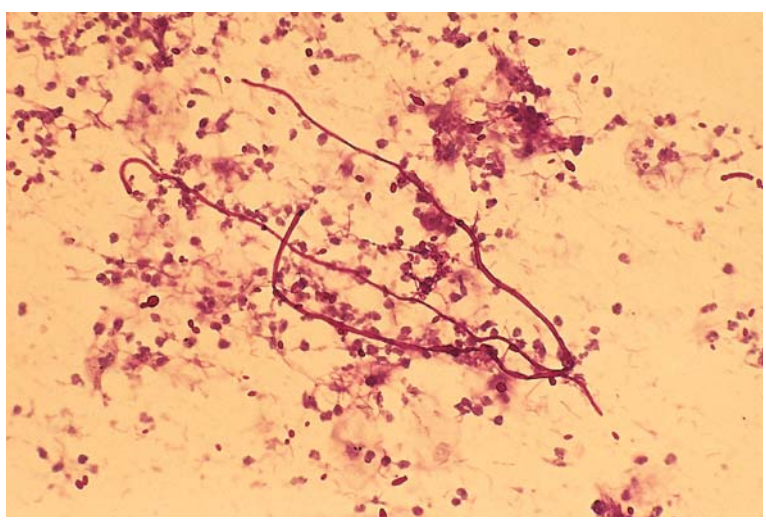


FIG. 5-19. Cytological appearance of fungal esophagitis (periodic acid–Schiff stain)

5.3. Bacterial Esophagitis

5.3.1. Tuberculosis

According to Takeshita et al. (1977), esophageal tuberculosis had already been seen in autopsy cases by 1878.

Of the various organs that may be affected by tuberculosis, the esophagus is one of the least frequent. Esophageal tuberculosis was found in 0.15% of a series of autopsies performed on patients who died of tuberculosis, reported in 1913. The incidence of esophageal involvement in other autopsy series of tuberculosis cases has mostly been between 0.04% and 0.2%. Spread from involved mediastinal lymph nodes is presumably the most frequent route of infection. Occasionally a tracheoesophageal fistula may result (Wigley et al. 1976). Perforation of the esophagus (Adkins et al. 1990) and formation of a fistula into an aortic aneurysm (Catinella and Kittle 1988) have also been reported.

There have been about 200 reported cases of esophageal tuberculosis from Europe and North and South America. Many case reports of this disease, particularly from Asia, have been published in gastroenterology journals (Seivewright et al.). About 20 cases of esophageal tuberculosis have been reported from Japan (Hoshika et al. 1988).

Esophageal tuberculosis is usually characterized macroscopically by protruding lesions or ulceration, and on esophagography it may sometimes be misdiagnosed as carcinoma.

Histologically, tuberculous granulomata composed of epithelioid cells, Langhans' type giant cells, lymphocytes, and caseous necrosis are observed (Fig. 5-20). There are usually some granulomata in the lamina propria, which can be sampled on biopsy (Takeshita et al.). Granulomata are also found in regional lymph nodes (Fig. 5-21). Figures 5-20 and 5-21 are from resection specimens of cases reported by Takeshita et al. *Mycobacterium tuberculosis* is usually stained using Ziehl–Neelsen, but sometimes fails to stain with this preparation. It can also be stained immunohistochemically, using antibodies to Bacillus Calmette–Guerin (BCG).

5.3.2. Atypical Mycobacterial Infection

Esophageal infections caused by atypical *Mycobacteria* have been reported in AIDS patients (Connolly et al.).

5.3.3. Other Types of Bacterial Esophagitis

Some cases of opportunistic infection of the esophagus caused by *Corynebacterium* have been reported. Esophageal infections by *Actinomyces* (Vinson and Sutherland) and *Lactobacillus acidophilus* (McManus and Webb 1975) have also been reported. Bacterial esophagitis may cause bacteremia in immunodeficient patients (Walsh et al.).

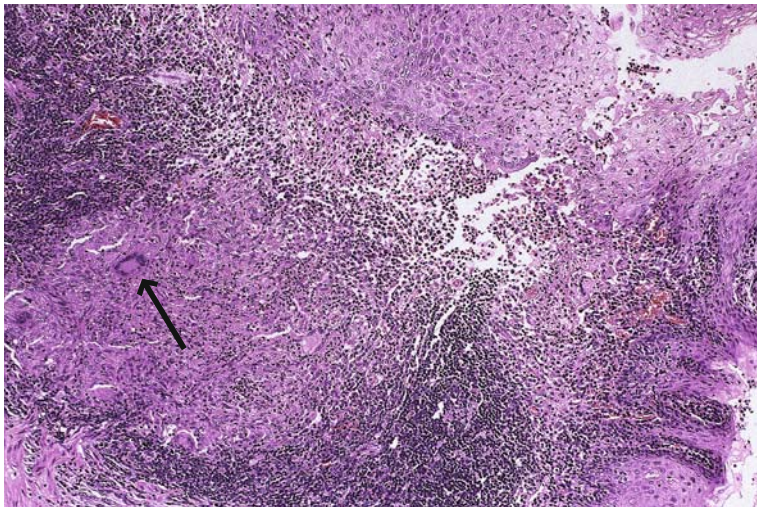


FIG. 5-20. Esophageal tuberculosis. A Langhans' type giant cell (*arrow*) is seen in a tuberculoma in the lamina propria of the esophagus

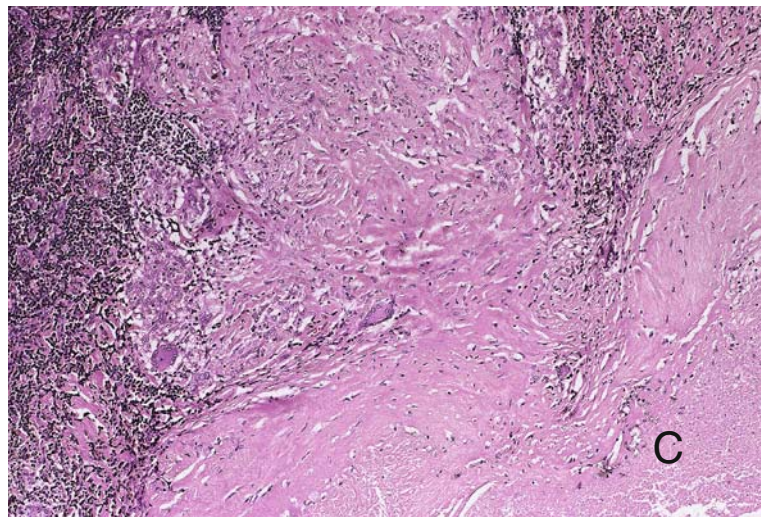


Fig. 5-21. Esophageal tuberculosis (lymph node). A typical tuberculoma accompanied by caseous necrosis (*C*) in a lymph node from the tracheal bifurcation of a patient with esophageal tuberculosis

5.4. Syphilis

Although the occasional occurrence of esophagitis from syphilis has been long known (Kampmeier and Jones), case reports of this condition have been infrequent, particularly in recent years.

Most of the reported patients have been in the tertiary stage of syphilis. They have often complained of difficulty in swallowing solid food, because of ulcerative lesions and granulomata (Stone and Friedberg 1961). These lesions may very occasionally cause esophagotracheal fistulae.

The histological features include chronic inflammation with numerous plasma cells, lymphocyte infiltration around blood vessels, periarteritis, and endarteritis. Esophageal stenosis resulting from scarring of these lesions has been reported (Hudson and Head).

5.5. Other Infections

A description of Chagas' disease is given in the previous chapter on achalasia (Section 4.2.1, p. 53). Leishmania esophagitis has recently been described in patients with AIDS (Villanueva et al.).

Chapter 6
Esophageal Manifestations of Collagen Vascular and Other Systemic Diseases

6.1. Progressive Systemic Sclerosis

According to a report by Treacy et al., the esophageal manifestations of progressive systemic sclerosis have been long known, the first case report being by Ehrman in 1903. Of all internal organs and tissues, the esophagus has the highest incidence of involvement in this condition. One autopsy study found that 74% of 58 cases of systemic sclerosis showed atrophy and fibrosis of the muscle layer of the esophagus and that 40% showed esophagitis and ulceration (D'Angelo et al.). Barrett's esophagus has also been reported in patients with progressive systemic sclerosis (Cameron and Payne; Goldblum et al.). Clinical investigations show abnormal motility of the esophagus in 50%–80% of patients with progressive systemic sclerosis. Of those patients with disordered motility, 50%–60% suffer from dysphagia. No significant relationship has been found between systemic sclerosis and esophageal carcinoma, however.

In most patients with this disease, the esophagus is dilated in its upper part but thickened and narrowed in its lower part. Histologically, the smooth muscle in the esophageal wall shows atrophy and mild fibrosis; this particularly affects the inner circular muscle layer (Figs. 6-1, 6-2). Muscle atrophy may be diffuse or localized. The changes are often more easily recognized in the inner circular than the outer longitudinal muscle layer because fibrotic changes occur later in the outer layer (see Fig. 6-1). Ganglion cells persist in nerve plexuses. There is thickening of the submucosa, with a mild infiltrate of inflammatory cells. Striated muscle

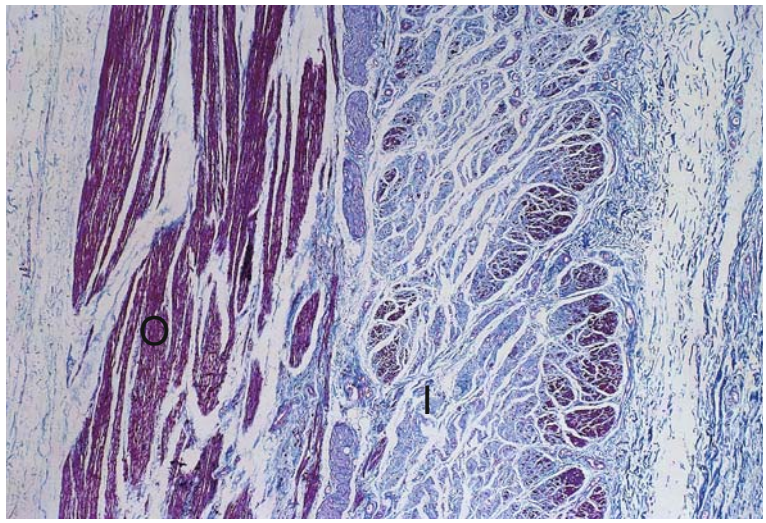


FIG. 6-1. Progressive systemic sclerosis (Azan stain). There is atrophy of fibers in the inner circular muscle layer (*I*) compared to those in the outer longitudinal muscle layer (*O*)

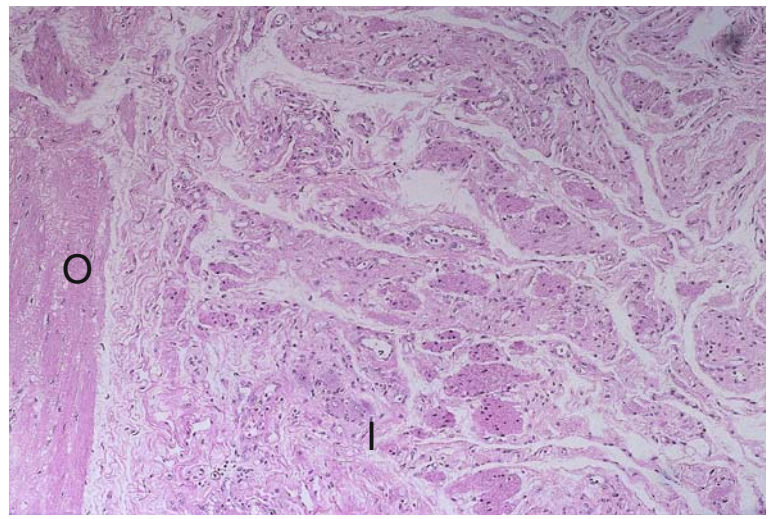


FIG. 6-2. Progressive systemic sclerosis. There is fibrosis in the inner circular muscle layer. *I*, inner circular muscle; *O*, outer longitudinal muscle

fibers in the upper esophagus are well preserved. Atrophy and hypertrophy of the muscularis mucosae may occur, but these changes are relatively mild. The intima of small blood vessels in the esophagus, similar to those at other body sites, may be thickened, but this change is not seen very frequently. Reflux esophagitis often occurs (Yarze et al.) as a result of insufficiency of the lower esophageal sphincter.

The present author's experience consists of four autopsy cases of progressive systemic sclerosis. There was marked atrophy of both the inner circular and outer longitudinal muscle layers in one case and distinct atrophy of the inner circular muscle layer alone in two cases. In the fourth case, histological examination of the inner circular muscle layer was hampered by the presence of deep ulcers and severe esophagitis. There was reflux esophagitis in all four cases.

6.2. Polymyositis, Dermatomyositis, Systemic Lupus Erythematosus, and Rheumatoid Arthritis

Esophageal involvement by polymyositis and dermatomyositis has been reported. Striated muscle in the upper esophagus and hypopharynx may show infiltration by chronic inflammatory cells, edema, and atrophy. There may also be atrophy of smooth muscle (De Merieux et al.). There has also been a report of concomitant esophageal carcinoma in a patient who had polymyositis with esophageal involvement (Okayasu et al.).

Patients with systemic lupus erythematosus (SLE) may complain of dysphagia (1%–6%), heart burn (11%–50%), and dysmotility (25%) (Dubois and Tuffanelli; Gutierrez et al.; Chua et al. 2002). Dysphagia is mostly caused by reflux esophagitis or peptic ulcerations. Angiitis has been reported in the esophagus in the disorders, but there have not been any detailed descriptions of other pathological findings.

Some patients with rheumatoid arthritis complain of dysphagia. Erosion and ulceration were seen in 2.4% of a series of 1008 Japanese patients (Yoshikawa et al. 2001), but there have not been any detailed descriptions of pathological findings in the esophagus in this disorder.

6.3. Sjögren's Syndrome

Esophageal motor dysfunction is a very frequent occurrence in patients with Sjögren's syndrome. In reports by Ramirez-Meta et al. (1976) and Tsianos et al. (1985), esophageal motor dysfunction was found in 36%–90% of cases. Achalasia is also associated with Sjögren's syndrome (Similä et al.). However, histopathological data relating to the esophagus in Sjögren's syndrome are scanty.

6.4. Idiopathic Eosinophilic Esophagitis

Idiopathic eosinophilic esophagitis was first described in 1977 (Dobbins et al.), and since then a further 15 cases have been reported (Horiki et al. 1998). The condition is characterized by prominent thickening of the esophageal wall, with marked edema and infiltration by eosinophils. About 85% of patients have been male, and 70% have had eosinophilia in their peripheral blood (Horiki et al.). Almost all affected patients have complained of dysphagia. In one reported case, a 2-cm-thick esophageal wall was demonstrated on computed tomography (CT) scan (Horiki et al.). Endoscopy in this case revealed a narrow lumen and a markedly edematous mucosa (Fig. 6-3). Eosinophilic esophagitis is occasionally associated with multiple esophageal rings (Siafakas et al. 2000). Esophageal biopsies showed elongated papillae, hyperplasia of the basal zone of the epithelium, and infiltration of the lamina propria and muscularis mucosae by eosinophils (Fig. 6-4).

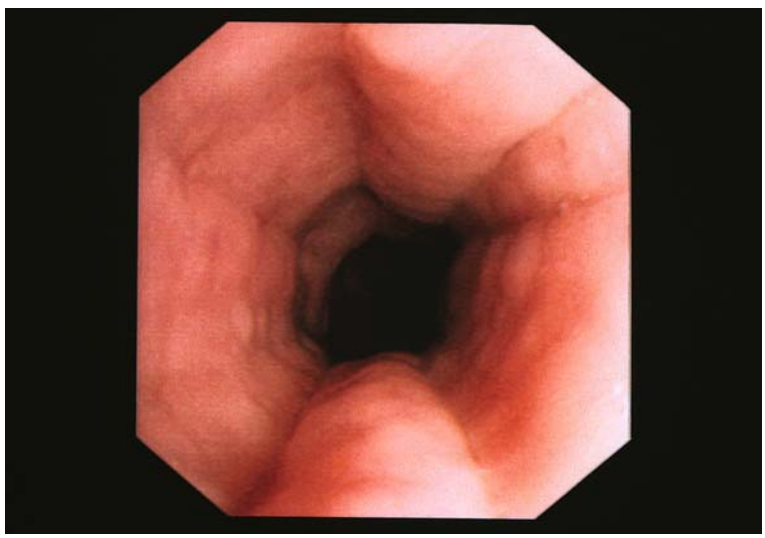


FIG. 6-3. Endoscopic appearance of idiopathic eosinophilic esophagitis. The lumen is narrowed and the mucosa markedly edematous

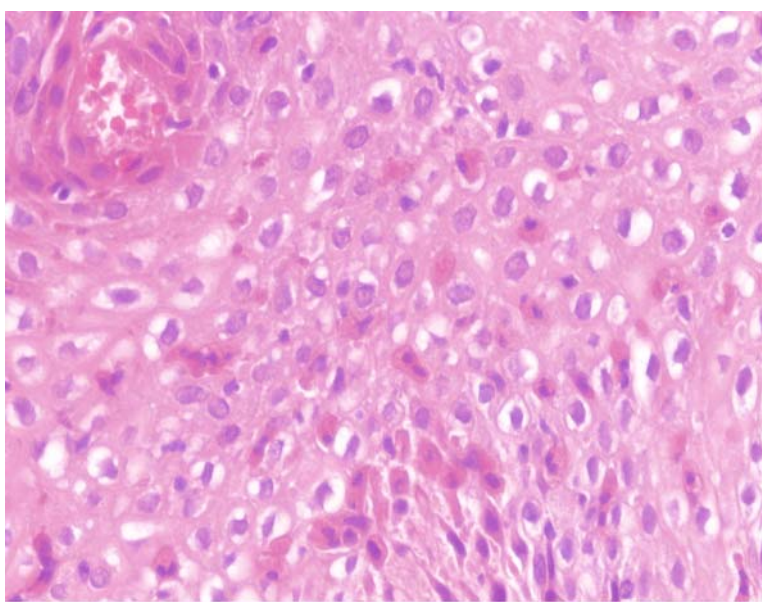


FIG. 6-4. Idiopathic eosinophilic esophagitis. There are many eosinophils in the squamous epithelium

There has been some discussion about a possible relationship between this disorder and the hypereosinophilic syndrome.

6.5. Skin Disorders

Skin disorders known to sometimes show esophageal manifestations include lichen planus, Darier's disease, acanthosis nigricans, and bullous disorders such as pemphigus and pemphigoid. The histological features of oral, pharyngeal, and esophageal mucosal lesions in these disorders are similar to those seen in the skin.

In patients with lichen planus, the skin and mucous membranes may be affected separately or together. The condition may be asymptomatic, or itching and soreness may be the main complaints. Biopsy specimens of esophageal lesions show epithelial erosions, fibrin deposition, and hemorrhage. There is vacuolar change in the basal layer of the epithelium, and a diffuse infiltrate of lymphocytes beneath the epithelium, with extension into the basal layers. A case of esophageal squamous cell carcinoma that occurred in association with lichen planus of the esophagus has been reported (Calabrese et al. 2003).

When bullous disorders involve the esophagus, the affected patients have severe dysphagia. In pemphigus vulgaris, there is exfoliation of the mucosa (Fig. 6-5) with bleeding, and biopsies reveal distinct acantholysis of epithelial cells with formation of suprabasal bullae (Fig. 6-6). Pemphigus vulgaris is characterized by the intercellular deposition of IgG in the esophageal epithelium, which can be visualized by immunofluorescence (Fig. 6-7). Although there have been reports of esophageal stenosis (Wood et al.; Raque et al.) and complete obstruction (Makino et al.) as a result of pemphigus vulgaris, these complications are considered to be relatively rare in patients who have esophageal involvement by skin disorders.

Around 25% of patients with bullous pemphigoid develop mucosal lesions (Kokawa et al.), particularly stomatitis with erosions and bullae of the oral mucosa. Eight cases of bullous pemphigoid with esophageal involvement have been reported (Kokawa et al.). Endoscopy in these cases was reported to show diffuse erosion and hemorrhage involving the entire esophageal mucosa (Fig. 6-8). Histology showed subepithelial bullae containing fibrin, red cells, neutrophils, and eosinophils. Immunofluorescence of bullous pemphigoid

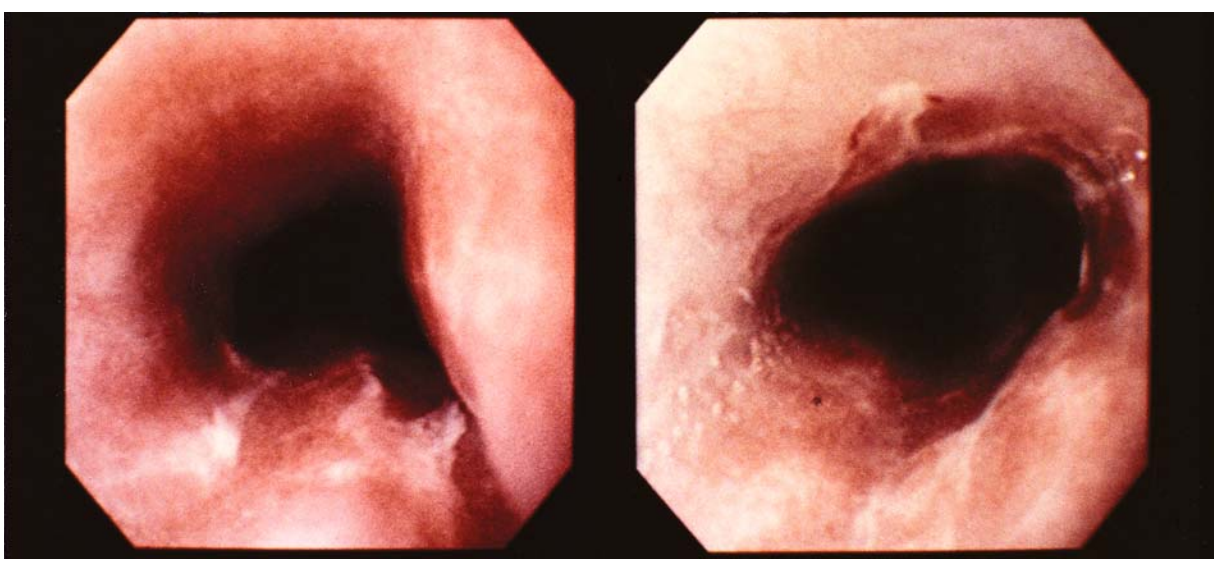


Fig. 6-5. Endoscopic appearance of pemphigus vulgaris of the esophagus. The lumen is mildly narrowed, the mucosa is edematous and hyperemic, and the epithelium is exfoliated

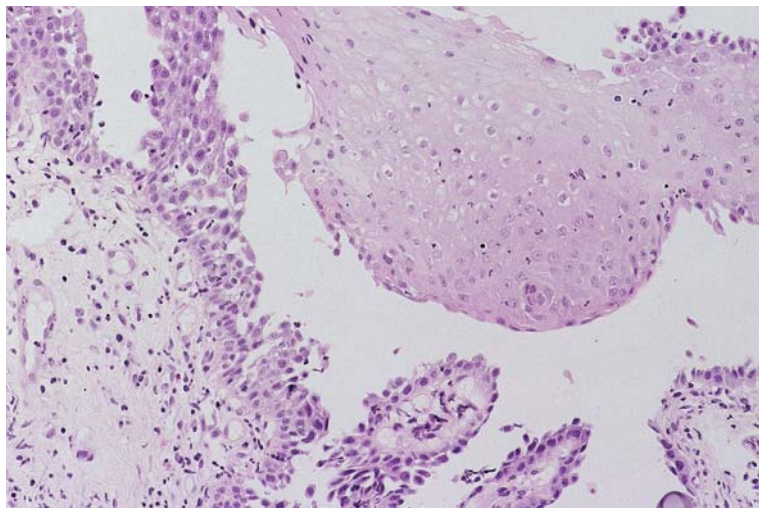


FIG. 6-6. Biopsy specimen from an esophageal lesion in pemphigus vulgaris. There is a suprabasal bulla in the mucosa

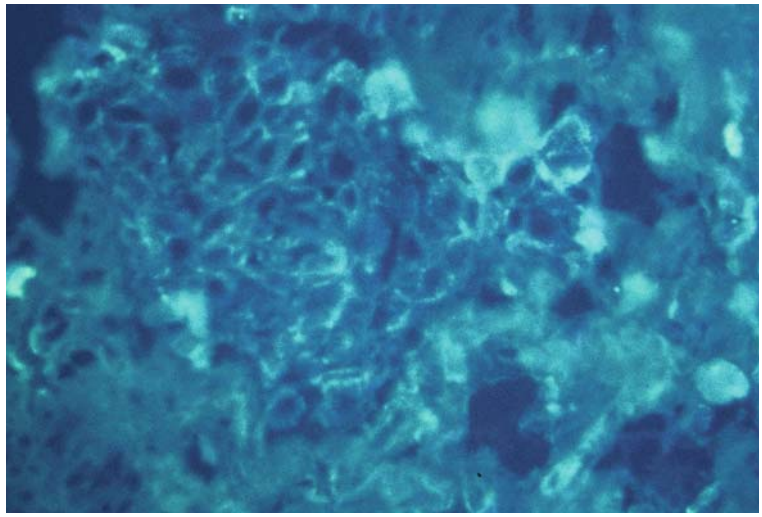


FIG. 6-7. Appearance of pemphigus vulgaris on immunofluorescence. Intercellular deposition of IgG is evident in the esophageal epithelium

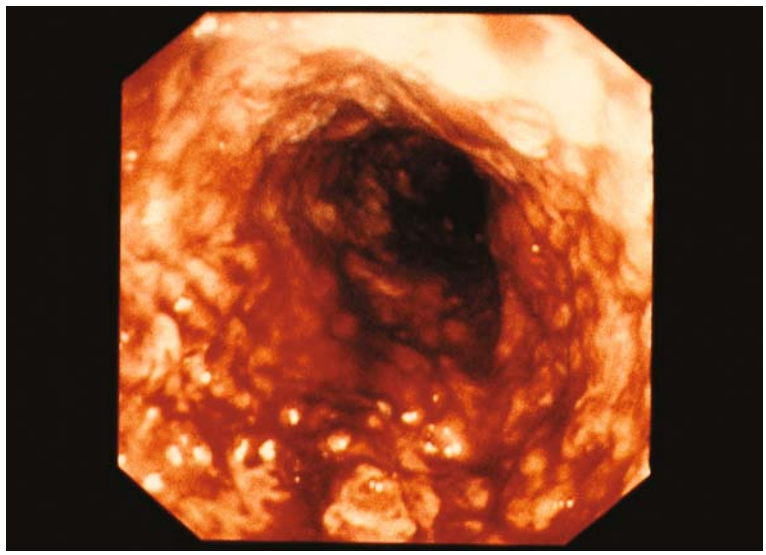


FIG. 6-8. Endoscopic appearance of bullous pemphigoid. There is diffuse erosion of the epithelium with hemorrhage

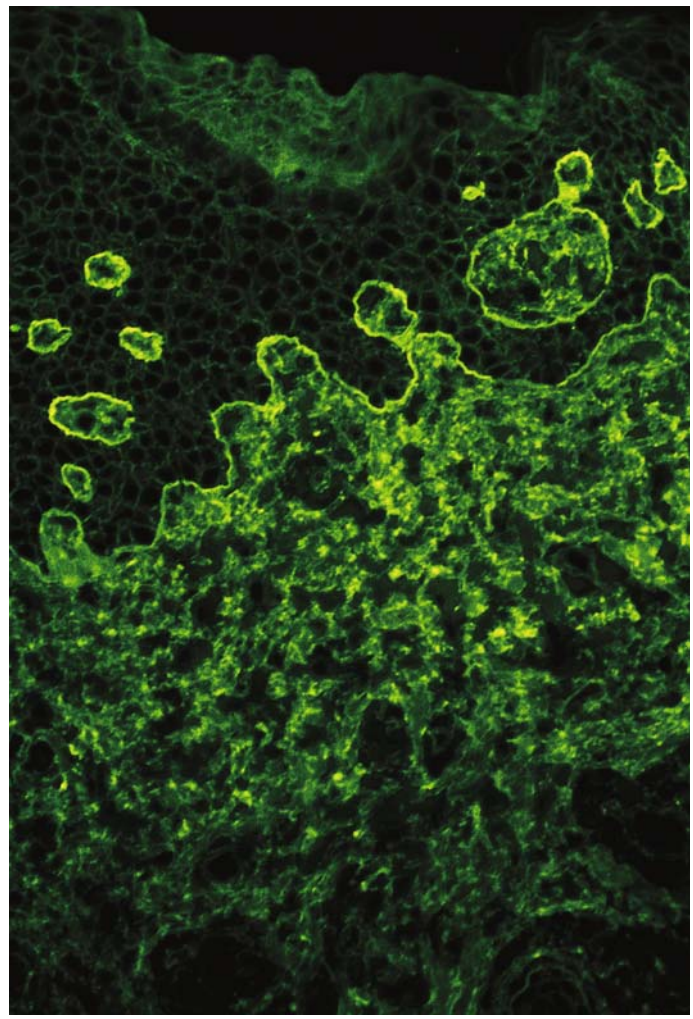


FIG. 6-9. Appearance of bullous pemphigoid on immunofluorescence (skin). Linear deposition of IgG is evident on the epidermal basement membrane

lesions generally shows linear deposition of IgG on epithelial basement membranes (Fig. 6-9). Reports of esophageal involvement by pemphigoid have rarely described deposition of IgG in the mucosa, however, because the epithelium has usually been extensively eroded.

Epidermolysis bullosa dystrophica is a hereditary blistering disorder that frequently involves the mucosa of the esophagus, in addition to the skin. Blister formation after minor trauma leads to erosions, ulceration, scarring, and strictures, and the patients experience dysphagia (Ergun et al. 1992; Inal et al. 2002).

6.6. Graft-Versus-Host Disease

There are no adequate histological data available on the esophageal manifestations of acute graft-versus-host disease (GVHD). Patients with chronic GVHD, occurring about 100 days or more after bone marrow transplantation, are known to sometimes suffer from dysphagia and a motility disorder of the esophagus. Histologically, exfoliation of the epithelium with infiltration by lymphocytes, neutrophils, and eosinophils into the mucosa, including the epithelium, and necrosis of basal cells have been demonstrated in the upper and

middle esophagus. These histological features are reported to be similar to those of pemphigoid. Although chronic GVHD shows fibrosis of the submucosa, there is no fibrosis in the muscularis propria, as seen in scleroderma (McDonald et al. 1981). The present author has seen five cases of GVHD affecting the esophagus; all these showed fibrosis of both lamina propria and submucosa.

6.7. Behçet's Disease

According to Mori et al. (1983), only 26 cases of esophageal involvement by Behçet's disease had been reported until 1983. The male to female ratio was 15:11, and the patients' ages ranged from 12 to 71 years. Since then, about 10 further cases have been added (Anti et al. 1986; Yashiro et al. 1986). Dysphagia and chest pain have been cited as accompanying symptoms but some case reports have not provided any data on esophageal symptoms.

Endoscopic findings have been reported in detail by Japanese authors. The middle esophagus is affected most frequently, showing a wide variety of lesions including erosions, deep and shallow ulcers, extensive esophagitis, and stenoses. There is no particular esophageal lesion specific for Behçet's disease. Figure 6-10 is an endoscopic photograph from one of the five cases reported by Mori et al.; there are irregular ulcers in the upper esophagus.

Histologically, the lesions consist of nonspecific ulcers with infiltration by lymphocytes and neutrophils (Fig. 6-11). The presence of angiitis, although rare, has also been documented (Mori et al.).

6.8. Crohn's Disease

Esophageal lesions are known to occur in Crohn's disease, but they are very rare, with a reported incidence of only 1.8%–2.4%. In reported cases, the esophageal lesions have usually been found after the diagnosis of Crohn's disease has been established. In only very occasional cases are esophageal lesions seen without involvement of other sites (Geboes et al.). There has been one review of 53 cases of esophageal Crohn's disease (Kuboi et al. 1988), and further cases have been reported more recently, including a review of 25 cases from Japan (Hiraga et al. 1995).

At endoscopy, there may be a large aphthous ulcer, or a slightly elevated lesion with a surface depression.

When involved by Crohn's disease, the esophagus, as elsewhere in the digestive tract, may show noncaseating granulomata, but there may be only nonspecific inflammatory changes. It is said to be

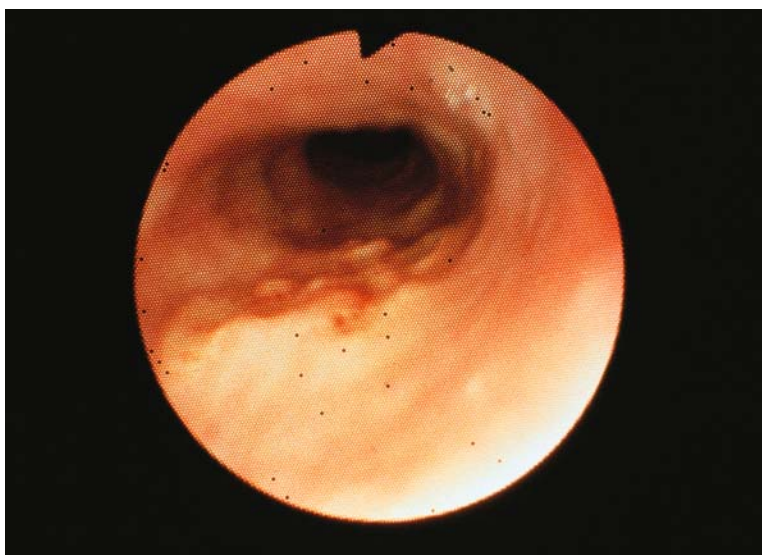


FIG. 6-10. Endoscopic appearance of esophageal lesions in Behçet's disease. There is irregular ulceration of the mucosa

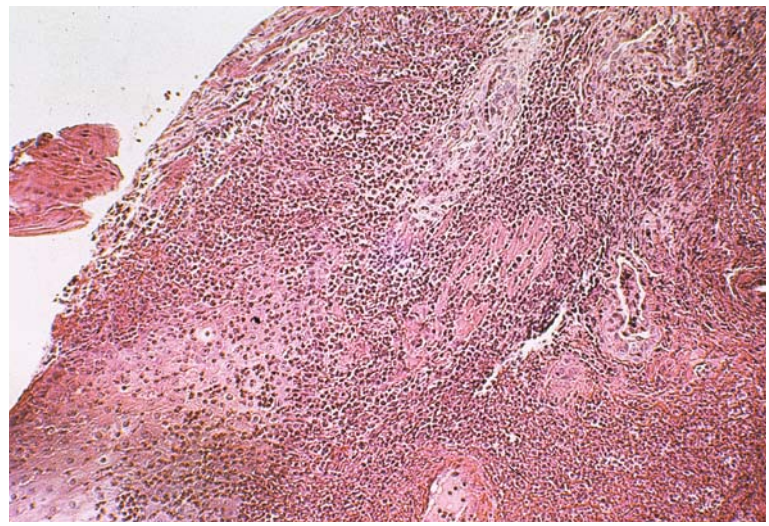


Fig. 6-11. Biopsy specimen of an esophageal lesion in Behçet's disease. There is nonspecific granulation tissue with numerous neutrophils

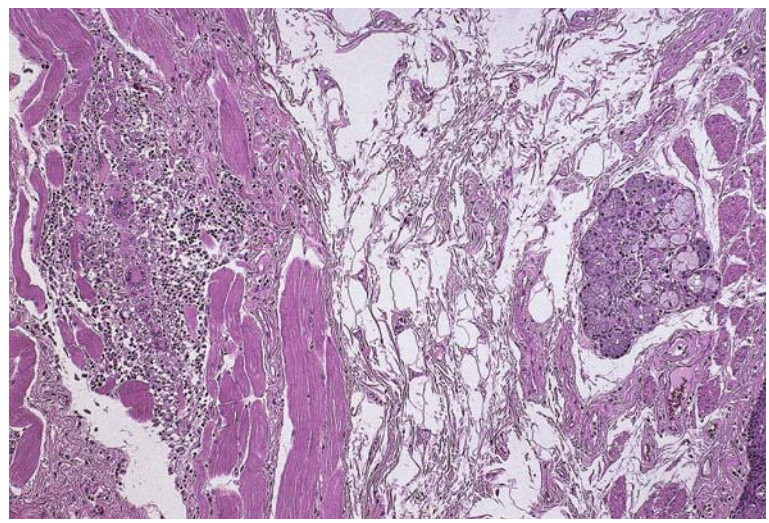


Fig. 6-12. Sarcoidosis. An epithelioid cell granuloma is seen in the striated muscle of the muscularis propria

rather unusual to see granulomata in biopsy specimens; granulomata were seen in the lamina propria in biopsy specimens from 3 of 14 cases of esophageal Crohn's disease in one series (Treem and Ragsdale; Kuboi et al.). Also, granulomata were observed in biopsy specimens of 12 (23%) of 52 Japanese cases of esophageal Crohn's disease (Shirai et al. 2003) and 27% in Western cases (Kudo et al. 1995).

6.9. Sarcoidosis

Very few cases of sarcoidosis with esophageal symptoms, such as dysphagia, have been reported. There has been a report of a circumferential esophageal stenosis, found at esophagography, in a patient with a positive Kveim test (Wiesner et al.). A patient with sarcoidosis and symptoms suggestive of achalasia and an esophageal motility disorder has also been reported (Dufresne et al.; Geissinger et al.). Histopathological features of sarcoidosis in the esophagus are similar to those seen elsewhere; thickening of the esophageal wall and the presence of noncaseating epithelioid granulomata in the lamina propria have been reported. This condition must be distinguished from other granulomatous disorders such as tuberculosis and Crohn's disease.

The present author has seen one autopsy case of sarcoidosis involving the esophagus; this occurred in an 81-year-old woman (Fig. 6-12). There were noncaseating granulomata mainly in

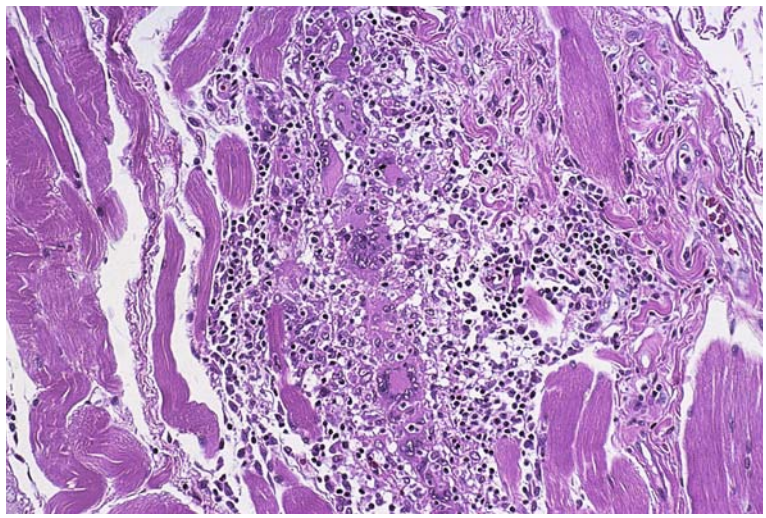


FIG. 6-13. Sarcoidosis. High-magnification view of Fig. 6-12. A granuloma is surrounded by degenerate striated muscle fibers. There are only a few epithelioid cells in this area

the muscularis propria of the upper esophagus (at this level consisting of striated muscle). A few granulomata were also seen in the muscularis propria more distally (where it consists of smooth muscle), but there was no involvement of the muscularis mucosae. The granulomata had giant cells of the Langhans' and foreign-body types, epithelioid cells, and lymphocytes, and showed fibrotic changes (Fig. 6-13). Lymphocytes and plasma cells were seen surrounding adjacent striated muscle fibers.

6.10. Ulcerative Colitis

A few cases of ulcerative colitis complicated by esophagitis or esophageal stenosis have been reported. The reported biopsy findings have been of a nonspecific esophagitis with infiltration by plasma cells, lymphocytes, and histiocytes (Rosendorff and Grieve).

6.11. Amyloidosis

Amyloid deposition may be found in the esophagus, as in other parts of the gastrointestinal tract, in all types of amyloidosis. It has been stated that amyloid deposition is found in the esophagus in 35%–100% of all patients with systemic amyloidosis (Eisen). Amyloid is deposited in vessel walls, smooth muscle, striated muscle, and nerve plexuses. Amyloid is easily seen in vessel walls with routine hematoxylin and eosin (H&E) staining. Blood vessels in the submucosa are particularly involved (Fig. 6-14). Features of reflux esophagitis are often seen in the mucosa. Achalasia has been reported to occur in some patients with amyloidosis (Costigan and Clouse).

Amyloid is a hyaline substance that is more lightly eosinophilic than smooth muscle. It stains red with Congo red and shows apple-green birefringence with polarized light. It can also be stained immunohistochemically using a commercially available antibody.

Electron microscopy reveals that amyloid is composed of unbranched fine filaments measuring 7–10 nm in diameter and 100–1000 nm in length. These filaments are arranged haphazardly.

6.12. Parkinson's Disease

Around half of patients with Parkinson's disease suffer dysphagia, although it is usually not severe (Lieberman et al.). In this disease, Lewy bodies, which are usually present in pigmented neurons in the substantia nigra and locus ceruleus of the brain, may also be seen in the ganglion cells of Auerbach's and Meissner's plexuses; these bodies may be both intracytoplasmic (Fig. 6-15) and

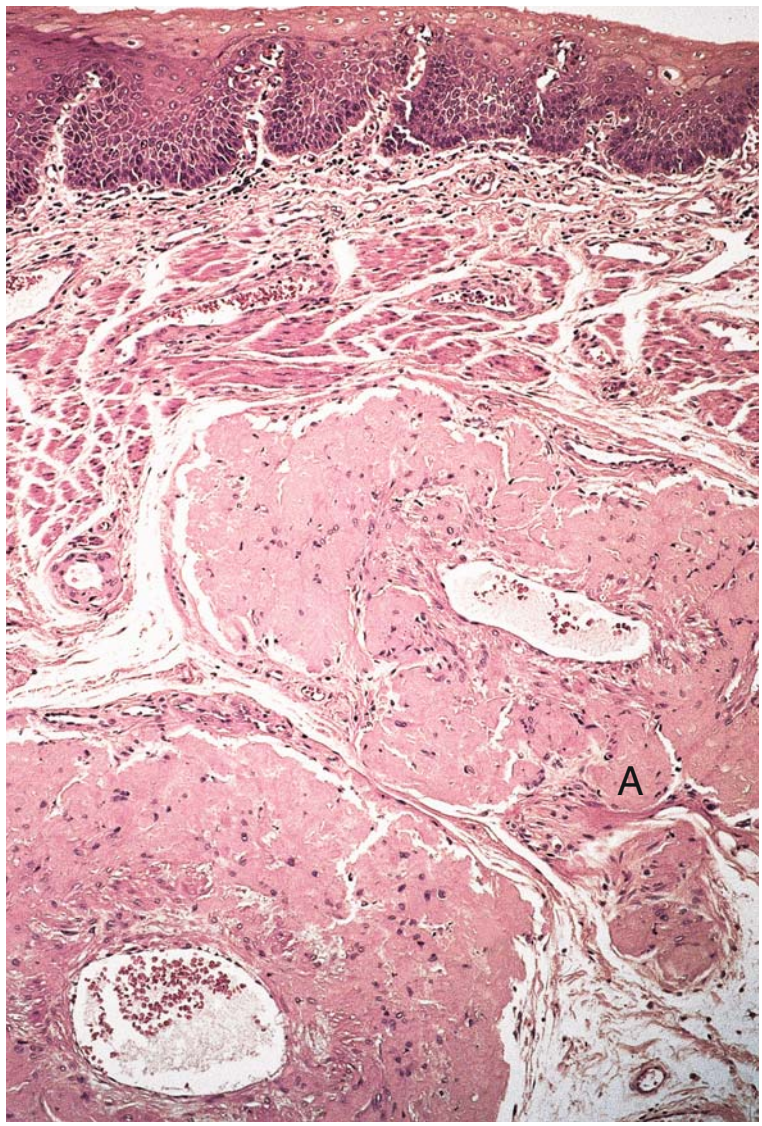


FIG. 6-14. Esophageal amyloidosis. There is amyloid deposition (*A*) around blood vessels in the submucosa, and the mucosa shows changes of esophagitis (hyperplasia of the basal cell layer and elongation of papillae in the lamina propria)

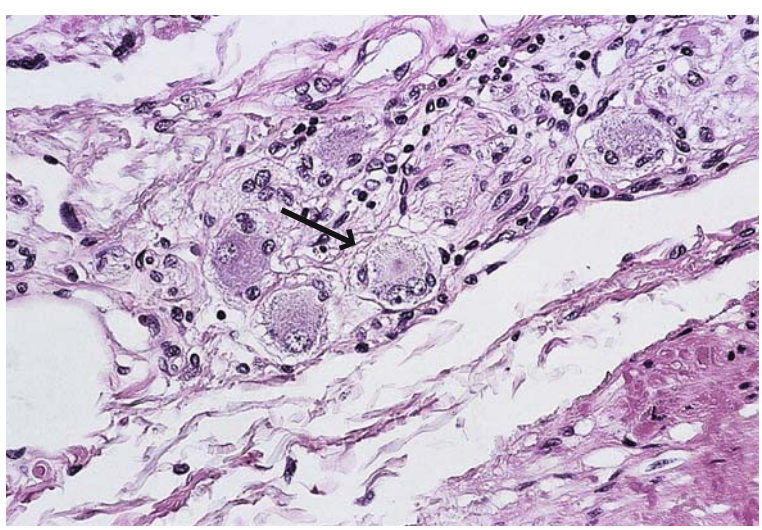


FIG. 6-15. Parkinson's disease. There is a relatively immature intracytoplasmic Lewy body (*arrow*) in a ganglion cell in Auerbach's plexus

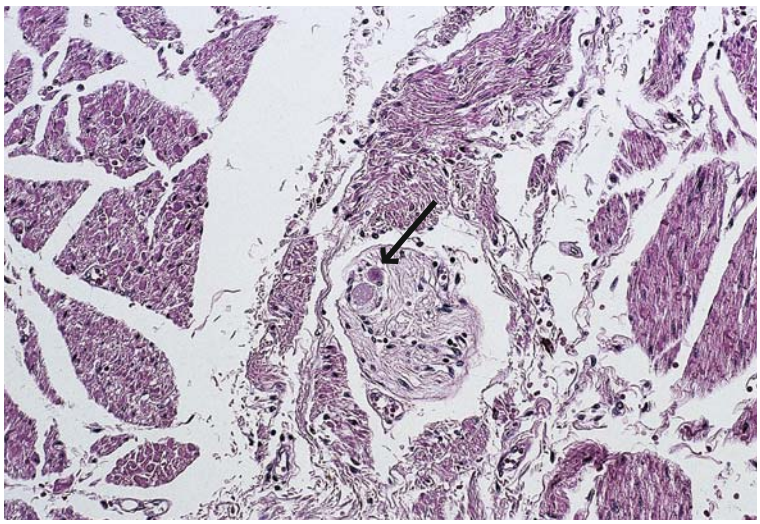


FIG. 6-16. Parkinson's disease. Mature, intraneuritic Lewy body (*arrow*) in Auerbach's plexus

intraneuritic (Fig. 6-16). The esophagus, particularly the lower part, is the most frequent site in the alimentary tract for Lewy bodies to be seen in Parkinson's disease. According to Wakabayashi et al. (1991), Lewy bodies are chiefly present in Auerbach's plexuses and are rarely found in Meissner's plexuses. They are more likely to be seen in neurites than in the perikarya of ganglion cells.

Lewy bodies are deeply eosinophilic on H&E staining and are enclosed by white halos. They can also be stained immunohistochemically with anti-ubiquitin and anti-α-synuclein antibodies (Takeda et al. 1998).

Lewy bodies may also be seen in ganglion cells of the esophagus in other disorders, including diffuse Lewy body disease (Yoshimura-Yasuhara).

6.13. Ceroidosis (Brown Bowel Syndrome)

Ceroidosis is characterized by the accumulation of ceroid in intestinal smooth muscle. It is caused by vitamin E deficiency, which is usually the result of a malabsorption syndrome or chronic pancreatitis. It is also called the brown bowel syndrome because the affected intestinal tract is brown in color (Toffler et al.). The ceroid in smooth muscle cells is thought to be derived from mitochondria (Foster). Endoscopically, a black appearance of the esophagus was reported in a patient with ceroidosis (Kimball 1978).

The accumulation of ceroid may be seen not only in the intestinal tract but also in the urinary bladder (Saito), stomach, and esophageal wall (Pappenheimer and Victor). The present author has not observed ceroid deposition in any surgically resected esophageal specimens but has seen it at autopsy.

The mucosal, cross-sectional, and adventitial surfaces of the esophagus appear brown macroscopically (Fig. 6-17).

Histologically, coarse dark brown granules are seen in the smooth muscle fibers of the muscularis propria and muscularis mucosae and in blood vessel walls (Fig. 6-18). These granules stain positive with periodic acid–Schiff (PAS), Giemsa, methenamine silver, and oil red O.

6.14. Myasthenia Gravis

Although it is considered that there are not usually any smooth muscle changes in myasthenia gravis, edema of the muscularis propria and degeneration and fatty infiltration of muscle fibers have sometimes been observed in the esophagus in this disorder (Huvos and Pruzanski).

Fig. 6-17. Macroscopic appearance of esophageal ceroidosis. The mucosal surface appears brown

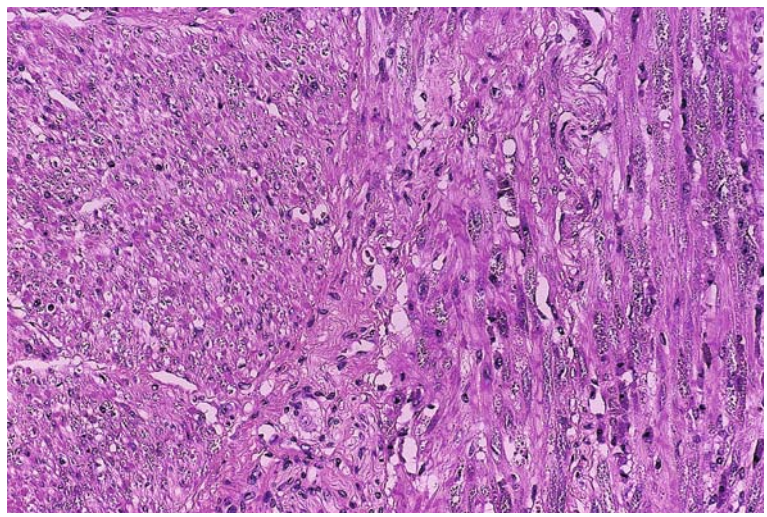


Fig. 6-18. Ceroidosis of the esophagus. Granular accumulation of ceroid is seen in smooth muscle cells of the muscularis propria

6.15. Myotonic Dystrophy

Patients with myotonic dystrophy frequently complain of symptoms related to the alimentary tract. Most of these can be attributed to esophageal dysfunction (Garrett et al.), and about half of patients suffer from dysphagia (Schuman et al.; Kurihara et al.). Although this is mainly a disorder of striated muscle, smooth muscle abnormalities have also been demonstrated. Manometric studies in patients with myotonic dystrophy have shown a decrease in upper esophageal sphincter pressure and peristaltic amplitude. The lower esophageal sphincter pressure may not be significantly different from that of controls (Eckardt et al.), or it may be lower (Tamura et al.).

There have been a few papers that have described histological changes in the esophagus in myotonic dystrophy. The changes are most prominent in the upper esophagus (Fig. 6-19), where striated muscle fibers show a marked variation in size with splitting, necrosis, and regeneration. The striated muscle nuclei are pyknotic and centrally located (internal nuclei) (Fig. 6-20). Smooth muscle in the middle and lower esophagus does not show any prominent changes on light microscopy.

There has been a reported case of a 55-year-old man with esophageal involvement by myotonic dystrophy who developed an esophageal squamous cell carcinoma (Uemura et al.).

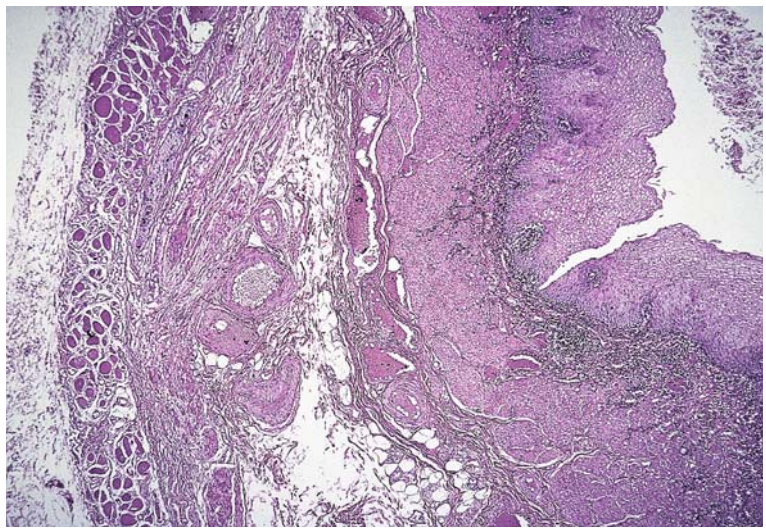


Fig. 6-19. Myotonic dystrophy. Prominent changes are seen in the muscularis propria of the upper esophagus, with marked atrophy of striated muscle and a marked variation in fiber size. The muscularis mucosae is unremarkable

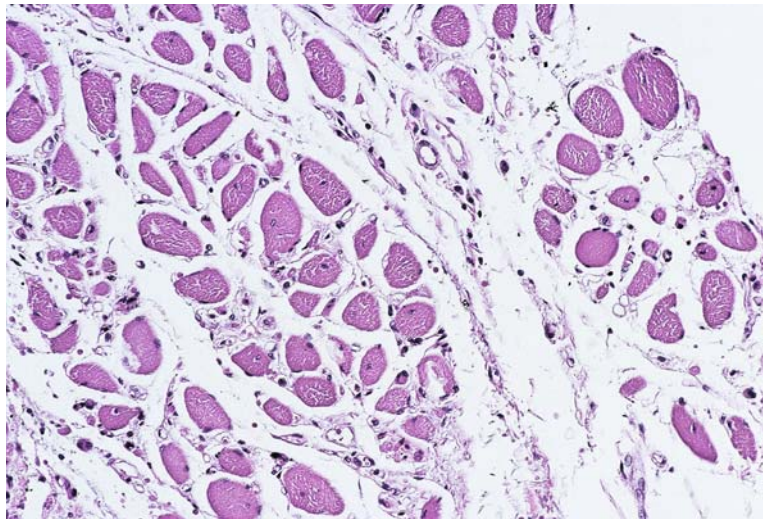


Fig. 6-20. Myotonic dystrophy. Striated muscle fibers in the upper esophagus show a marked variation in size with splitting, necrosis, and regeneration. The nuclei are located centrally in the muscle fibers (internal nuclei)

6.16. Hyperthyroidism and Hypothyroidism

Numerous papers have been published on the relationship between thyroid function and the transit time of food in the gastrointestinal tract. Hyperthyroidism causes rapid gastrointestinal transit whereas hypothyroidism causes slow transit (Shafer et al.). Motor dysfunction of the esophagus may occur in hyperthyroidism, and esophageal aperistalsis and weakness of the lower esophageal sphincter may occur in hypothyroidism. Barrett's esophagus may also occur in association with hypothyroidism (Eastwood et al.).

Patients with thyrotoxic myopathy may have dysphagia (Marks et al.).

6.17. Hyperparathyroidism

Dysphagia may rarely occur in association with hyperparathyroidism; this was described in 2 of 72 cases in one study (Palmer).

6.18. Uremia

Esophagitis may occur in patients with uremia (Boyle and Johnston; Hino et al.). Esophagitis was also described in 5 of 19 renal transplant patients in one study (Pahl et al.).

6.19. Diabetes Mellitus

Patients with diabetes mellitus may have dysphagia or heartburn as a result of motor dysfunction of the esophagus. Abnormal acid reflux has been reported in patients with diabetic motor neuropathy (Kinekawa et al. 2001). The histopathology of the esophagus in diabetes mellitus has not been fully studied. No characteristic histological changes have been reported in the esophagi of diabetic patients at autopsy.

6.20. Wegener's Granulomatosis

Gastrointestinal manifestations of Wegener's granulomatosis are uncommon, but there have been scattered reported cases of involvement of the small intestine, colon, pancreas, and oral mucosa. Erosive esophagitis with vasculitis was reported in a 54-year-old woman with Wegener's granulomatosis (Spiera et al. 1994). Oropharyngeal dysphagia was reported in a 68-year-old man with Wegener's granulomatosis (Miller et al. 2001).

6.21. Hepatolenticular Degeneration (Wilson's Disease)

Patients with hepatolenticular degeneration frequently suffer from dysphagia (Strickland and Leu).

Chapter 7
Esophagitis and Esophageal Ulcer

7.1. Gastroesophageal Reflux Disease (GERD), Reflux Esophagitis, and Esophageal Ulcer

Esophageal ulcers, from all causes, were reported in 2.3% of 9726 esophagoscopy examinations in one Japanese study (Endo et al.) and occurred slightly more frequently in men than in women. A review of esophageal ulcers complicating Barrett's esophagus (see Section 12.2. Primary Adenocarcinoma of the Esophagus) also indicated a higher incidence in men (Tominaga et al.). The regurgitation of gastric and duodenal contents into the esophagus causes mucosal injury and results in gastroesophageal reflux disease. There are several endoscopic classifications of gastroesophageal reflux disease. The Los Angeles Classification (Armstrong et al. 1996) divides esophagitis into four grades: grade A, one or more mucosal breaks, each no longer than 5 mm; grade B, at least one mucosal break more than 5 mm long, but not continuous between the tops of two mucosal folds; grade C, at least one mucosal break that is continuous between the tops of two or more mucosal folds, but which is not circumferential; and grade D, a circumferential mucosal break. In reflux esophagitis, reflux of gastric contents, or of intestinal contents after total gastrectomy (alkaline reflux esophagitis), induces esophageal erosions and ulceration, often resulting in scarring and stenosis if the reflux is recurrent (Fig. 7-1).

Cervical esophagitis can also occasionally occur after total thoracic esophagectomy with esophagogastrostomy. Mucosal bridges (Mihas et al.), esophagogastric fistulae (Diehl et al.), and esophageal rupture (Limburg et al.) have all been reported as complications of reflux esophagitis.

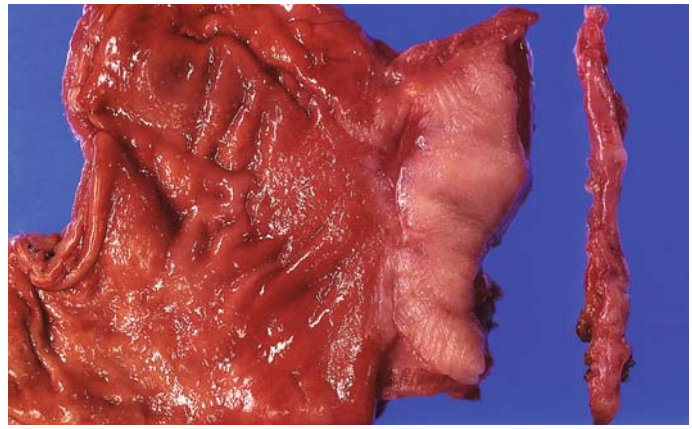


FIG. 7-1. Ulcer located just proximal to the esophagogastric junction. The ulcer is shallow without elevated margins

7.1.1. Perforation of Benign Esophageal Ulcer

Two unusual cases of perforation of chronic esophageal ulcers, one into the thoracic aorta that occurred in a 72-year-old man, and the other into a pulmonary vein in an 82-year-old woman with a hiatus hernia, were reported by Mo et al. (1988).

7.1.2. Minimal Change Esophagitis

Cases that, at endoscopy, show a cloudy-white (Fig. 7-2) and/or reddened mucosa (termed discolored mucosa or discoloring-type esophagitis in Japan) at deep inhalation, without mucosal breaks, have been classified as nonerosive reflux disease (NERD) (Narayani et al. 2003; Vieth et al. 2004), mucosa showing minimal changes (Takubo et al. 2005), or minimal change esophagitis (Kiesslich et al. 2004). Biopsy specimens from the cloudy-white epithelium show acanthosis and, sometimes, keratinization (Fig. 7-3a). The reddened mucosa shows a mixture of regenerated and regenerating squamous and columnar mucosa.

7.1.3. Endoscopy-Negative Gastroesophageal Reflux Disease

Occasionally patients having reflux symptoms do not have mucosal breaks but, instead, have a normal-appearing esophagus at endoscopy. This condition has been termed endoscopy-negative gastroesophageal reflux disease but it has often also been classified with minimal change esophagitis.

7.1.4. Endoscopic Stages of Reflux Esophagitis

The endoscopic findings in reflux esophagitis have been classified into three main stages by Makuuchi et al. (Takubo et al. 2005); active, healing, and scarring. Relapse and healing occur repeatedly in patients with gastroesophageal reflux disease (GERD), and a mixture of the stages is often seen in biopsy specimens.

7.1.5. Histological Findings in Reflux Esophagitis

Biopsy specimens from patients with benign esophageal ulcers and erosions show exudates of neutrophils and eosinophils, necrotic debris, and granulation tissue. Plasma cells, lymphocytes, and fibrotic connective tissue can be seen in chronic lesions. The histological criteria for esophagitis (Japanese Society for Esophageal Diseases 1978) stipulate that there must be infiltration by neutrophils in acute esophagitis, an epithelial defect in erosive esophagitis, and mucosal fibrosis in chronic esophagitis.

Many histological markers have been described in the esophageal squamous mucosa in patients

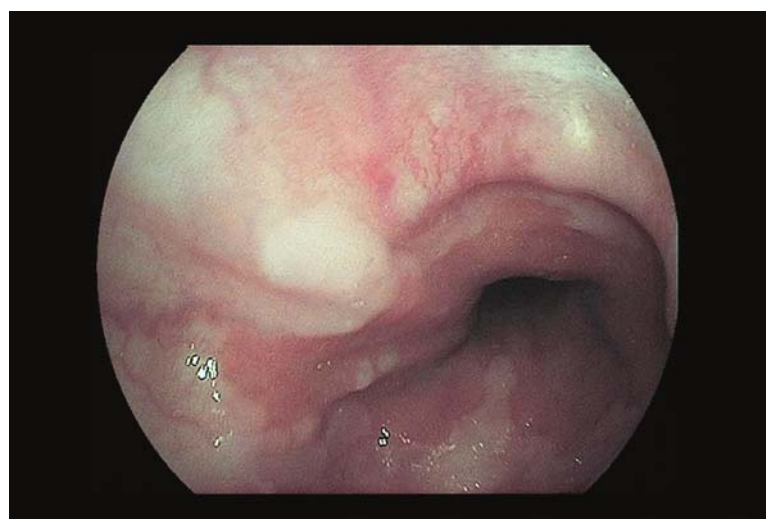


Fig. 7-2. Endoscopic appearance of gastroesophageal reflux without a mucosal break. The longitudinal vessels are not visible through the cloudy-white (opaque) squamous mucosa but are visible through the normal-appearing squamous mucosa

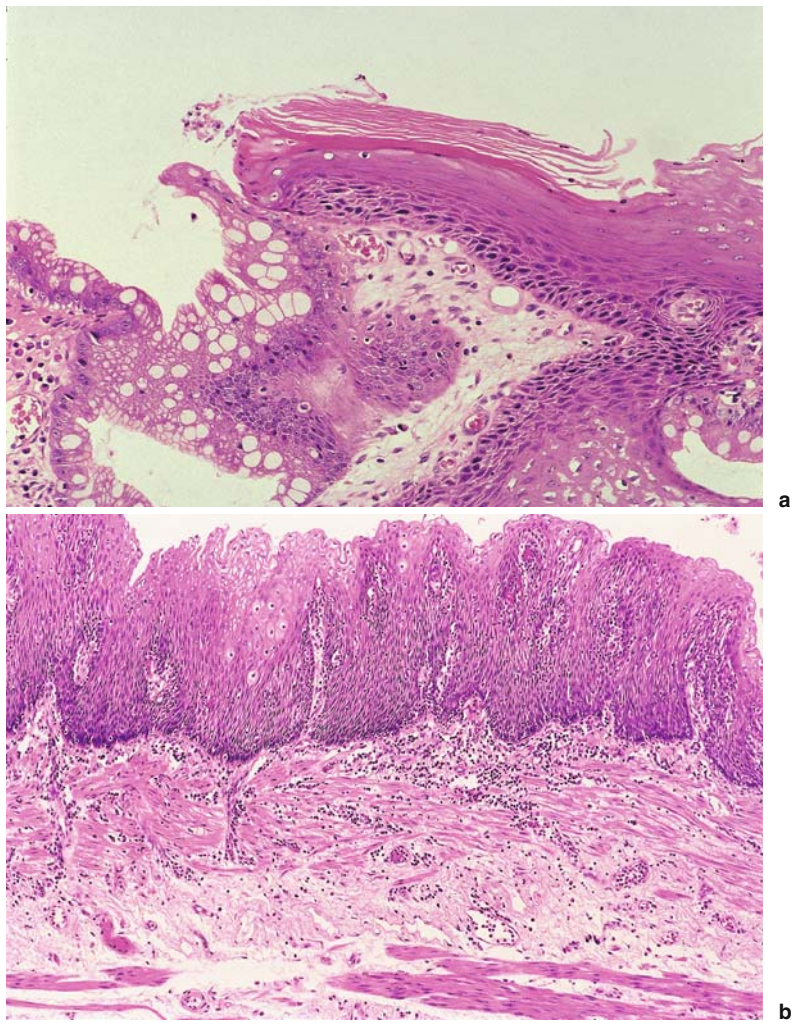


FIG. 7-3. **a** Biopsy specimen from a region of cloudy-white mucosa. Keratinization and acanthosis are evident. **b** Reflux esophagitis. Basal cell hyperplasia and elongation of papillae are evident

with gastroesophageal reflux disease (GERD), including dilated intercellular spaces (Solcia et al. 2000), balloon cells (Jessurun et al. 1988), intrapapillary vessel dilatation (Geboes et al. 1980), an increased number of papillae, elongation of papillae, and basal cell hyperplasia (Ismail-Beigi et al. 1970), acanthosis (Tummala et al. 1987), and increased numbers of intraepithelial eosinophils (Winter et al. 1982), Langerhans' cells (Geboes et al. 1983), and Ki-67-positive cells (Riddell 1996; Harber et al. 2002). The biopsy appearances are variable in patients with GERD, however, because the histological changes correspond to the observed endoscopic changes (Vieth et al. 2004) and are not representative of all sites and all stages of disease in a given patient (Takubo et al. 2005).

Ismail-Beigi and Pope, in a well-known study, concluded that if the basal cell layer is thickened to 15% or more of the total thickness of the mucosal epithelium (basal cell hyperplasia), and the rete pegs (papillae) are elongated to more than 60% of the thickness of the epithelium, then this represents clear evidence of early reflux esophagitis (Fig. 7-3b). Weinstein et al. disputed this, however, reporting these changes in the distal 2.5 cm of the esophagus in more than 50% of patients without reflux symptoms and, further, stating that these changes are of little diagnostic value even if seen 2.5 to 3 cm or more above the lower end of the esophagus. Eosinophils and

neutrophils are rarely found in the epithelium of the normal esophagus, and thus infiltration by these inflammatory cells suggests reflux of gastric or intestinal contents (Brown et al.). Any relationship between intraepithelial infiltration by lymphocytes, and reflux, remains unclear, however (see Section 2.2.1.1. Normal Mucosal Epithelium). Dilation of capillaries in the lamina propria, apart from that in the papillae, is not a diagnostic criterion for reflux. The muscularis mucosae often shows focal hyperplasia with an irregular pattern in biopsy specimens from cases of reflux esophagitis.

Regenerative squamous epithelium at ulcer margins is sometimes difficult to distinguish histologically from carcinoma (Makuuchi et al.). The distinction is often clear in surgical specimens (Fig. 7-4) but may not be in biopsy specimens (Fig. 7-5). The regenerating epithelial cells, both histologically and cytologically, are round and have barely thickened nuclear membranes and extremely fine chromatin. They often have large, irregular nucleoli and fairly abundant cytoplasm. Cells at various stages of maturation, toward large and thin superficial forms, can be found. These are the main features that distinguish regenerative

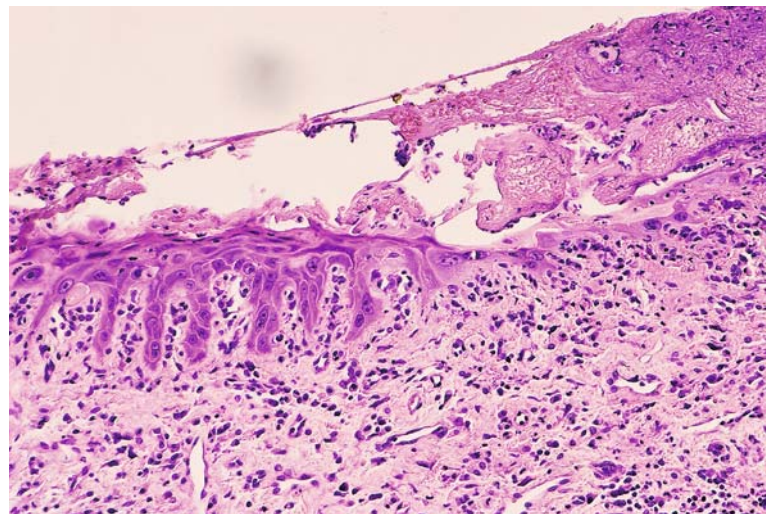


Fig. 7-4. Regenerating epithelium at an ulcer margin (surgical specimen)

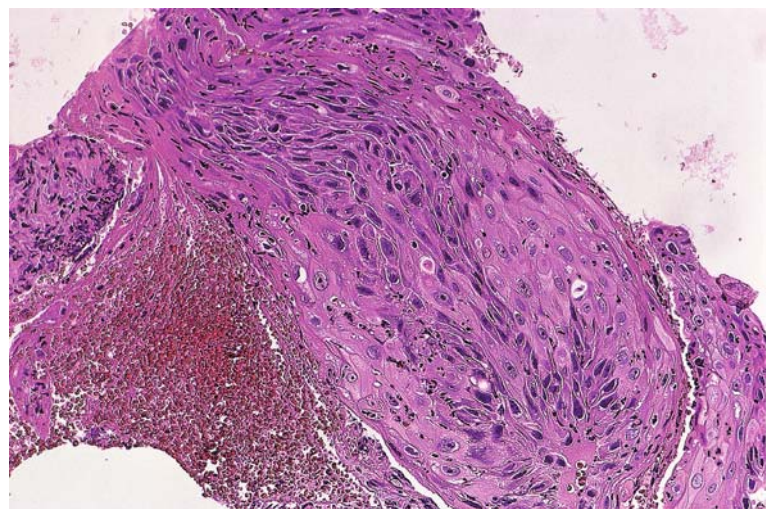


Fig. 7-5. Biopsy specimen of regenerating epithelium at an ulcer margin

squamous epithelium from squamous cell carcinoma. The cytoplasm of regenerating cells stains only weakly with eosin, so regenerative epithelium is often referred to as blue epithelium. Features of esophagitis and regenerative epithelium are occasionally found in lower esophageal specimens from middle-aged and elderly patients, and distinction from squamous cell carcinoma is particularly important in these cases. When it is not possible to clearly distinguish regenerative epithelium from carcinoma in a biopsy specimen, or if some concern remains, the pathologist should request the clinician to obtain another biopsy sample after treating the esophagitis.

Esophageal erosions and ulcers are characterized cytologically by the presence of regenerative cells with small round nuclei in an inflammatory background (Fig. 7-6). The regenerative epithelial cells show barely thickened nuclear membranes and have irregular, prominent nucleoli (Fig. 7-7). The cellularity is not as great as is usually seen in carcinomas, and cell cohesion is maintained (see Fig. 7-6). An increase in chromatin is less conspicuous in regenerative cells than in cancer cells, but nucleoli may be more conspicuous in the former. Fibroblasts may also be seen in cytology specimens from esophageal ulcers. The maintenance of cell cohesion and the lack of an increase in chromatin

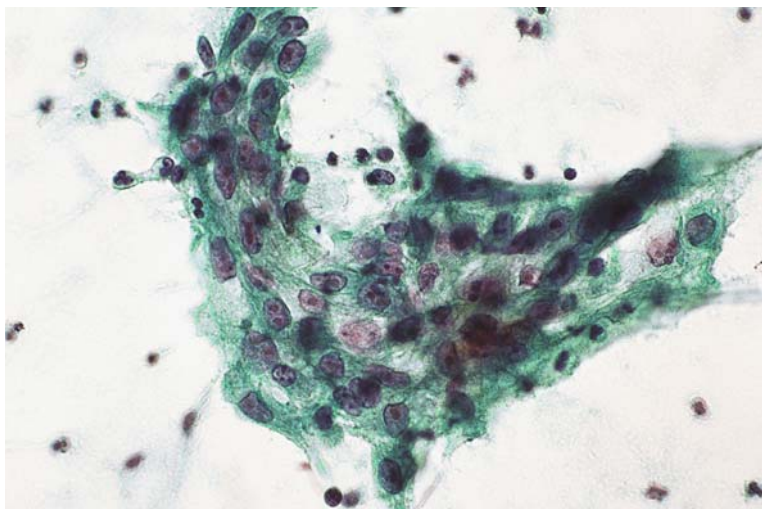


Fig. 7-6. Cytological appearance of an esophageal ulcer (Papanicolaou stain). Regenerating epithelial cells are cohesive, and there is an inflammatory background

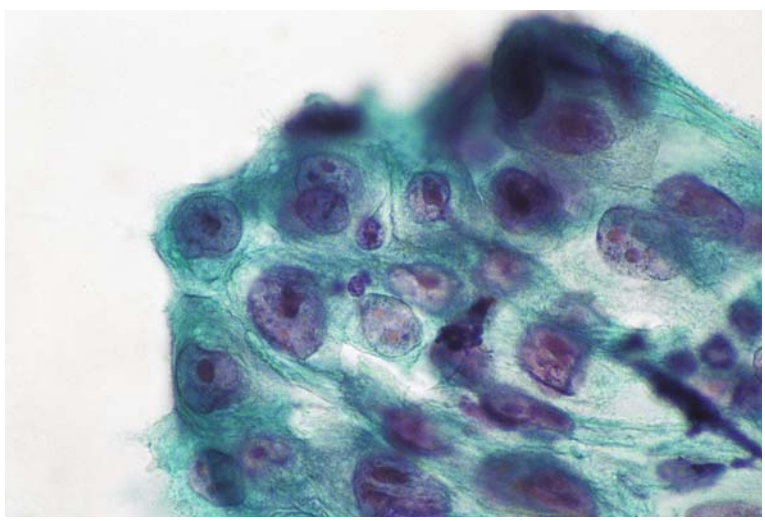


Fig. 7-7. Cytological features of an esophageal ulcer (Papanicolaou stain). Regenerating epithelial cells have one or more prominent nucleoli

are the important cytological features distinguishing regenerative epithelial cells from malignant cells.

7.1.6. Reflux Gastroesophageal Polyp, Inflammatory Reflux Polyp

Inflammatory polypoid lesions involving the mucosa at the esophagogastric junction have been reported in association with hiatal herniae and esophagitis (Fig. 7-8). This polyp is considered to be a mucosal regenerative response to surrounding mucosal injury (Abraham et al. 2001). In biopsy specimens the gastric mucosa is very edematous and has areas of granulation tissue and stratified squamous epithelium. Figure 7-9 shows a polyp from the gastroesophageal junction of a patient with reflux; there is esophageal epithelium in the hyperplastic cardiac mucosa. This polyp was removed endoscopically.

7.1.7. Esophagitis, Esophageal Stenosis, and Esophageal Rupture Following Pregnancy

There have been 14 reported cases of esophageal stricture since 1921 (Vinson) and 7 cases of esophageal rupture accompanying pregnancy

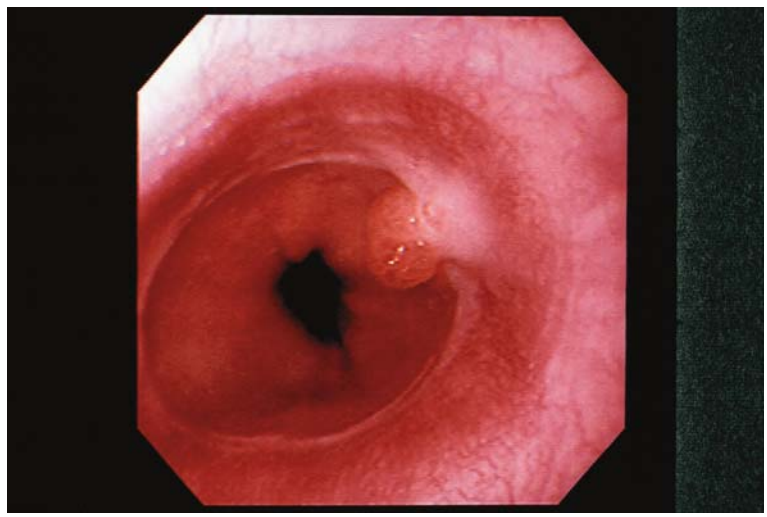


Fig. 7-8. Endoscopic appearance of a reflux gastroesophageal polyp. The polypoid tumor is situated at the esophagogastric junction

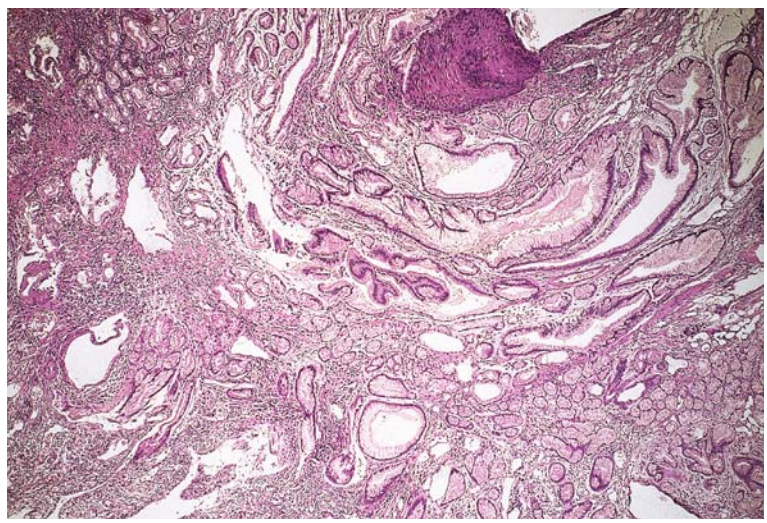


Fig. 7-9. Reflux gastroesophageal polyp. Esophageal epithelium is seen in hyperplastic cardiac mucosa

(Sato et al. 2006). The stricture in the cases is caused by esophagitis that results from repeated vomiting accompanying pregnancy or hyperemesis gravidarum. The rupture appears to develop by a mechanism similar to that of spontaneous esophageal rupture (see Section 8.3). Sato et al. reviewed the cases of esophageal stricture and rupture related to pregnancy.

7.1.8. Esophagitis and Esophageal Stenosis Associated with Anorexia and Bulimia Nervosa

A great variety of medical complications from self-induced vomiting have been documented (Chami et al.). The long-term consequences of vomiting include dental caries, parotid hypertrophy, calluses on the hand skin, esophageal rupture, development of hiatus hernia, reflux esophagitis, and Barrett's esophagus (Dessureault et al. 2002).

7.2. Corrosive Esophagitis

The swallowing of corrosive chemical substances such as acids and alkalis, by mistake or in attempted suicide, induces extensive necrosis of the esophageal and gastric mucosa. Mistaken swallowing is more frequent in children, but deliberate swallowing is more frequent in adults (Tucker et al.). Because alkaline chemicals are neutralized in the stomach, corrosion with these is more severe in the esophagus.

Corrosive esophagitis can be classified into three grades according to the severity of injury to the esophageal wall: (1) hyperemia and desquamation of the superficial mucosal layer, (2) injury to the full thickness of the esophageal wall, and (3) involvement of other organs or structures surrounding the esophagus (Gumaste and Dave). Nearly half of patients with grade 2 injuries and almost all patients with grade 3 injuries later develop esophageal stenosis. A few cases of esophageal diverticula caused by corrosive esophagitis have also been reported. Corrosive esophagitis can also be classified by its temporal course into (1) the acute necrotizing stage, (2) the ulcerative and granulation stage, and (3) the scarring stenotic stage.

Figure 7-10 shows the macroscopic appearance of the lower esophagus from an autopsy case of paraquat-induced corrosive esophagitis in the acute necrotizing stage. The mucosa has been extensively exfoliated and is ulcerated, with the surface covered by necrotic tissue. This stage is usually followed by perforation of the wall. Signs of stenosis usually develop within 2 to 4 weeks of the acute necrotizing stage but may take as long as 2 months to develop.

The present author has not had the opportunity to examine esophageal specimens at the acute necrotizing stage but has encountered three cases

FIG. 7-10. Macroscopic appearance of the acute necrotizing stage of corrosive esophagitis

some time after the swallowing of corrosive liquids. The first case was seen 2 months after the accidental swallowing of sodium hydroxide, and the second and third cases were seen at the scarring stenotic stage (Fig. 7-11).

In the first case, the luminal surface was covered by necrotic tissue and regenerating epithelium, and a great number of neutrophils were present. The muscularis mucosae was replaced by granulation tissue, which overlay the muscularis propria. The muscularis propria was interrupted in some areas, and the granulation tissue had extended to the adventitia (Figs. 7-12, 7-13). Part of the granulation tissue was already fibrotic. The presence of granulation tissue in the adventitia suggested that stenosis would have developed later.

In the second case, the lumina of the esophagus and stomach were narrowed by a stricture. The cut surface of the fixed specimen showed white, densely fibrotic tissue apparently similar to that of the thickened wall in scirrhous carcinoma of the stomach (see Fig. 7-11). Histologically, thick collagen fibers were present throughout the whole of the esophageal wall, being particularly prominent in the lamina propria and submucosa. The bundles of muscle fibers in the muscularis mucosae and muscularis propria were surrounded by collagen fibers. Thin regenerative epithelium was located on a wavy basement membrane. Although it has been reported that the stenosis frequently occurs at the level of the left main bronchus after the swallowing of corrosive chemicals, the esophagus in this case was diffusely narrowed to the same extent throughout its length.

The third case was seen 1 year after the swallowing of sodium hydroxide in a suicide attempt. The patient's chief complaint was severe dysphagia. Macroscopically the mucosal surface of the resected esophagus was covered by epithelium, apart from a very limited area of ulceration. There was severe stenosis of the lower esophagus. Histological examination of the stenotic segment revealed prominent fibrosis in the lamina propria and submucosa. The muscularis mucosae was absent, having been extensively replaced by fibrous tissue. There were no esophageal glands proper in the areas of absent muscularis mucosae (Fig. 7-14), and the submucosa was edematous.

7.2.1. Carcinoma Developing in Corrosive Strictures

It is known that esophageal cancer may develop after the swallowing of corrosive chemicals. The first such case was reported in 1896. Twenty-two cases of carcinoma of the esophagus developing after a corrosive stricture have been reported from Japan (Oufuchi et al. 1993). The swallowing of corrosive chemicals is considered to multiply the risk of developing esophageal cancer 1000 to 3000 times. The cancers often occur 25 or more years after the swallowing incident, but the shortest interval reported was a case of poorly differentiated squamous cell carcinoma that developed 12 years after swallowing in a 34-year-old woman (Gerami et al.). Patients with cancer developing in association with stenosis caused by corrosive esophagitis have been reported to be younger on

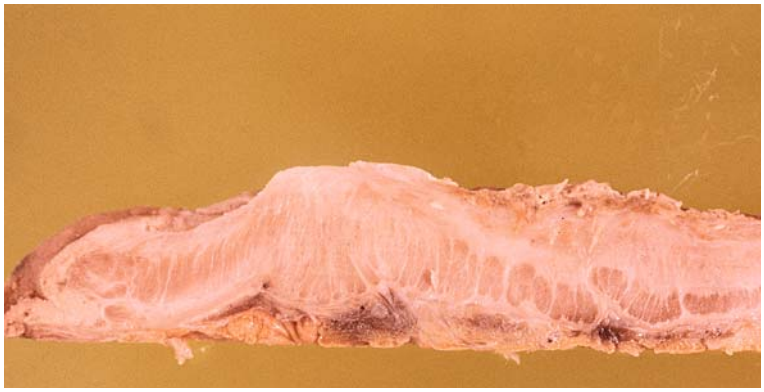


Fig. 7-11. Macroscopic appearance of the scarring stenotic stage of corrosive esophagitis (cut surface). There is marked thickening of the esophageal wall long after the swallowing of a corrosive fluid (longitudinal section). Marked fibrosis in the submucosal and muscle layers is evident

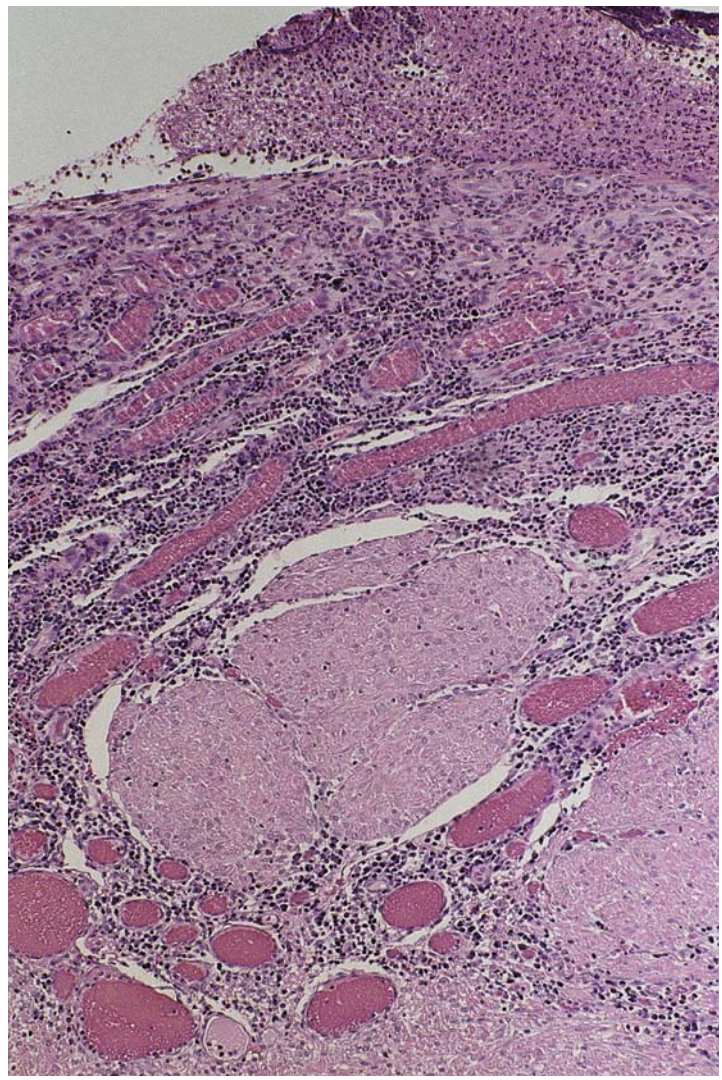


FIG. 7-12. Ulcerative and granulation tissue stage of corrosive esophagitis. The mucosa and submucosa are replaced by granulation tissue (2 months after the swallowing of sodium hydroxide)

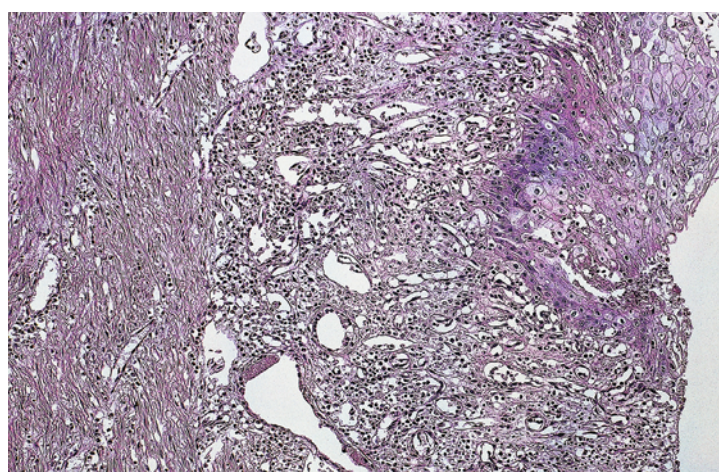


FIG. 7-13. Ulcerative and granulation tissue stage of corrosive esophagitis. There is regenerating epithelium and granulation tissue (2 months after the swallowing of sodium hydroxide)

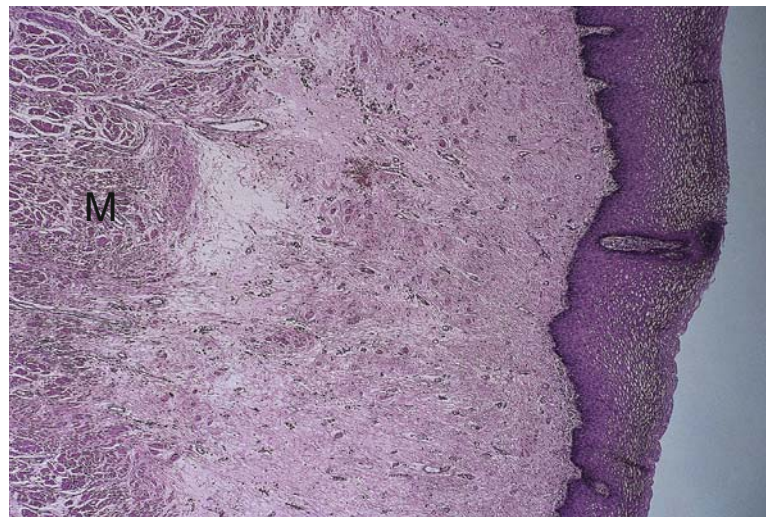


FIG. 7-14. Corrosive esophageal stenosis. No muscularis mucosae or esophageal glands proper are seen. There is obvious fibrosis. *M*, muscularis propria

FIG. 7-15. Macroscopic appearance of an esophageal cancer that occurred in association with corrosive esophageal stenosis. There is marked luminal stenosis and thickening of the wall (*arrows*) in the distal portion of the esophagus, seen on the *left side* of the figure. An ulcerative and infiltrative type advanced carcinoma is seen at the entrance to the stenotic segment

average (mean age, 43 years) than patients with the usual forms of esophageal cancer (Kiviranta). Most reported corrosive stricture-related carcinomas have been located just proximal to the stenotic segment. In general, the prognosis is said to be better for corrosive stricture-related carcinomas than for the usual forms of esophageal cancer.

Histologically, most of the reported cases have been squamous cell carcinomas. Two papers have reported other histological types, including an adenocarcinoma accompanied by Barrett's esophagus (Kano et al.) and an adenosquamous carcinoma (Nakayama et al.).

Figure 7-15 is the macroscopic appearance of the esophagus resected from a 63-year-old male patient reported by Maeda et al. (1992). The patient had drunk hydrochloric acid 32 years previously in a suicide attempt. In this case, as is usual, the carcinoma was located just proximal to the stenotic portion. This finding is in contrast to the situation in patients with achalasia, where carcinomas are usually located in the dilated portion, well away from the stenotic segment.

There have been very few reports that have adequately discussed the histogenesis of carcinomas developing in association with corrosive stenosis, from the point of view of the presence of dysplasia and other changes in noncancerous areas of mucosa. One report, by Tokunaga et al., described epithelial dysplasia in mucosa surrounding a squamous cell carcinoma situated at the entrance to a stenotic segment. The dysplasia was restricted to mucosa proximal to the stenosis. Also,

extensive hyperkeratosis, orthokeratosis, and parakeratosis were found in the proximal epithelium, with a granular layer developing under the keratin layer. The authors suggested that the development of carcinoma may be related to long periods of food retention.

7.3. Iatrogenic Esophagitis

7.3.1. Drug-Induced Esophagitis

There have been an increasing number of reports describing esophagitis and esophageal ulcers due to drugs and radiation. The causative drugs have often been KCl preparations, antibiotics, or anticancer drugs. Lugol's iodine solution, used during endoscopic examinations, also occasionally induces severe esophagitis. Taking a drug and assuming certain postures just before going to bed, or taking a drug with an insufficient volume of water, are considered to be risk factors.

Ulcers often occur at the level of the aortic arch, where tablets are likely to stick. In an extensive review of 221 cases of drug-induced esophagitis by Kikendall et al. (1983), 54% of cases were caused by antibiotics. Doxycycline-induced esophageal ulcers accounted for the majority (43%). The patients ranged in age from 9 to 96 years, with a sex ratio of nearly 1:1. This series included 4 deaths resulting from KCl preparations. Doxycycline was also the cause in 1 of 3 cases of drug-induced esophagitis reported from Japan by Tanaka et al. (1980).

Anticancer drugs are thought to lower the resistance of normal tissue to the effects of irradiation. In one study of esophagitis in children (Newburger et al. 1978), 7 (37%) of 19 cases were caused by irradiation of the mediastinum during adriamycin therapy. Adriamycin has not been reported to cause esophagitis on its own. O'Morchoe et al., however, stated that adriamycin, cytarabine, and prednisone could cause esophagitis, and atypical change in esophageal epithelial cells caused by cyclophosphamide has also been reported.

7.3.2. Radiation-Induced Esophagitis and Esophageal Stenosis

There have been reports of esophagitis and esophageal stenosis occurring as a result of radiation therapy for malignant tumors in organs or structures other than the esophagus, in the neck or mediastinum. There have also been case reports of esophagoaortic fistulae and esophagotracheal fistulae induced by radiation therapy for malignancies in extraesophageal tissues.

It is considered that the radiosensitivity of the flat stratified squamous epithelium of the esophagus is similar to that of oral epithelium, and that in the esophagus the submucosa is the first tissue to respond to irradiation (Berthrong and Fajardo).

Kuwahata (1980) examined a large number of cases of radiation-induced esophagitis and reported endoscopic and histological findings in 100 patients who underwent radiation therapy, at a dose of 2500 rads or higher, for the treatment of cancers of intrathoracic organs other than the esophagus. Endoscopy revealed some changes in all 100 patients, with mucosal redness and swelling being evident in 59 patients, erosion in 31, and ulceration and stenosis in 10. Patients in whom a longer segment of esophagus had been exposed to radiation showed more severe changes. With regard to radiation dose, esophageal perforation occurred in some patients given more than 6000 rads. Biopsy of the esophageal mucosa showed evidence of regenerating epithelium and granulation tissue. It is known that esophageal lesions are more common after combined radiation and chemotherapy than after radiation therapy alone (Lepke and Libshitz).

Histological examination soon after radiation therapy shows mucosal edema and vascular dilation. In more severe cases the epithelium is necrotic and eroded, and there is accompanying prominent edema of the submucosa. The terminal portions of the esophageal glands proper are atrophic and exhibit squamous metaplasia, or sometimes may even disappear.

In the late stage (6 months or more after radiation therapy), there may be epithelial atrophy and hyperplasia, sometimes with accompanying atypical cells and parakeratosis. Postirradiation epithelial dysplasia is described on p. 149. Submucosal edema becomes replaced by fibrosis, and this extends to involve the muscularis propria. According to a report by Kawano et al. (1990), histological examination of a late radiation-induced ulcer

showed the presence of a sparsely cellular fibrous scar.

Radiation-induced changes are relatively minor in the muscle layer, consisting of mild fibrosis, particularly in Auerbach's plexus. Fibrosis is also evident in the adventitia. Enlarged endothelial cells and atypical fibroblasts are also seen, and arterioles exhibit intimal thickening.

The author would also like to draw the reader's attention to radiation-induced changes in noncancerous tissue (pp. 149, 182), and radiation-induced carcinoma (p. 182).

7.4. Exfoliative Esophagitis

According to a report by Shikado et al., exfoliative esophagitis was first described in 1890 by Reichmann, under the name esophagitis exfoliativa. There have been very few reports of this entity in recent years. A total of 120 cases have been reported in the Japanese literature. This condition was induced by hot foods and drinks in 13, foods in 15, drugs in 15, bullous diseases in 12, alcohols in 6, sclerotherapy in 5, endoscopic examination in 5, diabetes mellitus in 3, chronic renal failure in 3, leukemia in 3, radiation in 2, and liver cirrhosis in 2 cases, respectively, in 84 of the 120 cases (Miyamoto et al. 2001). Exfoliative esophagitis is more frequent in the elderly. It occurs as a result of injury from hard or bulky food, a burn from hot food, or as a result of endoscopic examination. The esophageal mucosal epithelium is expectorated, and this is often painful. Hemorrhage may also occur. The prognosis is good, and no subsequent esophageal strictures have been reported.

Macroscopically, the expectorated epithelium is transparent, occasionally cylindrical in shape, and membrane like (Fig. 7-16). It may measure up to 30 cm in length. Figure 7-16 is a picture that appeared in a report by Iwasaki et al. (1981).

Histological examination reveals esophageal epithelium without atypical change (Fig. 7-17). Degeneration and necrosis are sometimes found in the basal and parabasal layers. The lamina propria is usually absent, and there may be fibrin deposited along the basal layer (Fig. 7-18). There are very few inflammatory cells in the epithelium.

Intramural hematoma of the esophagus, and submucosal dissection as an incomplete type of spontaneous rupture of the esophagus, have both been reported under the name "exfoliative esophageal damage." This entity is often confused with exfoliative esophagitis, but in exfoliative esophageal damage there is a wide dissection in the submucosal layer and the esophageal epithelium is not expectorated.

Exfoliative esophagitis may also occur in patients with pemphigus vulgaris and bullous pemphigoid (Murata et al.).

7.5. Decubital Ulcer

Prolonged use of nasogastric or ileus tubes, or the ingestion of foreign bodies, can cause decubital ulcers at sites of physiological narrowing of the esophagus. A detailed study by Nishihara et al. (1978) found pharyngoesophageal ulcers in 18.3% of 174 autopsies of patients in whom nasogastric tubes had been placed. The longer the placement of the nasogastric tube, the greater was the likelihood of ulceration; 37.5% of 56 patients who had

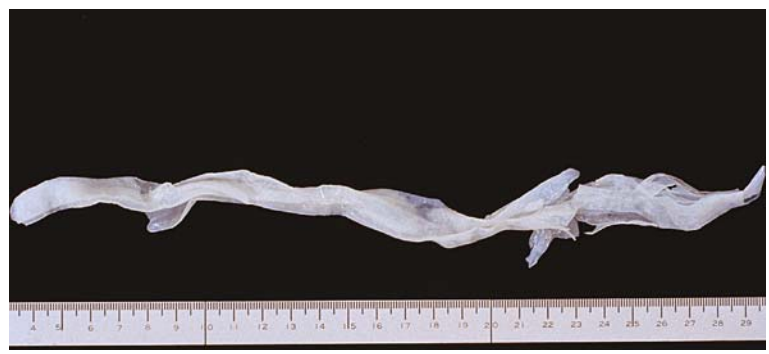


FIG. 7-16. Macroscopic appearance of exfoliative esophagitis. The expectorated epithelium is a transparent and occasionally cylindrical membrane

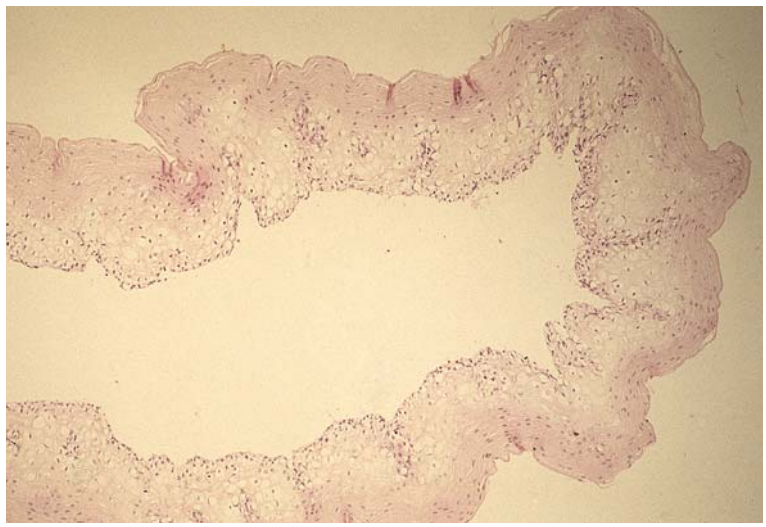


FIG. 7-17. Exfoliative esophagitis. A large expectorated epithelial fragment

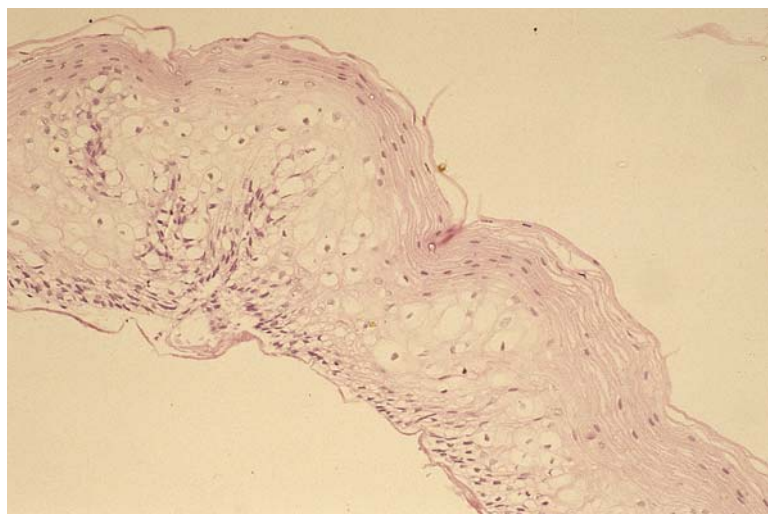


FIG. 7-18. Exfoliative esophagitis. Fibrin deposits are seen beneath the normal epithelium

had nasogastric tubes in place for 10 days or more had decubital ulcers. Decubital ulceration was seen more frequently in elderly patients and in men. Patients with cerebrovascular and malignant diseases, and hypoalbuminemia, were most at risk. In this study, all patients who had decubital ulcers were also hypoalbuminemic.

The sites of the ulcers corresponds to the sites of physiological narrowing, which are frequently located on the anterior wall at the esophageal inlet but occur toward the side of the lesser curve of the stomach when located in the mid- and lower esophagus. Although the ulcers are usually shallow, there have been some instances of penetration into the trachea.

The present author considers that the incidence of decubital ulcers is by no means low because ulcers located at sites of physiological narrowing at the inlet and in the midesophagus are quite often found at autopsy. Figure 7-19 shows the macroscopic appearance of a punched-out decubital ulcer in the midesophagus. The ulcer had extended to the muscularis propria. Although Nishihara et al. described instances of penetration into the trachea in their aforementioned report, the present author has yet to see such a case.

Fig. 7-19. Macroscopic appearance of a decubital ulcer. There is a punched-out ulcer in the midesophagus

7.6. Acute Necrotizing Esophagitis

Severe ischemia and antibiotic therapy can cause an acute necrotizing esophagitis. Eleven cases of acute necrotizing esophagitis were reported by Handa et al. (2003). It appears at endoscopy as black esophageal mucosa and has therefore been called "black esophagus." Fifty-two cases of black esophagus were reviewed in the English literature from 1963 to 2003 (Grudell et al. 2006).

Histologically, biopsy specimens show an absence of the mucosal epithelium and diffuse, shallow ulceration. Necrosis and abundant neutrophils and mononuclear cells are evident (Goldenberg et al.). Necrotizing esophagitis may occur as a result of nasogastric tubes, because of hypersensitivity reactions to antibiotic therapy, after endoscopy, or in alcoholic (Săftoiu et al. 2005), diabetic, and hypovolemic shock patients.

7.7. Esophageal Phlegmon

Cases of esophagogastric phlegmon have been reported by Kawakubo et al. (2002) and Imai et al. (2005).

7.8. Esophagitis Caused by Food Stasis Because of Kyphosis

Chronic erosive or ulcerative esophagitis caused by severe kyphosis may occur in aged females. Histologically there may be erosions or ulcers covered by necrotic debris, with granulation tissue, in the lower esophagus. The erosions or ulcers tend to be surrounded by acanthotic squamous epithelium. An aortoesophageal fistula caused by such an ulcer has been reported (see Section 8.11, p. 107).

Chapter 8
Other Nonneoplastic Disorders of the Esophagus

8.1. Thermal Burn

A series of 39 cases of esophageal ulceration due to thermal burns has been reported from Japan (Fujiwara et al. 2001). There have also been rare case reports of thermal burns from Western countries. Most esophageal thermal burns have occurred by mistake, from the ingestion of hot drinks or foods, and have been cured early, without the development of esophageal strictures. Multiple or circumferential ulcers and strictures may be seen, however, in people who habitually ingest hot drinks (Fujiwara et al.), gruel (Saito et al. 2004), or other hot foods.

8.2. Foreign Body

Esophageal foreign bodies have been reported in individuals of all ages, ranging from infants to the elderly. The incidence is said to be increasing slightly. This is one of the most common conditions of the esophagus, ranking with esophageal cancer, esophagitis, and benign esophageal stenosis (Hardy and Conn). Males slightly outnumber females, and infants and young children account for more than half the cases. Esophageal foreign bodies most frequently (more than 70% of cases) lodge at the first point of normal esophageal narrowing (at the level of C6), followed in order by the second (at T4–T5 level) and third (at T11 level) points of normal narrowing. In Japan, common foreign bodies include coins, fish bones, artificial teeth, and tablets in packages (Fig. 8-1). Coins are particularly common in infants, whereas artificial teeth and packed tablets are common in the elderly. Fish bones are common at all ages. At endoscopy, the mucosa around foreign bodies is seen to be edematous.

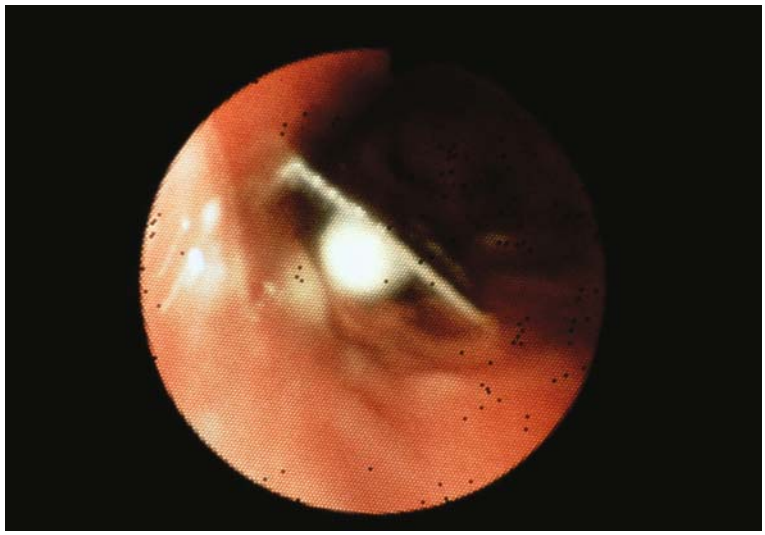


FIG. 8-1. Endoscopic appearance of an esophageal foreign body. There is a packaged tablet in the esophageal lumen

Mediastinitis, lung abscesses, and esophagoaortic fistulae may result from esophageal wall penetration by foreign bodies. Ninety-three cases of esophagoaortic fistula caused by foreign bodies have been reported (Saito et al. 1986); patient age ranged from 6 months to 63 years (mean, 29.5 years), with a male to female ratio of 1.9:1. The foreign bodies responsible were fish bones (17%), chicken bones (11%), other animal bones (40%), coins (9%), teeth (7%), and needles (7%). There has been one report of a patient who actually survived after developing an esophagoaortic fistula caused by a chicken bone (Ctercteko and Mok).

Cases of esophageal obstruction caused by phytobezoars or guar gum have also been reported.

8.3. Spontaneous Rupture

Boerhaave reported the first case of esophageal rupture in 1724; this followed severe vomiting (Derbes and Mitchell). Nowadays, esophageal rupture occurring after a sudden elevation of intraabdominal pressure is called spontaneous esophageal rupture or Boerhaave's syndrome. Strictly speaking, this condition is not spontaneous, being possibly attributable to vomiting or some other factor, but it is currently termed spontaneous rupture because there is no evident cause such as a foreign body. Abbott et al. have proposed the term atraumatic rupture of the esophagus.

About 400 cases of spontaneous rupture of the esophagus have been reported to date from Europe and America (Abbott et al. 1970; Reid 1979), and about 300 cases have been reported in the Japanese literature (Mizutani et al. 1993). Although spontaneous rupture has most commonly been related to vomiting (70% of cases), other causes have been swallowing, an abdominal blow, straining at defecation, hiccups, asthma, pregnancy (see Section 7.1.7), and neurogenic disease. The patients have typically been middle-aged, obese, alcoholic males with a history of strenuous vomiting (Ivey et al.), but neonatal cases have also been reported (Krasna et al.). A series of 191 Japanese patients consisted of 176 men and 15 women (Kijima). A case of esophageal perforation caused by vomiting was reported in a patient with advanced esophageal squamous cell carcinoma (Chino et al.).

Initial symptoms include severe chest pain, dyspnea, and subcutaneous emphysema. Hematemesis is not seen as often as in Mallory–Weiss syndrome, and if it does occur it is only mild.

Endoscopy allows observation of the affected site (Fig. 8-2). The rupture usually (84%) occurs along the long axis of the lower esophagus, above the diaphragm (Kijima), in the left lateral or left posterior wall (Callaghan); this is because the

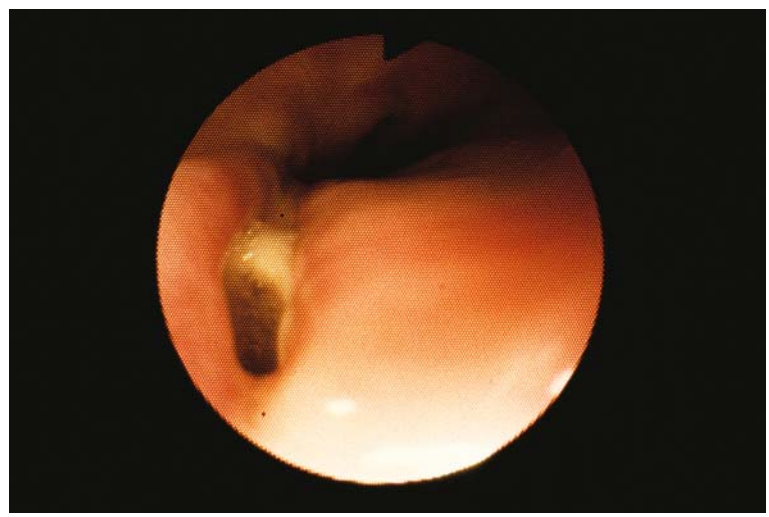


Fig. 8-2. Endoscopic appearance of a spontaneous esophageal rupture

lower esophagus lacks the support afforded to the upper and middle esophagus by such relatively unyielding structures as the trachea, bronchi, aorta, and pericardium. Although there has been no definite explanation for the greater tendency for rupture to occur along the posterolateral wall, it is believed that muscle fibers of the muscularis propria begin to disperse and decrease in number in the left and posterior walls of the lower esophagus.

The tears measure 2 cm in length on average, but occasionally have reached 6–10 cm or more (Kijima). The muscularis propria ruptures first, followed by the mucosa (Mackler). Miller et al. (1988) reported an unusual case of esophageal rupture that was associated with a lower esophageal ring.

A report by Kuwano et al. postulated that a congenital defect in the muscularis mucosae may be a contributing factor in spontaneous esophageal rupture. Of their six reported cases, two were treated by esophagectomy. These two resected specimens both showed an absence of muscularis mucosae in the wall surrounding the tear.

8.4. Mallory–Weiss Syndrome

In 1929, Mallory and Weiss reported 15 cases of gastric bleeding and hematemesis that occurred with vomiting after a heavy alcohol intake. Four of the 15 patients had autopsies, and bleeding from mucosal tears along the longitudinal axis of the esophagus was confirmed. The tears were mainly in gastric mucosa at the esophagogastric junction (Figs. 8-3, 8-4). None of the tears had reached the muscularis propria. Since their report, more than 500 additional cases have been documented in the English literature (Hixson et al. 1979). In addition, 1%–13% of all cases of gastrointestinal bleeding have been reported to be caused by Mallory–Weiss syndrome (Knoblauch et al.; Michel et al.).

Recent studies have shown that a substantial proportion of patients with this syndrome have had an initial episode of hematemesis unrelated to vomiting. It is also now known that Mallory–Weiss syndrome may occur in association with defecation, coughing, and hiccups. Therefore, more recently, this syndrome has often been defined as bleeding resulting from a laceration in the vicinity of the cardia, occurring as a result of elevated intraabdominal pressure (Okuyama et al.).

There is usually a single tear (see Fig. 8-3), but sometimes there is more than one, and the tear may reach the muscularis propria. In a series of 310 cases reported by Sugawa and Masuyama (1986), 82% had one tear, 11% had two tears, and 6% had three or four tears. As to the location, 78% occurred on the lesser curvature, 8% on the

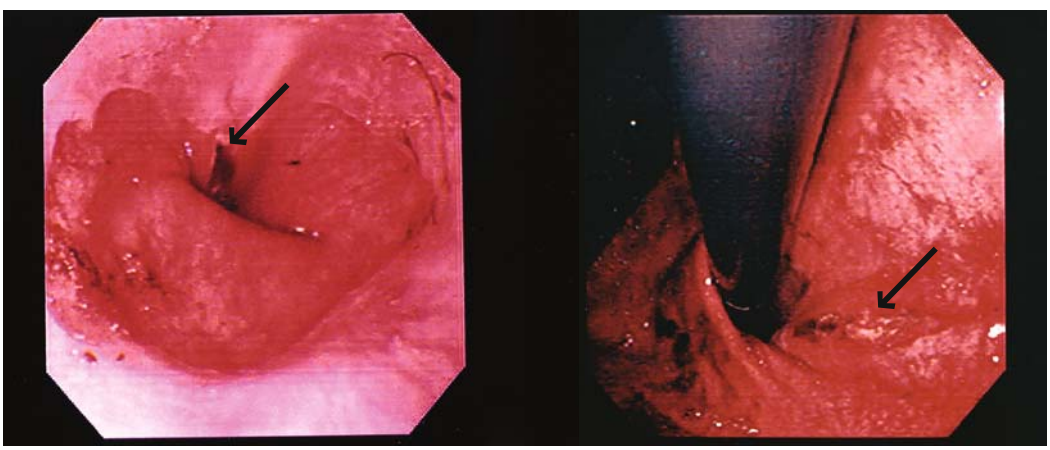


FIG. 8-3. Endoscopic appearance of Mallory–Weiss syndrome. There is a tear (*arrows*) running toward the esophagogastric junction. *Left*, endoscopic appearance from the proximal (esophageal) side; *right*, endoscopic appearance from the distal (stomach) side

FIG. 8-4. Macroscopic appearance of Mallory–Weiss syndrome (autopsy case). There is a tear with evidence of bleeding in the region of the esophagogastric junction

greater curvature, 10% on the posterior wall, and 5% on the anterior wall. Eight percent of the cases affected the esophagus alone. Of the 310 patients, 12 (4%) died.

Most patients with Mallory–Weiss syndrome are middle-aged men, but a neonatal case has also been reported (Baptist et al.). It has been stated that there is a coexisting hiatal hernia in about 50% of cases (Michel et al.). A review of the literature by the present author found that the reported incidence of an accompanying hiatal hernia ranged from 35% to 100%. Chronic pancreatitis and/or alcoholic liver disease may also coexist with Mallory–Weiss tears.

This condition is easily diagnosed at endoscopy. Mallory–Weiss syndrome has a lower mortality rate than spontaneous rupture of the esophagus. Okuyama et al. (1976) reported that all their 63 Japanese patients with Mallory–Weiss syndrome recovered within a short period of time.

8.5. Intramural Hematoma

A number of cases of esophageal hematoma related to a bleeding tendency from hemophilia, anticoagulant therapy, renal failure, thrombocytopenia, or leukemia, or to an esophageal foreign body, have been reported. Some examples of intramural hematoma of the esophagus, which could be regarded as incomplete forms of spontaneous esophageal rupture or Mallory–Weiss syndrome, have also been described. This condition has also been called intramural rupture, submucosal dissection, submucosal hematoma, esophageal apoplexy, and hemorrhagic dissection of the submucosa.

Shay et al. (1981) reviewed 26 cases of esophageal intramural hematoma. In a more recent review of 58 cases (Furukawa et al. 1993), which included 20 men and 38 women who ranged in age from 21 to 87 years (mean, 57 years), the mortality rate was found to be low. The first Japanese case was reported by Shima et al. in 1984, and since then only 8 further Japanese cases (4 males, 4 females) have been reported (Yamada et al. 1995). In all the reported Japanese cases the condition has resolved with conservative treatment only, without a need to resort to esophageal resection. Intramural hematoma usually occurs in the mid- to lower esophagus. Severe thickening of the esophageal wall is apparent on computed tomography (CT) or magnetic resonance imaging (MRI) scanning, and at endoscopy a smooth dark red-colored mass is seen within the esophageal lumen (Fig. 8-5). Endoscopic ultrasonography has also been used to demonstrate a submucosal hematoma (Yamada et al.).

A condition intermediate between idiopathic esophageal rupture and intramural hematoma has also been reported in which there were mucosal lacerations with a hematoma but without perforation (Steadman et al. 1990).

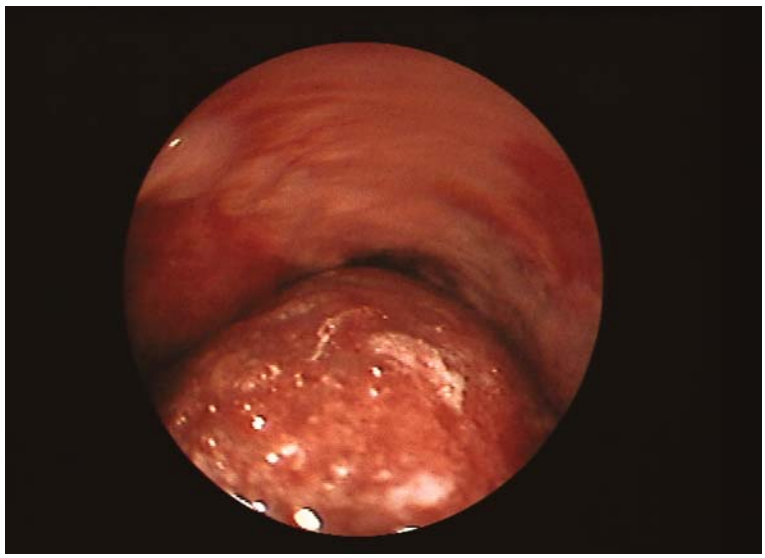


FIG. 8-5. Endoscopic appearance of an intramural hematoma. The esophageal lumen is obstructed by a very large, dark red hematoma

In addition, there have been case reports of iatrogenic intramural hematomas occurring after esophagoscopy, sclerotherapy of esophageal varices (van Steenbergen et al.; Inoue et al.; Brosolo et al.), and esophageal dilation (Molina et al.).

8.6. Trauma

Trauma to the esophagus may lead to rupture. The trauma is usually iatrogenic, the rupture occurring during endoscopic examination, insertion of a nasogastric tube, or gastric lavage (Krasna et al.). Esophageal foreign bodies may also be a cause.

There were 24 cases of traumatic esophageal rupture attributable to blunt trauma or to causes other than iatrogenic procedures or foreign bodies reported from Japan between 1985 and 2001 (Nakazawa et al. 2003).

8.7. Esophageal Diverticula

Esophageal diverticula are often found by chance during radiologic investigation of the upper gastrointestinal tract. The rate of detection in Japan has been reported to be 0.5%–1.0% of all upper gastrointestinal radiologic procedures (Ishida et al.; Ide et al.). The corresponding rate was 0.6% in a series of 660 autopsy cases examined over a 3-year period (1992–1994) at the Tokyo Metropolitan Geriatric Hospital. All diverticula found in this series were located at the level of the tracheal bifurcation.

Esophageal diverticula can be classified into congenital and acquired forms, the latter being subclassified into traction and propulsion forms. In terms of location, diverticula are divided into those of the upper esophagus, including pharyngoesophageal diverticula (Zenker's diverticula), those of the midesophagus (mainly occurring at the level of the tracheal bifurcation), and epiphrenic diverticula. Most esophageal diverticula are acquired, congenital types being rare. In fact, most congenital diverticula are better classified as esophageal duplications.

Zenker's diverticula are the commonest type in Europe and America, but those occurring at the level of the tracheal bifurcation are the most common in Japan, followed in order by epiphrenic diverticula and Zenker's diverticula.

Esophageal diverticula are also classified by the characteristics of the diverticular wall into true diverticula, which have muscularis propria in their walls, and false diverticula, which lack muscularis propria.

Traction diverticula occur because of periesophageal inflammation, mainly lymphadenitis and mediastinitis, extending into the esophageal wall. The scarring process during healing of the inflammation produces traction on the esophageal wall,

resulting in a diverticulum. Traction diverticula most often occur at the level of the tracheal bifurcation and are therefore considered synonymous with diverticula of the midesophagus (Fig. 8-6). These are usually true diverticula and are often attributable to scarring associated with tuberculous lymphadenitis.

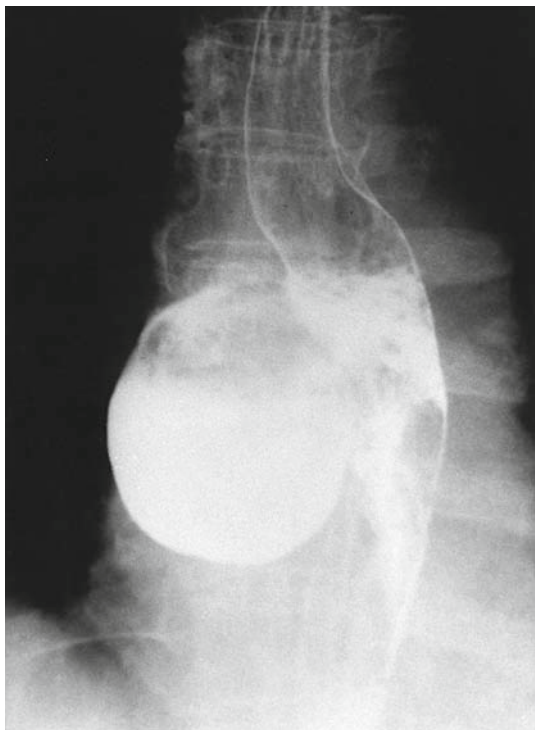


Fig. 8-6. Esophagogram of a diverticulum of the midesophagus. There is an extremely large diverticulum at the level of the tracheal bifurcation

Tuberculosis was very common in Japan before World War II, and so traction diverticulum is the commonest form of esophageal diverticulum seen in autopsy series, even now. They are usually small, measuring up to about 2 cm in diameter, are usually found incidentally at autopsy, and have a very narrow lumen (Fig. 8-7). Large diverticula of the midesophagus, such as the one shown in Fig. 8-6, are rare.

Propulsion diverticula are outpouchings of the esophageal wall caused by increased intraesophageal pressure or abnormal esophageal motility. They may be either true or false, and in terms of location are either pharyngoesophageal or epiphrenic. Epiphrenic diverticula are usually false, and can measure up to 10 cm in diameter.

Zenker's diverticula are not esophageal diverticula in the strict sense, as they occur in the hypopharynx. They occur because of prolapse of the mucosa through the posterior wall of the muscle layer and have been reported to occur in 0.1% of normal subjects (Wheeler), and in 0.03% of normal Japanese (Yamasaki et al.). This condition has been reported to be present in 4.4% of all patients with esophageal symptoms (Hardy and Conn). These diverticula seem to be very rare in Japan, with only 52 Japanese cases (male : female ratio, 3 : 2) having been reported (Kawamura et al. 1993). The reason for this low incidence is unknown. Zenker's diverticula are considered to be caused by the development of abnormally high intrapharyngeal pressure during swallowing. They are often false.

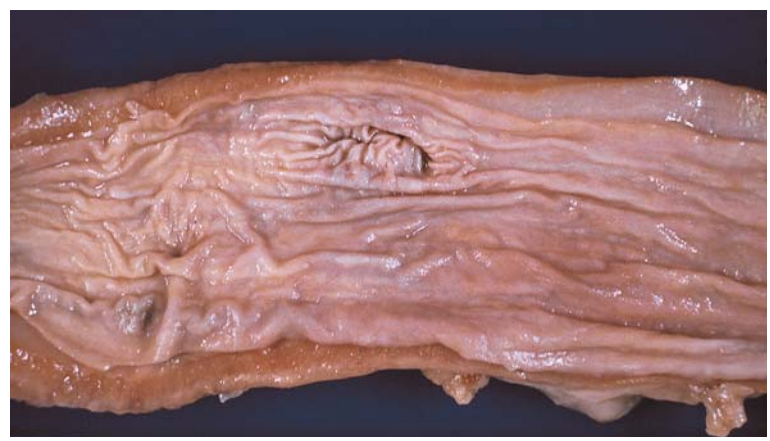


Fig. 8-7. Macroscopic appearance of a traction diverticulum (autopsy case). A small diverticulum with a very narrow lumen is seen at the level of the tracheal bifurcation

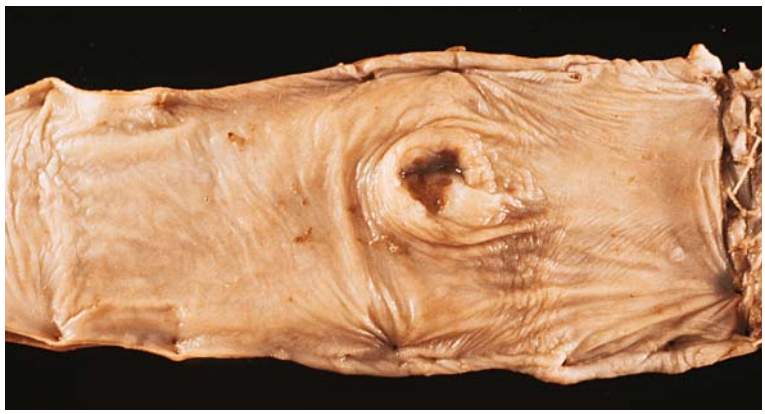


FIG. 8-8. Macroscopic appearance of a carcinoma within an esophageal diverticulum. The carcinoma fills the lumen of the diverticulum and is surrounded by the elevated diverticular wall

Diverticula attributable to collagen diseases such as scleroderma have also been reported (Clements et al.), and there has been a report of an esophageal diverticulum that formed in a patient who ingested sulfuric acid in a suicide attempt (Plavsic and Robinson). Also, a case of coexisting esophageal leiomyoma and diverticulum has been reported (Ide et al.).

8.7.1. Diverticula and Carcinoma

It might be expected to be relatively common for esophageal carcinomas to develop in diverticula, because of prolonged retention of food debris, but there have only been a few reports of this occurring. However, judging from the fact that such carcinomas which have been reported from Japan have been relatively small, whereas esophageal carcinomas in general are usually large and already advanced at the time of diagnosis, there is a possibility that an advanced carcinoma might mask the presence of a preexisting diverticulum, thus leading to underreporting.

Yaita et al. found 7 cases of squamous cell carcinoma of 1169 cases of esophageal diverticulum in Japan. Fifty cases of carcinoma arising in esophageal diverticula have been previously reviewed worldwide (Fujita et al. 1980; Okamura et al. 1983). Thirty (60%) of the 50 originated in pharyngoesophageal diverticula, 11 (22%) in epiphrenic diverticula, and 9 (18%) in parabronchial diverticula. Carcinomas of the upper esophagus have been more frequent in European and American patients, but 8 of the 9 carcinomas in Japanese patients occurred in the midesophagus. A more recent review from Japan of 30 cases of squamous cell carcinoma arising in esophageal diverticula was also published (Ebihara et al. 2003); of the 30 cases, 21 occurred in men, 7 occurred in women, and 2 were unknown. Male patients have also predominated in cases reported from Europe and America. These tumors have occurred at a similar age to usual esophageal squamous cell carcinomas.

The outcome of patients with carcinomas arising in diverticula has been worse than that of usual carcinomas of the esophagus.

Histologically, almost all carcinomas reported in esophageal diverticula have been of squamous type, and most have been advanced (Fujita et al.). In a case reported by Okamura et al. dysplasia and carcinoma in situ were found in diverticular mucosa away from the main tumor. Figure 8-8 shows a relatively small carcinoma, 1.2 cm in diameter, reported by Kuwano et al. (1982), which occurred in a diverticulum at the level of the tracheal bifurcation. The raised area surrounding the carcinoma is mucosa forming the wall of the diverticulum and is not infiltrated by tumor (Fig. 8-9). A case of adenocarcinoma occurring in a midesophageal diverticulum has also been reported (Avisar and Luketich 2000).

8.8. Esophageal Webs

An esophageal web is a thin mucosal membrane that projects into the esophageal lumen (Fig. 8-10). These structures can form at any level of the esophagus. They mostly occur in the anterior or

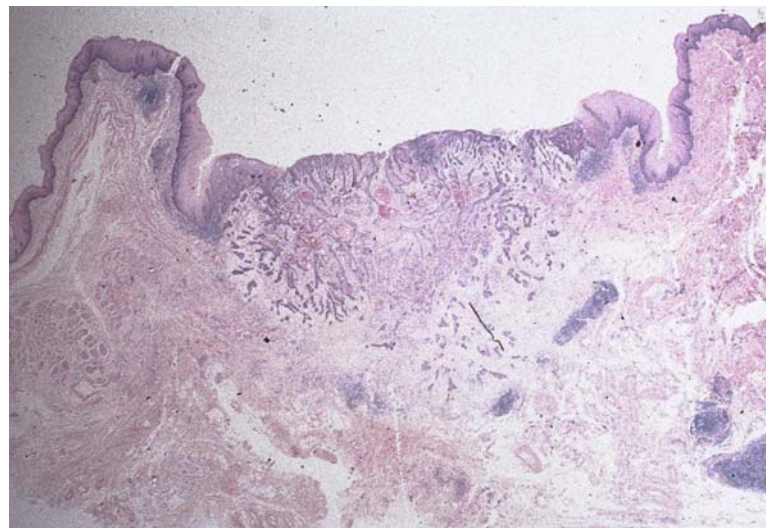


FIG. 8-9. Squamous cell carcinoma within an esophageal diverticulum (histological appearance of the carcinoma shown in Fig. 8-8). The carcinoma is located at the base of the diverticulum

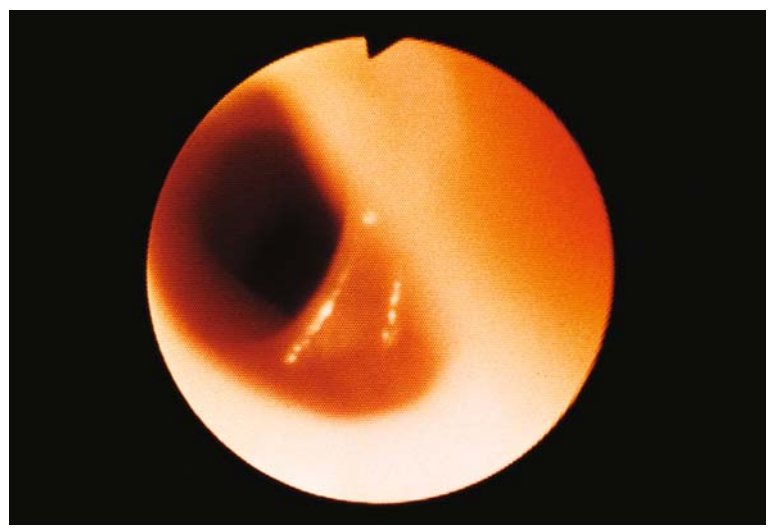


FIG. 8-10. Endoscopic appearance of an esophageal web. The web appears as a thin membrane

anterolateral wall and sometimes assume a circular shape (Nosher et al.). Esophageal webs occur more frequently in women than men, and affected patients usually present with dysphagia. Although it has been reported that there is little difference in the incidence of esophageal webs between Japan and Western countries (Suzaki), they are generally considered to be rare in Japan.

It is said that some esophageal webs are congenital, whereas others are acquired. Congenital esophageal webs are usually largely asymptomatic and of little clinical significance, but they have been described to cause the regurgitation of saliva.

Acquired esophageal webs occasionally occur in association with other disorders such as Plummer–Vinson syndrome, dystrophic epidermolysis bullosa (Tidman et al.), previous radiation therapy, or dyskeratosis congenita (Herman et al. 1997; de Roux-Serratrice et al. 2000).

Esophageal webs are rarely subjected to pathological examination, so few reports have described the histological features on biopsy.

An esophageal web is typically about 2 mm in thickness and is covered by squamous epithelium (Clements et al.). The epithelium is nearly normal or shows basal cell hyperplasia with elongation of papillae in the lamina propria (Janisch and Eckardt 1982), resembling the epithelium seen in esophagitis. The stroma may exhibit edema, a chronic inflammatory cell infiltrate, and lymphoid follicles. Webs are said to consist of epithelium and lamina propria only, with no muscularis mucosae (Clements et al.). Some webs found at autopsy have been reported to show no abnormal histological findings.

There have been reports of coexisting esophageal squamous cell carcinoma and esophageal webs; the carcinomas have mainly arisen in mucosa above the webs (Oda et al.).

8.8.1. Plummer–Vinson Syndrome

Plummer–Vinson syndrome is characterized by dysphagia, iron deficiency anemia, stomatitis (oral mucosal atrophy), and acquired upper esophageal webs. This condition was named after Vinson's report in 1922. According to Vinson's descriptions (1922, 1940), the condition was first recognized by Henry S. Plummer in 1912, although he did not publish any scientific papers on it. Textbooks of pathology published in the UK, however, refer to this condition as Paterson–Kelly syndrome, because Paterson and Kelly independently reported it in 1919.

Although considered to be relatively rare in Japan, in contrast to Europe and America, there have been 69 Japanese case reports of this syndrome (Fujii et al. 1983). It is more common in women. The web is often located at the level of the cricoid cartilage or at the level of the fifth or sixth cervical vertebra. Biopsy specimens show hyperplastic squamous epithelium (Fujii et al.).

Squamous cell carcinomas have been reported in patients with Plummer–Vinson syndrome, the tumors particularly arising in the pharynx or esophagus above the web (Chisholm). Severe dysplasia of pharyngeal and esophageal epithelium above the web has also been described. It is considered that systemic factors probably play a more important role in carcinogenesis than mechanical irritation resulting from stenosis by the web (Suzaki).

8.9. Lower Esophageal Ring (Schatzki's Ring)

Lower esophageal ring, or Schatzki's ring, is a circular mucosal ring at the squamocolumnar junction of the lower esophagus. The first report of this condition was that of Schatzki and Gary in 1953. The annular mucosal elevation is covered by squamous epithelium on the esophageal side and by columnar epithelium on the gastric side (Goyal et al.). The pathogenesis remains unclear and is still controversial. Suggested causes have included the reflux of gastric contents, hiatus hernia, congenital abnormality, and the prolonged use of medication (Jamieson et al.).

A relationship between the size of the lower esophageal ring and the incidence of dysphagia has been demonstrated. Follow-up studies of clinical cases have shown that there is often little change in the size of lower esophageal rings over time (Schatzki 1963).

The rings consist of squamous and columnar epithelium, with underlying lamina propria, muscularis mucosae, and submucosa (MacMahon et al.). Acanthosis and hyperkeratosis are seen in the squamous epithelium, but the columnar epithelium is generally unremarkable.

It is known that on rare occasions the upper portion of a lower esophageal ring may spontaneously rupture (Miller et al.).

8.10. Esophageal Mucosal Bridge

Mucosal bridges may extend obliquely or horizontally across the esophageal lumen (Fig. 8-11). The first such case was reported in 1969 by Dafoe and Ross. More recently, incidental mucosal bridges have often been demonstrated at endoscopy, but only a few patients with symptoms attributable to this disorder have been reported. Sixty-five cases of esophageal mucosal bridge have been reported in the Japanese literature and 11 cases in the English literature (Yamashita et al. 1991; Zeniya et al. 1993). The male : female ratio has been about 1 : 1. Multiple lesions were reported in 13 (23%) of the 57 cases reviewed by Zeniya et al. Mucosal bridges usually occur in the mid- and lower esophagus.

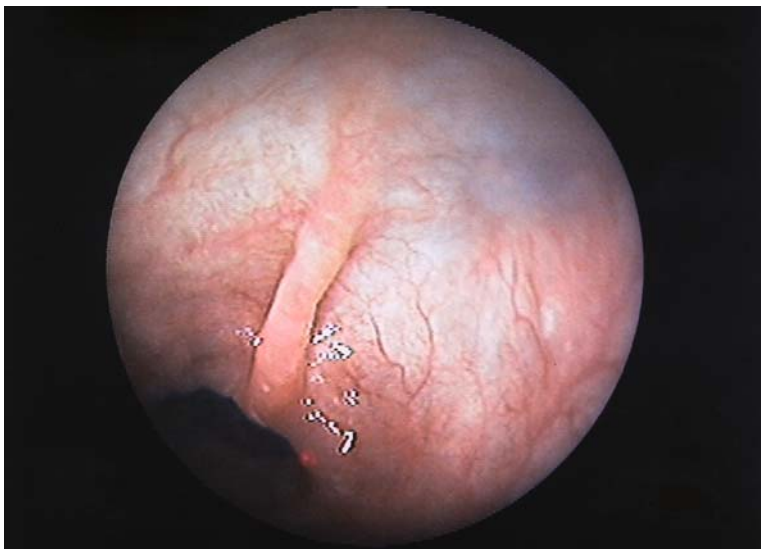


FIG. 8-11. Endoscopic appearance of a mucosal bridge. The mucosal bridge is oriented in the long axis of the esophagus

Mucosal bridges are classified into congenital and secondary types. Congenital mucosal bridges are rare. There have been two reported cases that were associated with esophageal diverticula, and one reported case was associated with a tracheoesophageal fistula. Cases of unknown etiology have often been reported as congenital; however, in most of these, the mucosal bridges have been discovered after middle age.

Secondary mucosal bridges have been associated with reflux esophagitis, Barrett's mucosa (Kogawa et al.), sclerotherapy, hematoma (Handa et al.), malignant tumors, corrosive esophagitis, drug-induced esophagitis, radiation esophagitis, submucosal dissection (hematoma), systemic lupus erythematosus (SLE), dermatomyositis with esophageal ulcer (Zeniya et al.), Mallory–Weiss syndrome, and candidiasis. Yamashita et al. (1991), in a review of 65 cases of esophageal mucosal bridge, found that 13 (20%) had developed after sclerotherapy for esophageal varices, 8 (12%) had resulted from reflux esophagitis, 6 (9%) had resulted from submucosal dissection, 19 (29%) were of unknown etiology, including congenital cases, and 3 (5%) were caused by candidiasis or other miscellaneous causes.

A few cases of coexisting esophageal mucosal bridge and esophageal carcinoma have occurred, but there is not thought to be any etiological relationship between these two conditions.

In one reported autopsy case, the mucosal bridge consisted of mucosa and submucosa, and showed changes of chronic esophagitis (Kogawa et al.). Smooth muscle fibers were observed in mucosal bridge in a case reported by Handa et al. Biopsy specimens from mucosal bridges have shown normal histology, epithelial hyperplasia, and esophagitis.

8.11. Aortoesophageal Fistula

Around 30% of aortoesophageal fistulae result from an aortic aneurysm (Fig. 8-12). The other reported causes have included foreign body, malignancy (see Section 2.2.5), radiation, postoperative state, esophageal ulcer caused by gastroesophageal reflux disease or food stasis from kyphosis (Fig. 8-13), esophagitis, tuberculosis, and esophageal diverticulum.

Of 1604 Japanese cases of aortic aneurysm rupture, 24 (1.5%) demonstrated an aortoesophageal fistula (Hamaya et al.). In another series, endoscopy was performed in 22 of 25 cases of aortoesophageal fistula; hemorrhage only was confirmed in 6 cases, an ulcer was seen in 3 cases, external compression was seen in 4 cases, and a submucosal tumor was seen in 9 cases. Approximately 100 cases of aortoesophageal fistula resulting from an esophageal foreign body have been reported since 1818 (Fukunaga et al. 1989).

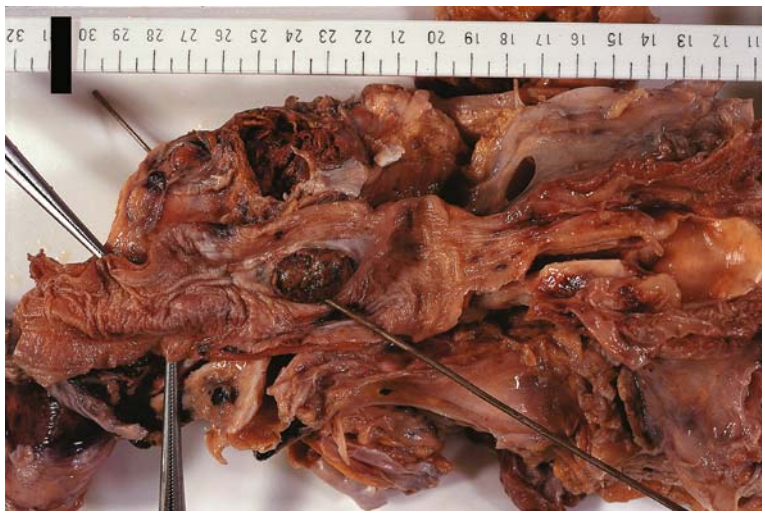


FIG. 8-12. Macroscopic appearance of an aortoesophageal fistula in a patient with an aortic aneurysm. There is a dark red mass in the esophagus. This patient died of bleeding from the aortoesophageal fistula into the esophageal lumen

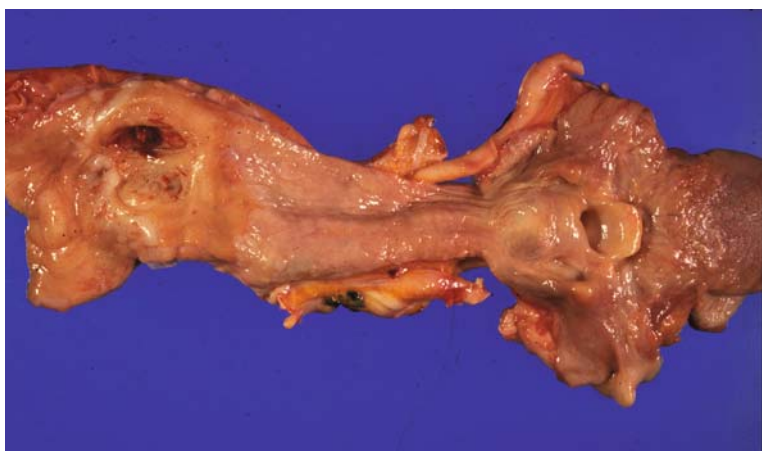


FIG. 8-13. Macroscopic appearance of an aortoesophageal fistula in a patient with a chronic esophageal ulcer that resulted from chronic food stasis because of severe kyphosis. A wide erosion and deep ulcers are seen in the dilated esophagus. This patient died of bleeding from the aortoesophageal fistula into the esophageal lumen. No Barrett's mucosa is seen

Figure 8-12 shows the macroscopic appearance of an aortoesophageal fistula from a patient with an aortic aneurysm. There is a dark red mass in the esophagus. This patient died of bleeding from the aortoesophageal fistula into the esophageal lumen.

Figure 8-13 shows an aortoesophageal fistula that occurred because of an ulcer from chronic food stasis; this was an autopsy specimen from a 76-year-old woman with kyphosis (Ro et al. 2004). Bacterial colonies and tissue necrosis were seen in the fistula.

At endoscopy, aortoesophageal fistula usually appears as a dark red mass with pulsation, and macroscopically there is a dark red mass in the esophagus.

8.12. Other Miscellaneous Disorders

Cases of retroperitoneal fibrosis causing esophageal varices (Mitchell) or obstruction of the lower esophagus (Nelson et al.) have been reported.

There has also been a reported case of intraesophageal pneumatosis cystoides, which resulted in stenosis of the lower esophagus (Vanasin et al.).

Esophageal stenosis or obstruction resulting from an abnormal vascular ring has also been described (Beachley et al.), and a case of esophageal bezoar has been reported (2004).

Chapter 9
Benign Epithelial Tumors and Tumor-Like Conditions

9.1. Retention Cyst, Esophageal Intramural Pseudodiverticulosis (Cystic Esophagitis)

The excretory ducts of the esophageal glands proper extend from the lamina propria to the submucosa. These ducts may form retention cysts (Fig. 9-1), containing mucus or contrast material evident on esophagogastrography (Fig. 9-2). The cysts form elevated lesions, evident from the mucosal aspect. Six cases of esophageal retention cyst have been reported (Furukawa et al. 1998); these cysts measured up to 3 cm in size.

FIG. 9-1. Macroscopic appearance of a retention cyst of the excretory duct of an esophageal gland proper

Multiple cysts may form, mainly in the submucosa, in association with esophagitis or other disorders; this condition is called intramural pseudodiverticulosis and has characteristic radiographic features (Fig. 9-3).

The pathological features of esophageal intramural pseudodiverticulosis have been long known. According to Piazza and Palma (1977) this entity was reported as early as 1899, in Germany and Italy, under the name cystic esophagitis. The characteristic esophagographic features, however, were not described until 1960 (Mendl et al.). Even though the condition is relatively rare it is becoming widely known, and more than 100 cases have been reported to date; these published reports have focused mainly on the esophagographic features. A review by Sabanathan et al. (1985), which covered 97 cases, and a report by Kim et al. (1989), have been cited frequently in subsequent papers, but the classic original articles from Germany and Italy are rarely cited.

Although intramural pseudodiverticulosis most frequently occurs in the seventh and eighth decades, pediatric cases have also been reported. It is slightly more common in men than in women. There have been reports of intramural pseudodiverticulosis coexisting with Barrett's esophagus and with *Candida* infection (Sabanathan et al.).

Intramural pseudodiverticulosis has been attributed to reflux esophagitis and to the retention of food resulting from esophageal stenosis caused by

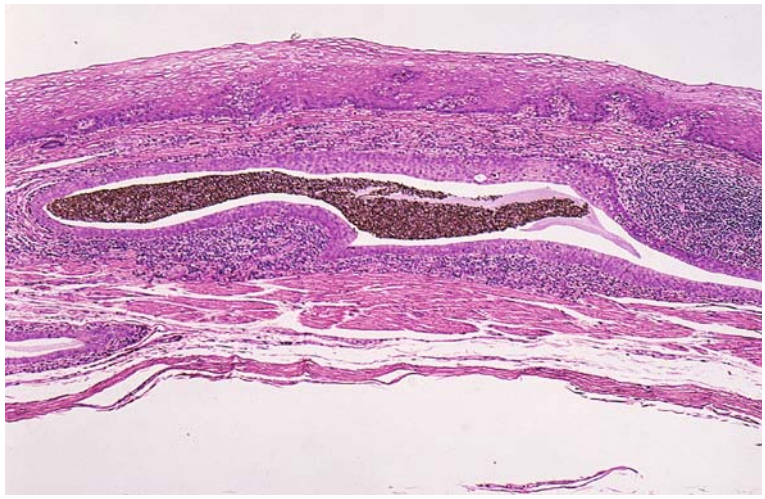


Fig. 9-2. Retention cyst of the excretory duct of an esophageal gland proper. The duct is enlarged and contains contrast medium

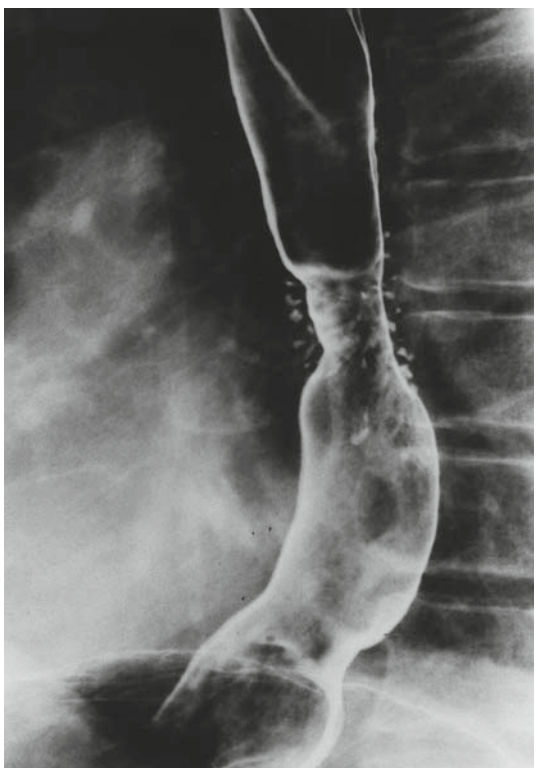


Fig. 9-3. Esophagogram of esophageal intramural pseudodiverticulosis

corrosive esophagitis, but these may not be the only causes (Muhletaler et al.). One report concluded that it results from dilation of the excretory ducts of the esophageal glands proper following inflammatory obstruction, and another stated that it sometimes occurs in association with diabetes mellitus (Iguchi et al.).

Treatment of inflammation and esophageal stenosis usually results in a favorable clinical outcome, but a few cases of perforation have been reported (Murakami et al.; Kim et al.; Rahlf et al.). There have been very few published autopsy reports of the condition (Umlas and Sakhuja).

In esophageal intramural pseudodiverticulosis, the orifices of the excretory ducts are reported to be macroscopically red and slightly raised above the surrounding mucosa, but the scarcity of autopsy reports has meant that only a few papers have described the macroscopic features.

Histology of biopsy specimens often shows only esophagitis, without evidence of cysts. In the cases this author has seen that even multiple biopsies performed on separate occasions have shown only esophagitis. According to published reports, the multiple cysts are mainly located in the submucosa and often contain mucus, inflammatory cells, and exfoliated ductal epithelial cells. There is often also squamous metaplasia of the ductal epithelium (Fig. 9-4).

It is recommended that this condition be renamed to better reflect its true nature; more suitable names would be cystic esophagitis or multiple ductal cysts of the esophageal glands proper.

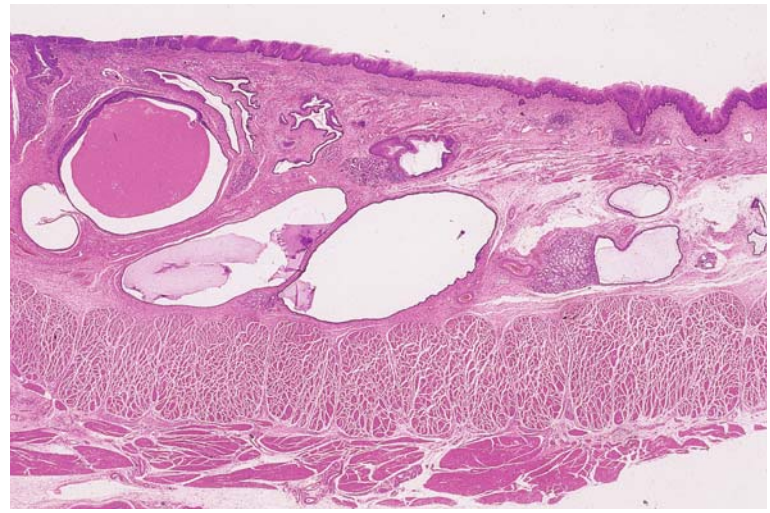


Fig. 9-4. Intramural pseudodiverticulosis. Many cystically dilated ducts of esophageal glands proper are seen in the submucosa. The ducts contain inspissated mucus

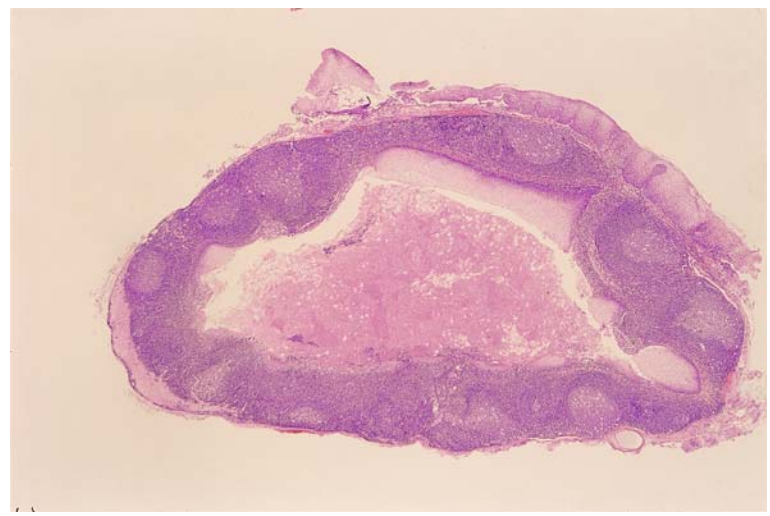


Fig. 9-5. Lymphoepithelial cyst. The cyst contains keratin and is lined by stratified cuboidal epithelium. It is surrounded by lymphoid tissue in which there are multiple follicles

9.2. Lymphoepithelial Cyst

A case of esophageal lymphoepithelial cyst has been reported (Asami et al. 2006) and this is illustrated in Figs. 9-5 and 9-6. This lesion is a counterpart of lymphoepithelial cysts that sometimes occur in the salivary glands, thyroid, and lung. The cyst contains keratin and is lined predominantly by flat stratified squamous epithelium but also focally by stratified cuboidal epithelium. It is surrounded by lymphoid tissue in which multiple lymphoid follicles are seen.

9.3. Squamous Papilloma

The first case of a histologically confirmed esophageal squamous papilloma is said to have been reported by Adler et al. in 1959 (Nuwayhid et al.). There had, however, been other case reports before this. Although esophageal squamous papilloma has long been known as an entity it is extremely rare, and only about 40 case reports have been published to date. On the other hand, reviews of autopsy series have described the presence of esophageal squamous papillomas in 2 of 7

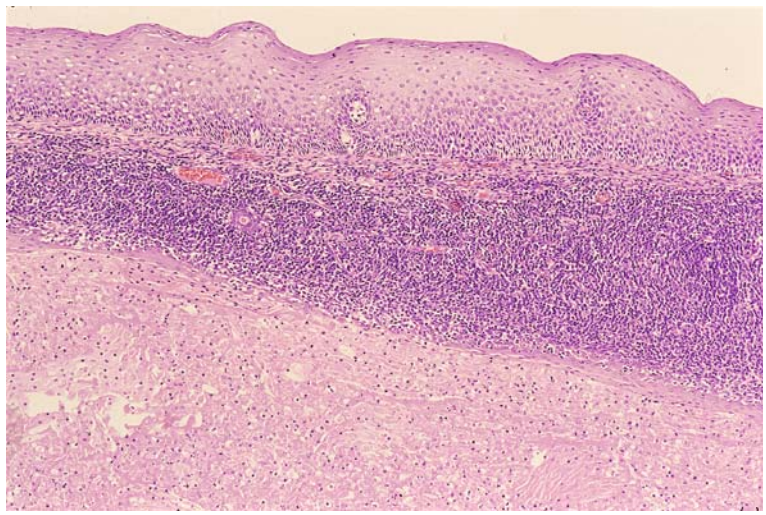


FIG. 9-6. Wall of lymphoepithelial cyst. The cyst is lined by benign flat stratified squamous epithelium. The cyst contains keratin and is surrounded by lymphoid tissue

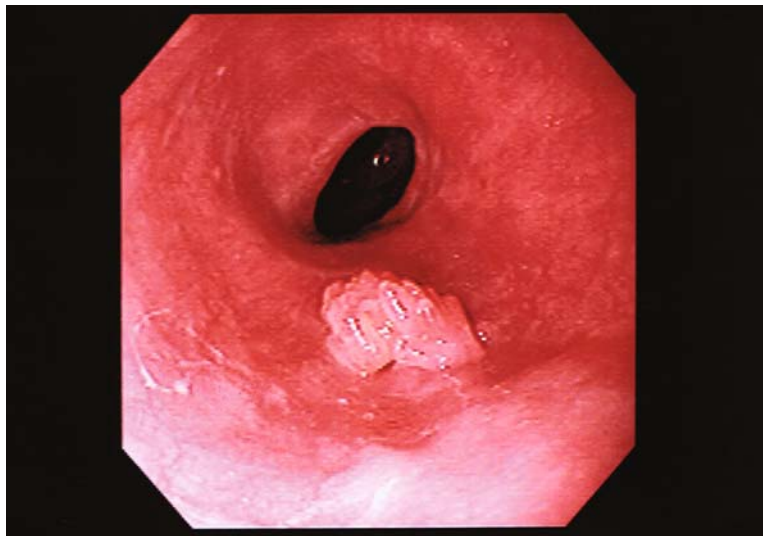


FIG. 9-7. Endoscopic appearance of an esophageal squamous papilloma. A cauliflower-like elevated lesion is seen on the esophageal mucosa

459 cases (Moersch and Harrington) and in 3 of 19 982 cases (Plachta). Another study described esophageal squamous papillomas in 0.01–0.04% of all autopsy cases (Odze et al.). Recently there has been an increase in the number of cases reported from Japan, probably due to the increasing use of endoscopy. They have been detected clinically in 0.05% of all endoscopic examinations performed at the Endoscopy Department of the Tokyo Metropolitan Geriatric Hospital (Kino).

Squamous papillomas occur more frequently in men than women (3:1). They are usually pedunculated polyps (Figs. 9-7, 9-8), several millimeters to several centimeters across (Walker), and most often occur in the posterior wall of the lower esophagus. From the dominant site and the high

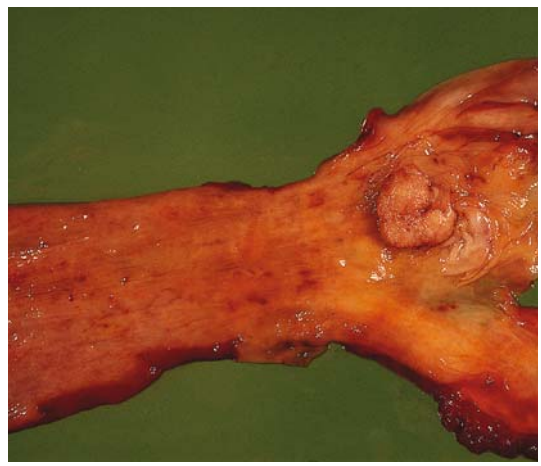


FIG. 9-8. Macroscopic appearance of a squamous papilloma in the proximal esophagus (autopsy case)

incidence of concomitant hiatal hernia, irritation of the esophageal mucosa due to inflammation or some other factor is speculated to be a cause.

Some studies have reported a relationship between esophageal squamous papilloma and human papillomavirus (HPV) infection (Syrjänen et al. 1982; Winkler et al. 1985). A recent study using the polymerase chain reaction demonstrated HPV infection in about half the cases of squamous papilloma examined, and infection by HPV types 16 and 18 was particularly frequent (Odze et al. 1993). Other subtypes of HPV have also been reported in association with esophageal squamous papillomas (Carr et al.). Other studies, however, have failed to demonstrate HPV DNA in esophageal squamous papillomas (Poljak et al.). In this regard, readers are referred to the section on HPV infection of the esophagus (see p. 64).

There have been three cases of squamous cell carcinoma associated with esophageal squamous papilloma reported (Carr et al. 1994), but it is debatable whether squamous papilloma of the human esophagus is a premalignant lesion.

Esophageal squamous papillomas may be subdivided histologically into three types; the exophytic, endophytic and spiked types. The exophytic type is commonest (Odze et al.). Histologically, squamous papillomas consist of vascularized loose stromal tissue and a papillary proliferation of hyperplastic flat stratified squamous epithelium (Fig. 9-9), showing few atypical cells and mitotic figures. There is hyperkeratosis in the spiked type but usually not in the exophytic or endophytic types (Fig. 9-10). It is important to distinguish squamous papillomas from verrucous carcinoma and from acanthosis nigricans. The former is difficult to distinguish from squamous papilloma by endoscopy alone; helpful distinguishing histological features include the presence of epithelial cell atypia in verrucous carcinoma (Fig. 9-11a) and a generally more papillary, arborescent architecture in squamous papilloma. Acanthosis nigricans is a diffuse mucosal lesion.

Squamous papillomas are characterized cytologically by the presence of numerous superficial epithelial cells in a background of abundant neutrophils. It has been reported that there are koilocytes with distinct perinuclear haloes in some cases, suggesting viral infection (De Borges et al. 1986).

9.4. Esophageal Acanthosis Nigricans

Acanthosis nigricans may occur not only in the skin but may also involve the esophageal mucosa. A case of esophageal acanthosis nigricans was reported by Ide and Endo (1984); the patient was a 67-year-old man who also had gastric cancer. Itai et al. (1976) reported two cases of esophageal acanthosis nigricans; one was a 67-year-old man who had gastric cancer, and the other a 58-year-old man who had an esophageal squamous cell carcinoma. Both the skin and oral mucosa were also said to have been involved by acanthosis nigricans in these cases.

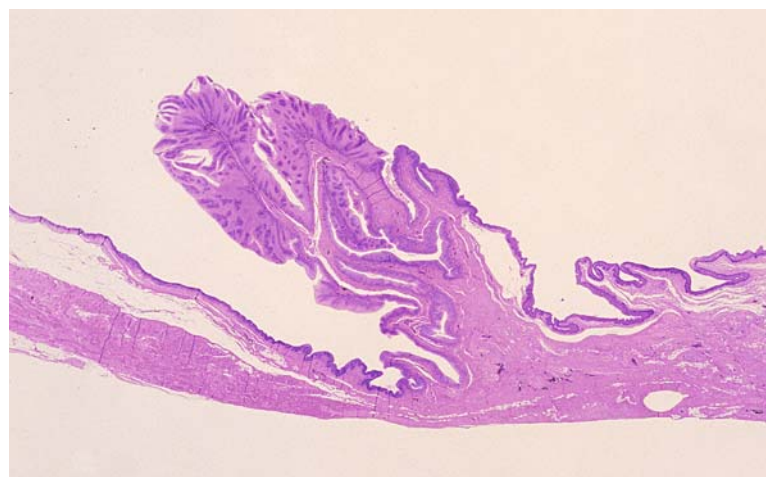


Fig. 9-9. Squamous papilloma at low magnification. An exophytic tumor is seen projecting from the esophageal wall

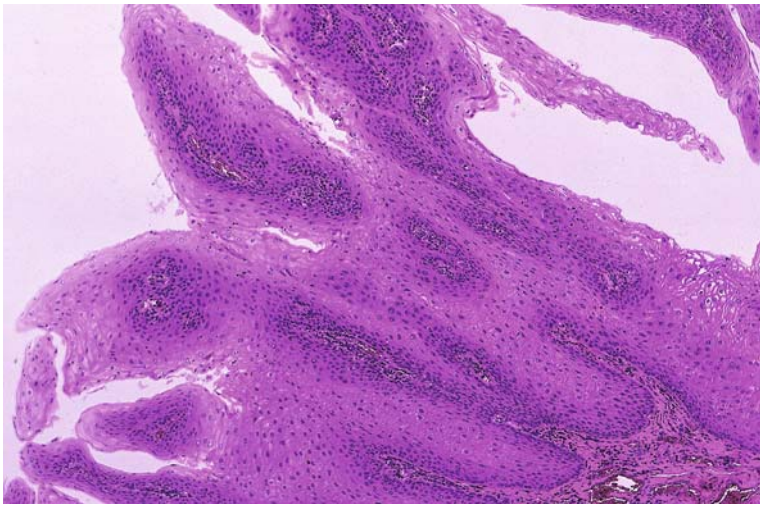


FIG. 9-10. Squamous papilloma. The lesion is composed of markedly acanthotic squamous epithelium

More recently, 12 cases (9 males, 3 females) of acanthosis nigricans of the esophagus have been reported from Japan (Yokoyama et al. 2004). The patient ages ranged from 58 to 83 years (mean, 67). Their malignancies comprised 9 gastric carcinomas, 1 esophageal carcinoma, 1 carcinoma of the renal pelvis, and 1 patient who had both a gastric and an esophageal carcinoma. In 4 of the cases, the acanthosis nigricans abated after treatment of the carcinoma.

An esophagogram shows small irregular papillary tumors. Endoscopically, multiple papillary protruded lesions with white apices are observed in the entire esophageal mucosa (Fig. 9-11b). Judging from the published color photograph of the esophagus taken at autopsy, the esophageal mucosa was white and finely granular. Distinctive histological findings included epithelial hyperplasia and papillomatosis, but there did not seem to be any pigmentation (Fig. 9-11c). Acanthosis nigricans also involved the lips and oral mucosa in this case but no description of the skin was given. Figure 9-11b,c was obtained from a patient reported by Yokoyama et al. 2004.

9.5. Hyperplastic Polyp of Ectopic Gastric Mucosa in the Cervical Esophagus

Only four cases of hyperplastic polyp occurring in the cervical esophagus have been reported. Oguma et al. (2005) reported a case of hyperplastic polyp that arose from ectopic gastric mucosa (inlet patch) and was resected endoscopically (Fig. 9-12). The histological appearance of the polyp was similar to that of a gastric hyperplastic polyp, with foveolar hyperplasia and a chronic inflammatory cell infiltrate. Intestinal metaplasia may also be seen in these polyps (Chatelain and Fléjou 1998).

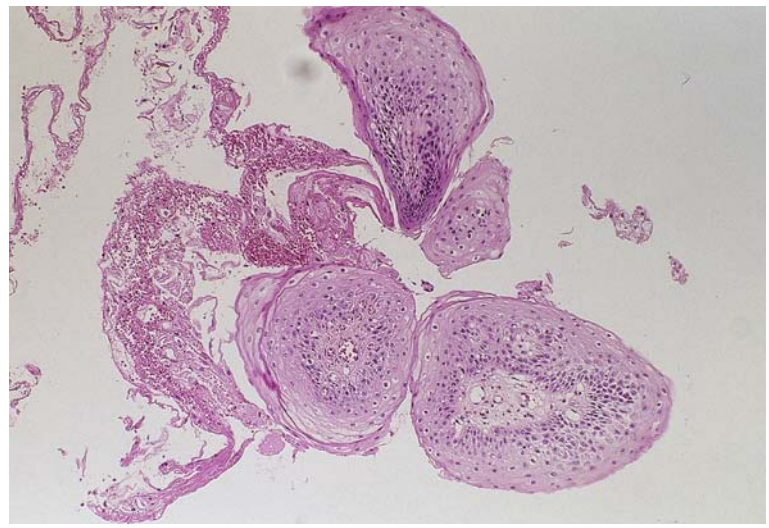
Ectopic gastric mucosa and adenocarcinoma arising in ectopic gastric mucosa in the cervical esophagus have been discussed in Chapters 2 (p. 22) and 12 (p. 209).

9.6. Adenoma

According to a report by Moersch and Broders (1935), the first example of an adenoma of the esophagus (an autopsy case) was reported by Weigert in 1876. Only a small number of cases have been reported since, although a few more cases have been reported recently.

Some examples of esophageal adenoma arising in Barrett's esophagus have been reported (McDonald et al.) but, although adenomatous lesions and severe dysplasia of Barrett's epithelium are considered to often be the precursors of cancer, there is a point of view in Japan that in fact these lesions are themselves very well differentiated intramucosal adenocarcinomas.

It is possible that islets of ectopic gastric mucosa may sometimes give rise to adenomas, but no actual cases demonstrating such an origin have yet been reported.



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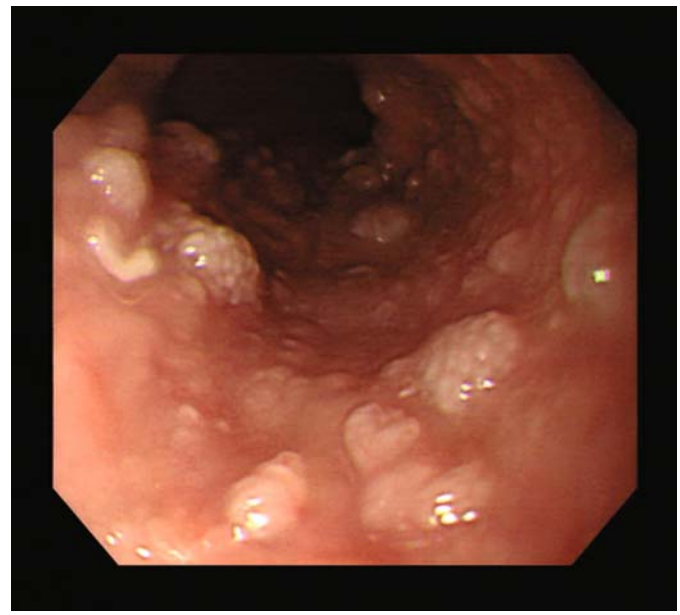

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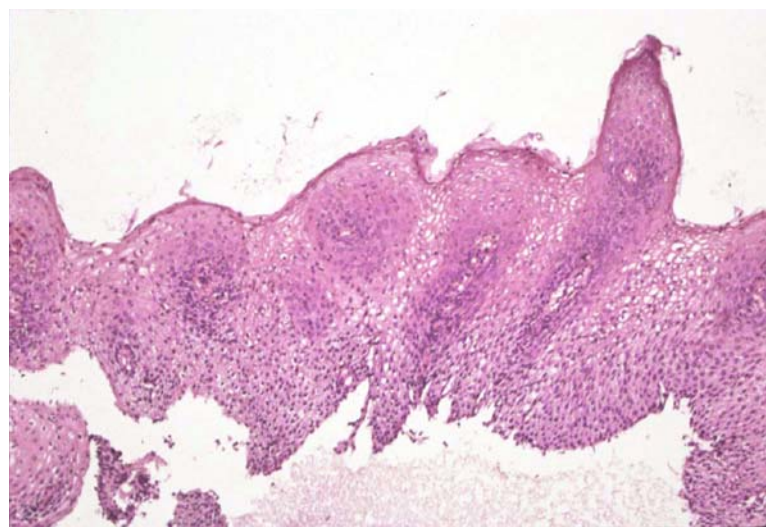


c

FIG. 9-11. **a** Biopsy specimen from an esophageal squamous papilloma. There are no atypical cells evident in the epithelium. **b** Endoscopic appearance of esophageal acanthosis nigricans. The esophageal mucosa is white and finely granular. Multiple protruded papillary lesions with white apices are evident in the entire esophageal mucosa. (From Yokoyama K with permission). **c** Acanthosis nigricans of the esophagus. There are epithelial hyperplasia and papillomatosis without melanosis. (From Yokoyama K with permission)

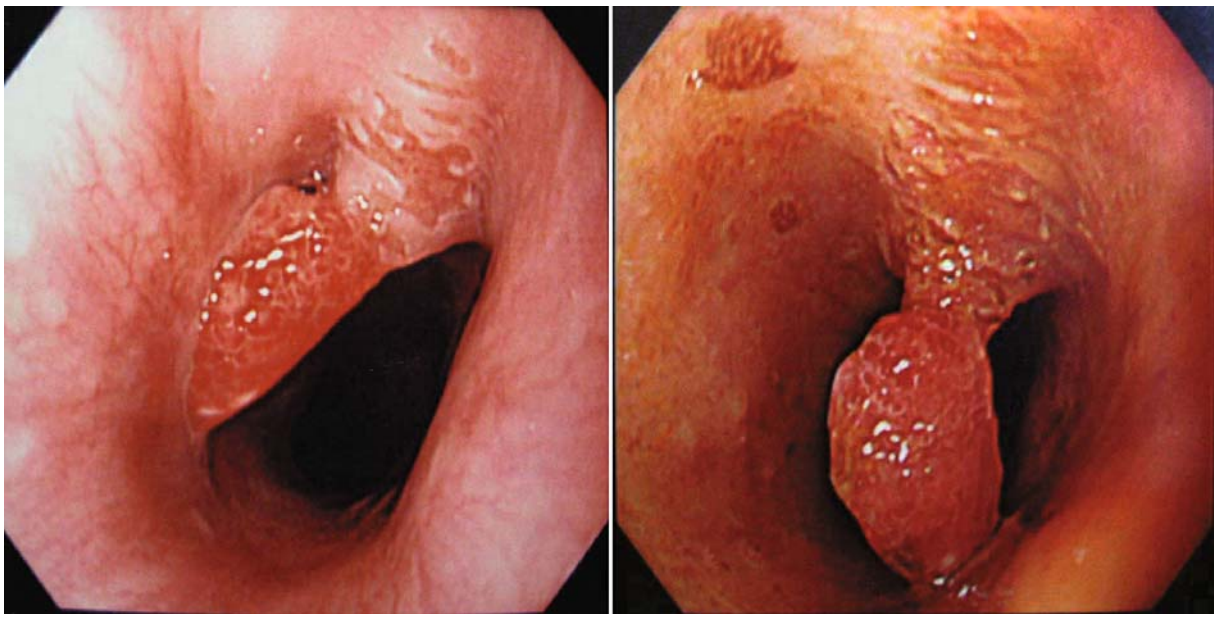


FIG. 9-12. Endoscopic appearance of a hyperplastic polyp of ectopic gastric mucosa in the cervical esophagus. *Left:* The polyp arises from columnar-lined mucosa light red in color. *Right:* After Lugol's iodine staining, the polyp is not stained brown. (Gastroenterol Endosc 2005;61:335–337)

Several examples of esophageal adenoma presumed to have arisen in the esophageal glands proper have been reported. Tumors reported by Moersch and Broders, and by Spin, were situated in the lower esophagus, and the published photomicrographs show well-differentiated tubular structures lined by columnar epithelium. Lesbros et al. (1981) reported a case that was said to have had the same histological appearance as that of a "bronchial adenoma." Moreover, two other rare types of adenoma have been reported in the esophagus: an oxyphilic adenoma (oncocytoma) of the cervical esophagus in an 86-year-old woman (Mansour et al. 1986), and a pleomorphic adenoma of the cervical esophagus in a 26-year-old man (Banducci et al. 1987). Another tumor from a 77-year-old man, reported from Japan, showed features of a serous cystadenoma (Tsutsumi et al.); this measured 10 mm in diameter and was located in the lamina propria. It was resected endoscopically, and its histological appearance suggested an origin from the excretory duct of an esophageal gland proper. The present author and colleagues reported a case of coexisting squamous cell carcinoma and esophageal adenoma (8×6 mm), in a 58-year-old man. There was no Barrett's epithelium with the adenoma, and this represented the 10th reported case of an esophageal adenoma that lacked Barrett's epithelium. Rouse et al. reported the 11th case (a 15×10 mm tumor in an 88-year-old man) and Su et al. (1998) reported the 12th case (a $10 \times 5 \times 5$ cm tumor in a 70-year-old woman); Su et al. called their tumor a sialoadenoma papilliferum. Two cases of esophageal submucosal adenoma were later reported; Agawa et al. (2003) reported a 71-year-old man with a 15 mm-diameter tumor, and Chinen et al. (2004) reported an adenoma in a 64-year-old woman. Moreover, the 15th case of adenoma (an $11 \times 8 \times 5$ mm tumor in a 60-year-old woman) was recently reported by us (Hayashi et al. 2004). The 16th case (a 13-mm tumor in a 45-year-old man) and 17th case (a 10×7 mm tumor in a 70-year-old man) were also reported (Shirahige et al. 2005; Minamino et al. 2006).

Macroscopically, these tumors, which are presumed to have arisen in the esophageal glands proper, formed rather broad, elevated lesions (Fig. 9-13), sometimes with a surface depression. The tumor reported by Shirahige et al. (2005) exceptionally showed a pedunculated polyp with a papilloma-like granular surface.

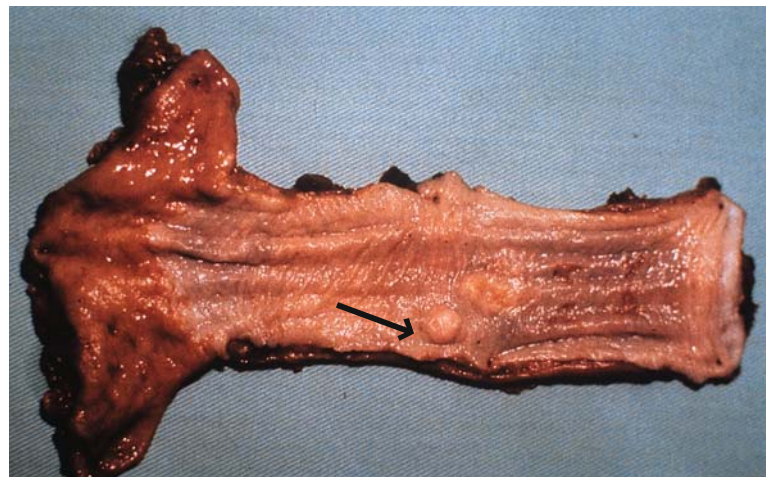


FIG. 9-13. Macroscopic appearance of an esophageal adenoma. The domelike lesion is an adenoma (*arrow*), and the more proximal lesion with a small ulcer is an early squamous cell carcinoma

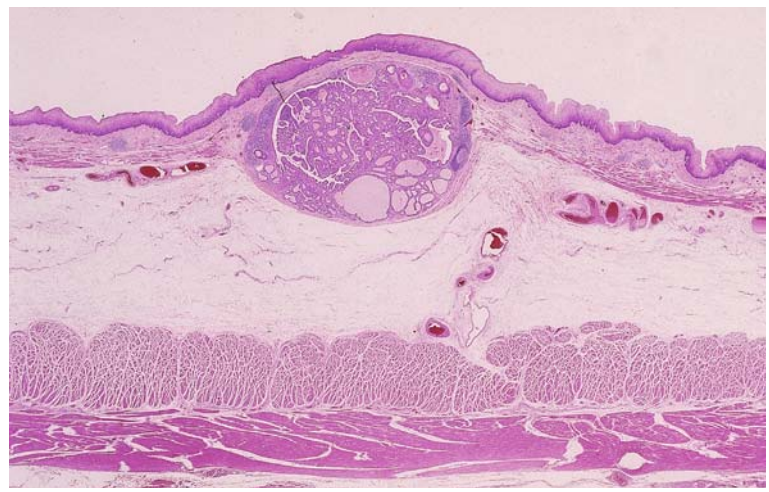


FIG. 9-14. Adenoma at low magnification. The lesion is situated in the submucosa and lamina propria

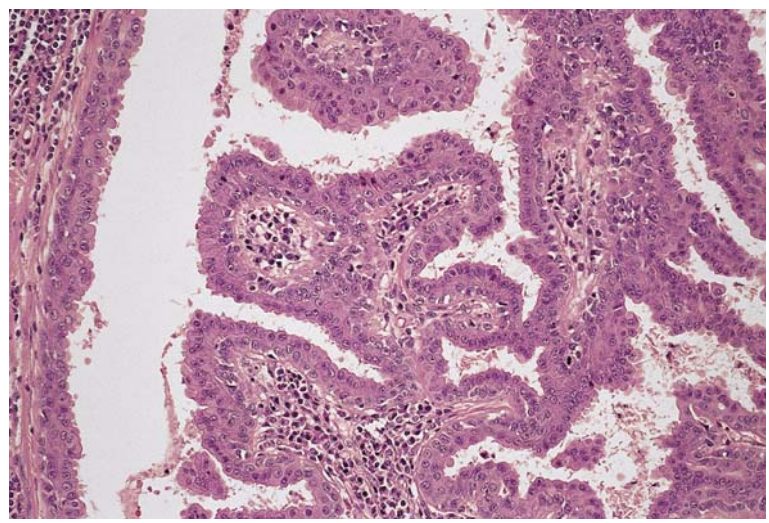


FIG. 9-15. Adenoma. There are characteristic papillary structures covered by a double layer of cuboidal epithelium

Histologically, the tumor in the author's first case was mainly submucosal. It had tubular and papillary structures lined by two layers of cuboidal epithelium, with a resemblance to the epithelium lining the excretory ducts of the esophageal glands proper (Figs. 9-14, 9-15). The stroma was infiltrated by lymphocytes and plasma cells. The tumor resembled an intraductal papilloma of the breast or a syringocystadenoma papilliferum of the skin, further suggesting origin from an esophageal gland proper. Mucin stains demonstrated positive material in gland lumina, but there was very little mucin in tumor cells. Tumor cells were negative for carcinoembryonic antigen (CEA) but positive for secretory component (SC) and lactoferrin, as is the case for the epithelial cells lining the peripheral excretory ducts of the esophageal glands proper. Esophageal adenomas seem to be histologically diverse because this tumor and other reported esophageal adenomas have had varying histological features.

Rouse et al. (1995) reported a similar tumor, however, and demonstrated positivity for smooth muscle actin in the basal layer of the twolayered epithelium lining the tubules and papillae. This indicated myoepithelial differentiation in the basal cells. Myoepithelial cells are present around both acini and ducts in the esophageal glands proper. Rouse et al. noted that their tumor was histologically similar to one which had been reported by Weigert in 1876. This author has encountered four adenomas of the esophagus to date, including the reported tumors, and all four have had a histological appearance similar to that of the tumor reported by Rouse et al.

No data on the cytological or ultrastructural features of esophageal adenomas have been reported.

Chapter 10
Benign Nonepithelial Tumors and Tumor-Like Conditions of the Esophagus

10.1. Xanthoma of the Esophagus

Xanthomas were described in the esophageal mucosa for the first time in 1984 (Remmele and Engelsing). They appear as smooth yellow and slightly elevated lesions (Fig. 10-1a,b) (Stolte and Seifert 1985). Xanthomas were identified in the upper gastrointestinal tract in 17 (0.23%) of a series of 7320 patients who underwent upper gastrointestinal endoscopy (Gencosmanoglu et al. 2004). Of these, 2 (0.03%) had esophageal xanthomas.

Histologically, many xanthoma cells are seen in dilated papillae in the lamina propria, with associated fibrosis and a chronic inflammatory cell infiltrate (Figs. 10-2a, 10-2b). Xanthoma cells show positive staining for CD-68 (Herrera-Goepfert et al. 2003).

10.2. Reflux Gastroesophageal Polyp, Inflammatory Reflux Polyp

Reflux gastroesophageal polyp is caused by reflux esophagitis and occurs at the esophagogastric junction. This entity is described in Section 7.1.6. (p. 89)

10.3. Inflammatory Fibroid Polyp, Inflammatory Fibrous Polyp, and Inflammatory Pseudotumor

This entity, whether found in the stomach or large or small intestine, is known by various terms, but inflammatory fibroid polyp is considered to be the most appropriate name. A few inflammatory fibroid polyps of the esophagus have been reported; these have measured up to 5 cm in diameter. Suzuki et al. (2000) reported 19 cases of esophageal inflammatory fibroid polyp from Japan. Histological examination shows a polypoid tumor consisting of fibrous and granulation tissue with infiltration by neutrophils, eosinophils, lymphocytes, and histiocytes (LiVolsi and Perzin 1975). The surface is covered by squamous epithelium, which may have some erosions. Electron microscopy has shown that the proliferative fibrous tissue is composed mainly of myofibroblasts.

10.4. Pyogenic Granuloma of the Esophagus

Seventeen cases of pyogenic granuloma of the esophagus have been reviewed (Yokomine et al. 2001). Endoscopically, a polypoid mass is covered by a white coating (Fig. 10-3). Macroscopically, pyogenic granuloma is a polypoid mass with a brown cut surface. Histologically, the mass has an eroded surface covered by acute inflammatory cells, with underlying dilated capillaries in loose and edematous fibroconnective tissue. The histological features of this lesion are identical to those of pyogenic granuloma of the skin and oral mucosa (Fig. 10-4a). There are dilated capillaries and granulation tissue with an associated acute and chronic inflammatory cell infiltrate. Pseudomalignant erosive lesion (please see Section 10.7) is occasionally seen in association with pyogenic granuloma (Fig. 10-4b).

One report described a pyogenic granuloma that occurred in Barrett's esophagus (Craig et al.).

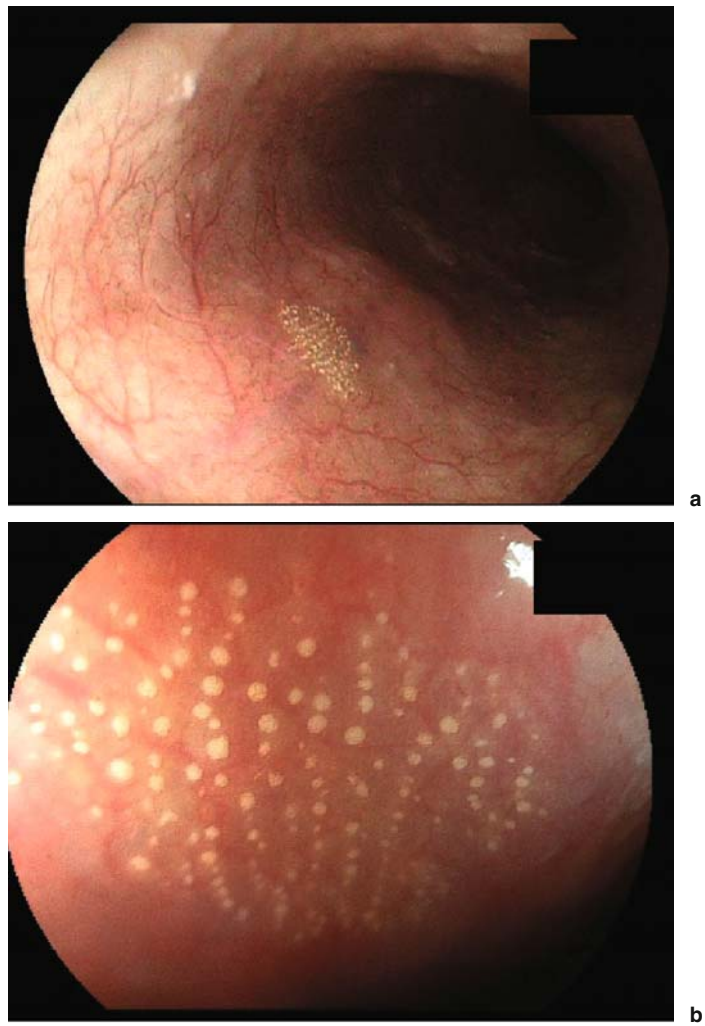
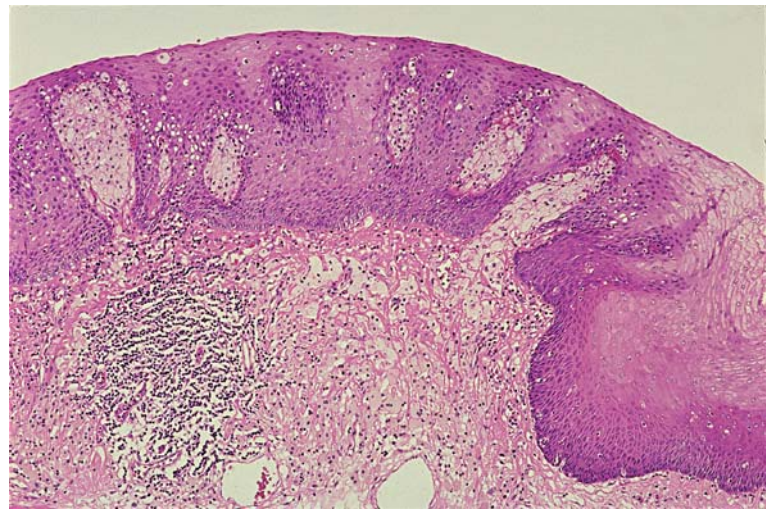


FIG. 10-1. **a** Endoscopic appearance of a xanthoma of the esophagus. Xanthoma shows a localized and elevated area of multiple yellow spots. **b** Endoscopic appearance of a xanthoma of the esophagus (close-up view of **a**). The lesion consists of multiple yellow spots

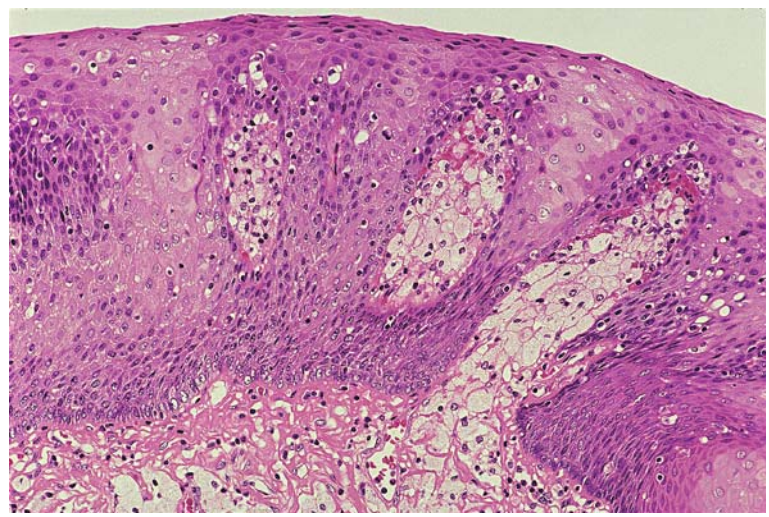
10.5. Fibrovascular Polyp

This entity was initially characterized by Stout and Lattes. Ninety cases of fibrovascular polyp of the esophagus have now been reported (Takeuchi et al. 1995), 18 of them from Japan (Chikuba et al. 1993). The 18 Japanese cases have included 14 men and 4 women. In Western countries, about 85% of fibrovascular polyps have been reported to arise in the upper esophagus, whereas of the Japanese cases 5 arose in the upper, 2 in the mid-, and 11 in the lower esophagus. Most cases occur in adult males, but a 5-month-old girl with fibrovascular polyp has also been reported (Paik et al.).

Fibrovascular polyps may become very large, the largest reported to date measuring 25 × 6 cm (Lodmell). Asphyxia caused by laryngeal obstruction by prolapse of a giant fibrovascular polyp into



a



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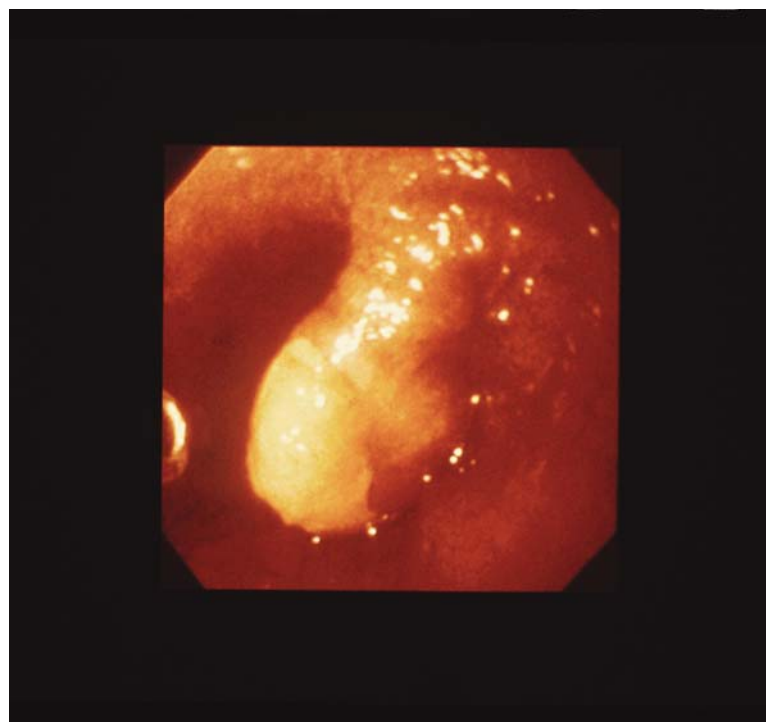


FIG. 10-2. **a** Xanthoma of the esophagus. There are multiple xanthoma cells in dilated papillae in the lamina propria, with associated fibrosis and a chronic inflammatory cell infiltrate. **b** Xanthoma of the esophagus. There are clear xanthoma cells in dilated papillae in the lamina propria, with fibrosis (close-up view of **a**)

FIG. 10-3. Endoscopic appearance of a pyogenic granuloma. The polyp is covered by a white coating. (From Yokomine K with permission)

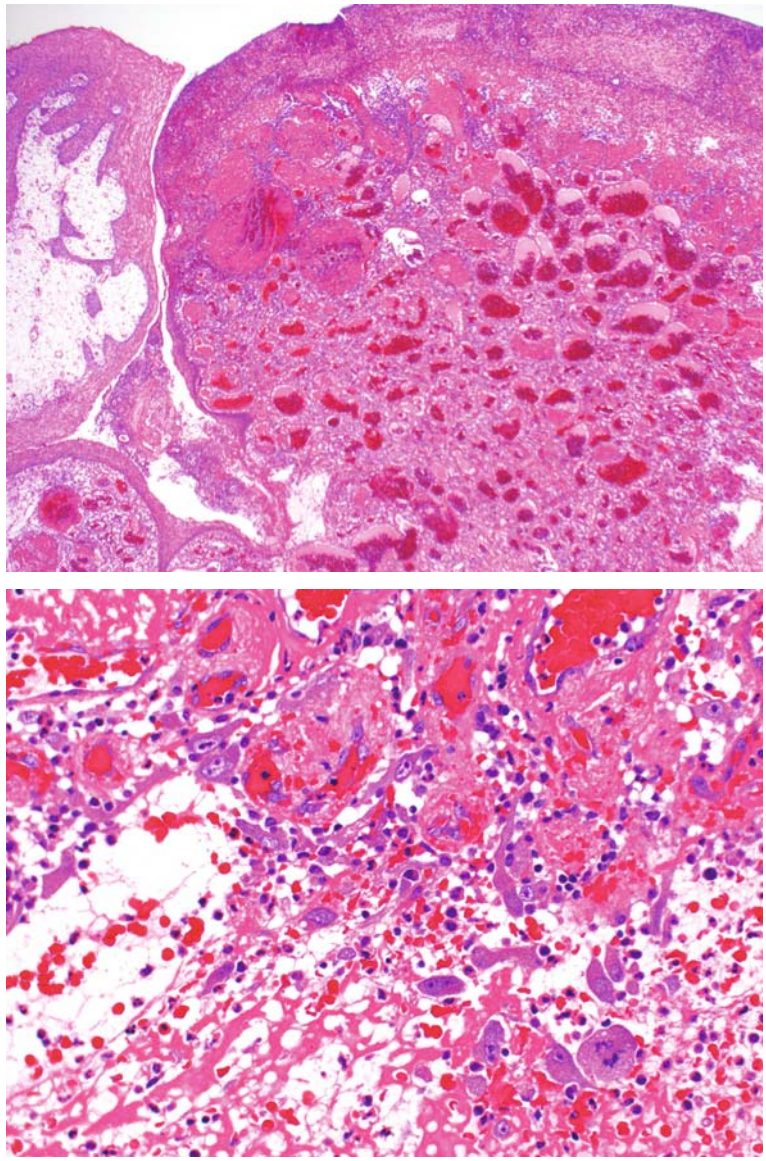


Fig. 10-4. **a** Pyogenic granuloma of the esophagus. There are dilated capillaries in granulation tissue, with overlying squamous epithelium and inflammatory exudate. **b** Pyogenic granuloma of the esophagus. There are atypical cells in eroded areas beneath necrotic debris and inflammatory exudates. These histological findings are consistent with those of pseudomalignant erosion

the hypopharynx has been reported, and this is the most feared complication of this entity.

Fibrovascular polyps are elastic and soft before fixation. Macroscopically, they appear as pedunculated tumors and the cut surfaces have a fibrous appearance with yellow areas (Figs. 10-5, 10-6). Histologically there are numerous dilated arteries and veins in fibroconnective tissue. There is a mild inflammatory cell infiltrate, and the polyps are covered by normal squamous epithelium (Figs. 10-7, 10-8). Surface erosion occasionally occurs, and ossification (Lolly et al.) and smooth muscle fibers (Chikuba et al.) may also be seen.

The nature of this entity is still uncertain, but it is thought to be nonneoplastic. It has been suggested that it begins as a nodular submucosal

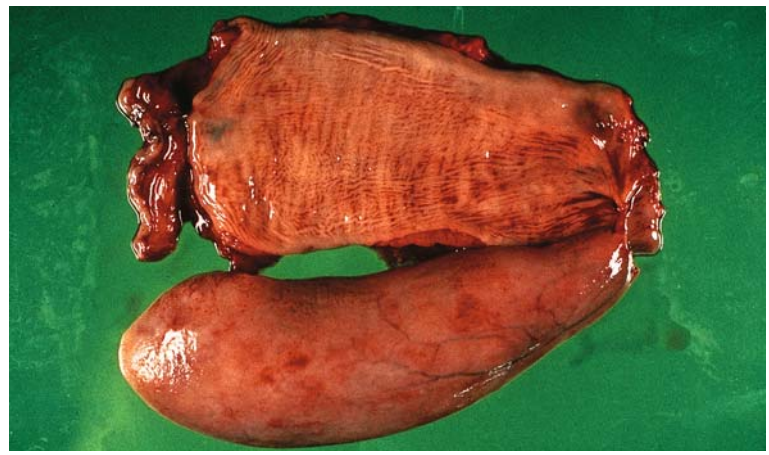


FIG. 10-5. Macroscopic appearance of a fibrovascular polyp of the esophagus. The tumor is pedunculated and covered by normal epithelium

FIG. 10-6. Macroscopic appearance of the cut surface of a fibrovascular polyp of the esophagus. The tumor has a brown fibrous appearance with several yellow areas centrally

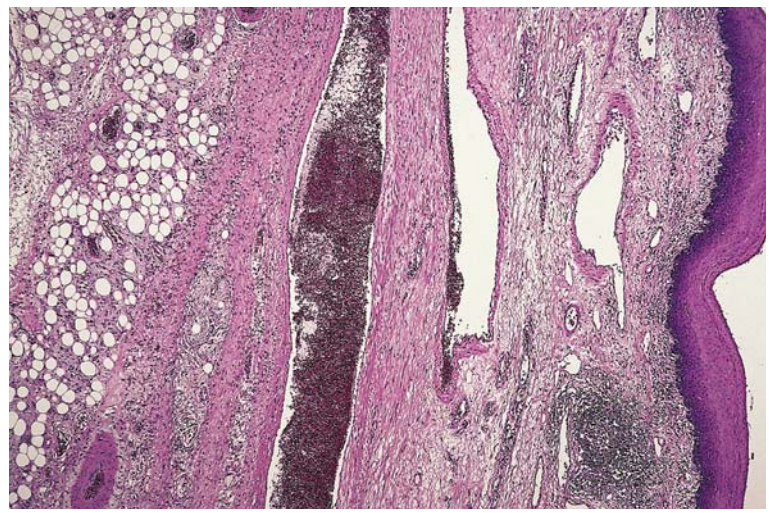


FIG. 10-7. Fibrovascular polyp of the esophagus. Many dilated arteries and veins are evident in the edematous fibrous tissue beneath the stratified squamous epithelium. Mature fatty tissue is seen in the tumor core

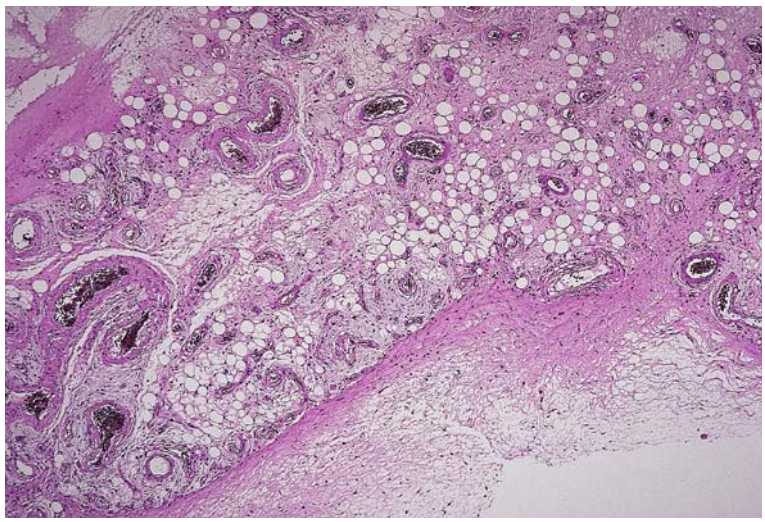


FIG. 10-8. Fibrovascular polyp of the esophagus. Many arteries and veins are evident in the mature fatty tissue in the tumor core

thickening or a redundant fold that enlarges as the result of propulsive forces generated during swallowing (Avezzano et al.), but fibrovascular polyps have been described under the terms fibroma, fibrolipoma, and fibroepithelial polyp. Moreover, most reported cases have contained fatty tissue, and the relationship between fibrovascular polyps and lipomas is unclear. The present author believes that fibrovascular polyps, or most of them, may be lipomas with modified histology, including many vessels and a fibrous stroma, caused by stimulation by esophageal peristaltic movements during swallowing and infection resulting from erosion. Both lipomas and fibrovascular polyps arise predominantly in the cervical esophagus, and fibrovascular polyps have often been reported to have a core of mature fatty tissue. A few cases of fibrovascular polyp and associated squamous cell carcinoma have been reported (Lawrence et al.). Figures 10-5 through 10-8 show the gross and histological features of a fibrovascular polyp from a 43-year-old man, reported by Takeuchi et al. (1995).

10.6. Hamartomatous Polyp

Three cases of esophageal hamartomatous polyp have been reported (Shah et al. 1975). The first, which occurred in a 61-year-old man, was an elevated lesion (4.5 cm in largest dimension) located in the upper esophagus (Fuller). It was covered by squamous epithelium and contained fibroadipose tissue, mucous glands, and retention cysts, but lacked cartilage. The second occurred in a 6-year-old girl; it measured 4 cm in largest dimension and was attached by a broad pedicle to the esophageal wall (Dieter et al.). Histology showed gastric mucosa, respiratory epithelium, cartilage, and adipose tissue. The third, which occurred in a 60-year-old man, arose in the upper thoracic esophagus (Shah et al.). Histology showed cartilage and fat with a covering of flat stratified squamous epithelium.

There has been one case report of an esophageal osteochondroma (p. 143); this could also have been classified as a hamartomatous polyp. A further example of a hamartoma of the esophagus was added by Lakhkar et al. (1991); this tumor did not contain cartilage.

Similar tumors have also been reported as choristoma (Sakurai et al. 1999) and tracheobronchial choristoma (Mahour and Harrison) (see Section 10.15. Osteochondroma).

10.7. Pseudomalignant Erosive and Ulcerative Lesion

Atypical stromal cells with large nuclei may sometimes be found beneath intact or eroded mucosa in biopsy specimens from the gastrointestinal

tract. Called the pseudomalignant erosive and ulcerative lesion, this was first reported in 1982 by Isaacson as an entity that may be confused with malignancy (Figs. 10-9, 10-10). It has only rarely been reported in the esophagus but may occur in association with pyogenic granuloma, reflux gastroesophageal polyp, and inflammatory fibroid polyp. It has also been reported in association with a squamous papilloma of the esophagus (Yuki et al. 1993). Japanese textbooks of gastrointestinal pathology have often given only a cursory description of this lesion, describing atypical cells in granulation tissue that may be confused with carcinoma.

Similar atypical cells are frequently found in superficial stroma beneath surface erosions in hyperplastic polyps of the stomach and in inflammatory polyps or adenomas of the large intestine. The presence of atypical cells in association with these entities, together with an often polypoid endoscopic appearance and the presence of apparent atypical mitoses, may make correct histological diagnosis difficult.

With immunohistochemical stains, the atypical cells are positive for vimentin (Fig. 10-11) but negative for carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), early membrane antigen (EMA), desmin, factor VIII, and α-1-

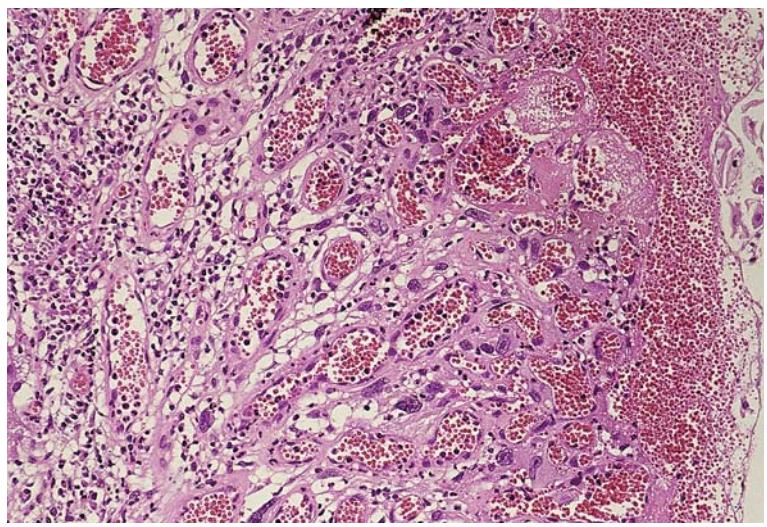


Fig. 10-9. Pseudomalignant erosive and ulcerative lesion. This lesion was found in an inflammatory polyp at the esophagogastric junction. There are cells with large nuclei in the stroma

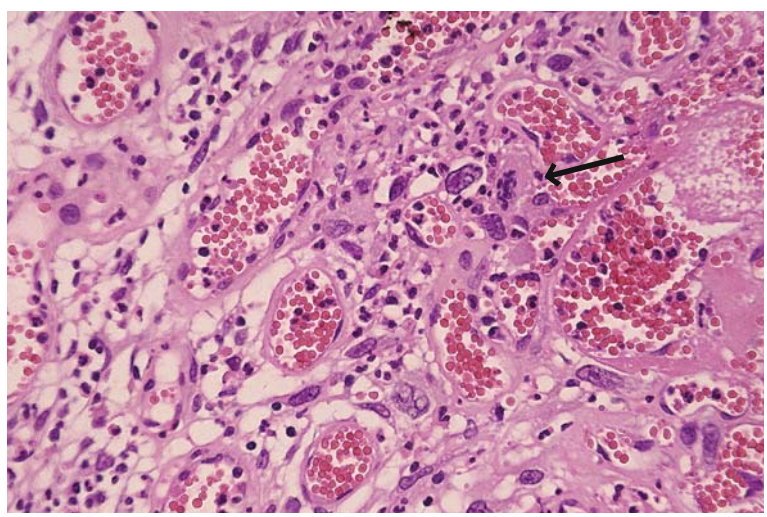


Fig. 10-10. Pseudomalignant erosive and ulcerative lesion. The lesion shows occasional mitotic figures (*arrow*) and giant cells

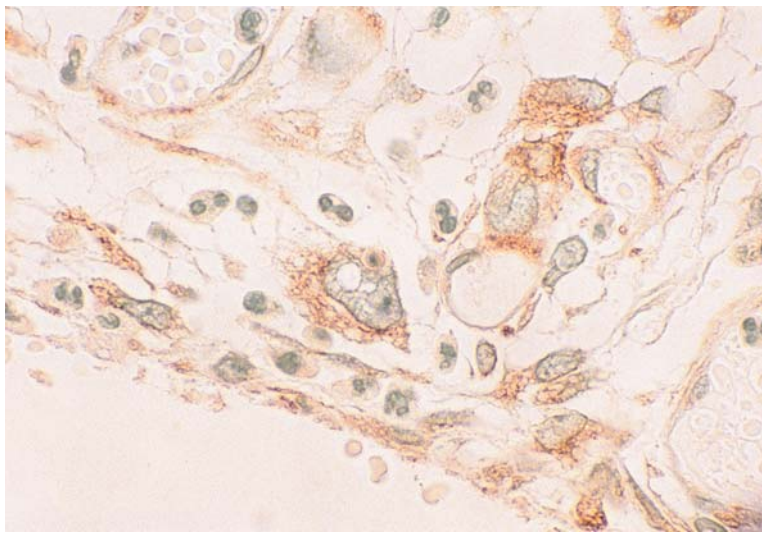


FIG. 10-11. Pseudomalignant erosive and ulcerative lesion (vimentin immunostain). The atypical cells are vimentin positive

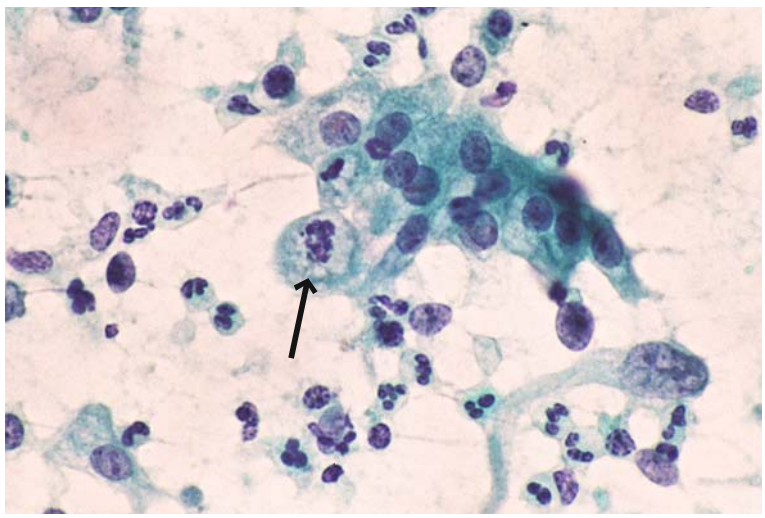


FIG. 10-12. Cytological appearance of pseudomalignant erosive and ulcerative lesion (Papanicolaou stain). A mitotic figure (*arrow*) is evident

antitrypsin. Intranuclear pseudoinclusions, sometimes seen in these cells, are also vimentin positive.

On electron microscopy, there is abundant cytoplasmic rough endoplasmic reticulum. It is suspected that these large atypical cells are myofibroblasts.

This author has seen one example in the esophagus, which occurred in an inflammatory polyp from the esophagogastric junction. In this case, the atypical cells were large and irregular and suggestive of malignancy. Although the chromatin was finely granular and the nuclear membranes only mildly thickened, there were figures suggestive of atypical mitoses.

The atypical cells can be distinguished from the sarcoma-like cells of esophageal carcinosarcoma by the degree of dyskaryosis, but the distinction may sometimes be difficult.

The cytological distinction between this entity and a malignant tumor may be even more difficult. The atypical cells occur in sheets or are dispersed singly, with a background of inflammatory cells. Naked nuclei are occasionally found, may be up to four times larger than erythrocytes, and have a rather coarse chromatin pattern. Mitotic figures are frequent (Fig. 10-12), and variably sized multinucleate cells may be found (Dirschmid et al.).

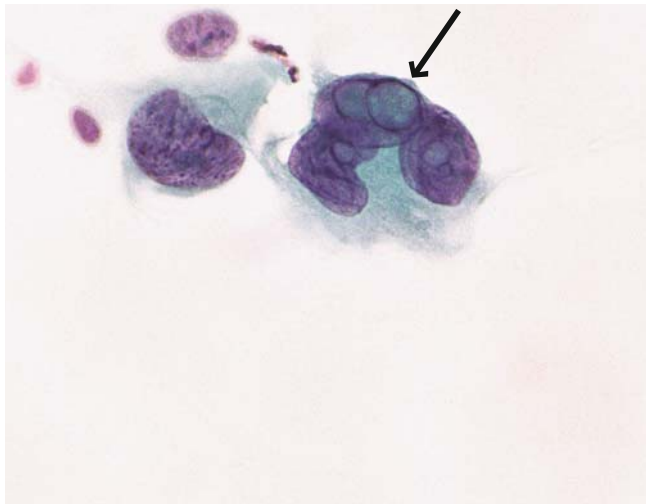


Fig. 10-13. Cytological appearance of pseudomalignant erosive and ulcerative lesion (Papanicolaou stain). Atypical nuclei and intranuclear pseudoinclusion bodies (*arrow*) are evident

Intranuclear pseudoinclusion bodies may also be seen (Fig. 10-13) (Ohno et al.). The possibility of this entity should be borne in mind when biopsies and cytological specimens from the esophagus are examined.

10.8. Leiomyoma

According to a paper by Rose, reports of esophageal leiomyoma can be traced back to 1797. Storey and Adams stated that the first resection of an esophageal leiomyoma was reported in 1932 or 1933. Leiomyoma is the most common tumor of the esophagus. Leiomyomata, including minute ones (seedling leiomyomata), have been found in more than 10% of all this author's autopsy cases (Takubo et al.). The frequency is similar in esophageal cancer resection specimens, almost the same incidence being found in the author's studies of subserial sections of esophagi resected for esophageal cancer.

Esophageal leiomyomata were formerly believed to be rare, as a report pointed out their absence in a series of 4000 autopsy cases (Daniel and Williams 1950). However, Barrett (1964) inferred that many may be overlooked at autopsy. Sweet et al. (1954) suggested that 200–300 autopsy cases should be studied in a precise manner to determine the accurate incidence. In this regard, the present author and coworkers (1981) studied subserial sections of esophagi from autopsy cases and surgically resected specimens and obtained the aforementioned figure of about 10%. This frequency of seedling leiomyoma has often been cited in textbooks of gastrointestinal pathology. Macroscopic examination of the mucosal surface at autopsy failed to detect 92% of the minute leiomyomata in our series. Aside from our observations, Postlethwait and Musser (1974), in an extensive pathological study, reported that esophageal leiomyomata were present in 5.1% of all their autopsy cases. The discrepancy between their percentage and ours seems to be attributable to different methods of observation, as pointed out in their book (1991).

Leiomyomata of the esophagus have been found to most frequently arise in the inner circular muscle layer (74%), followed by the muscularis mucosae (18%), whereas development in the outer longitudinal muscle layer is infrequent (8%). They are often located in the 4-cm-long esophagogastric junction zone (66% of cases), suggesting a relationship to the lower esophageal sphincter, although details of this issue remain unclear. They are more frequent in men than women, the sex ratio being 2:1. Botting et al. (1965) found an esophageal leiomyoma in a 14-year-old girl, but there was not a single instance of an esophageal leiomyoma in a child in this author's autopsy series. Therefore, the author speculates that esophageal

leiomyomata are extremely rare in children. It is not rare for leiomyomata to be multiple; in our series there were multiple tumors in 26% of cases. There are reports of esophageal leiomyomata causing severe disruption to the passage of food (Rubin et al.), and also perforation (Schabel and Rittenberg), but these complications are rare.

Macroscopically, leiomyomata are submucosal (Fig. 10-14). They are nodular and hard (Fig. 10-15) and appear white in color because of their collagen fiber content. Small tumors can often be detected with the naked eye if careful attention is paid to the cut surface of the esophageal wall (Fig. 10-16).

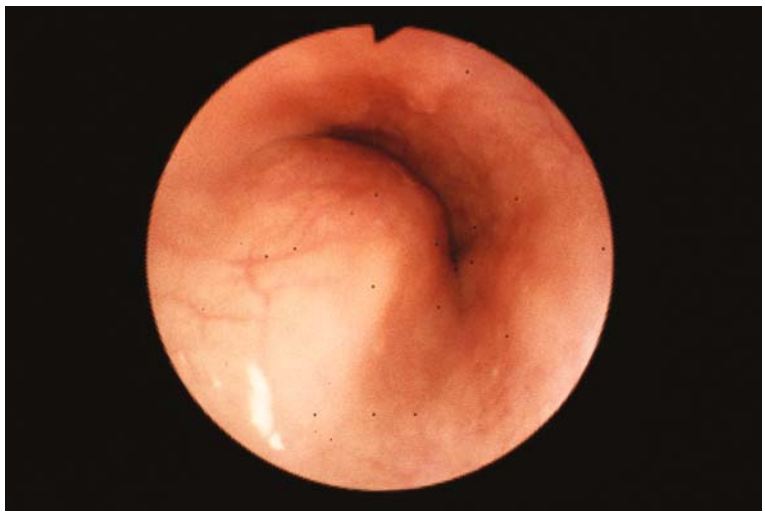


Fig. 10-14. Endoscopic appearance of an esophageal leiomyoma

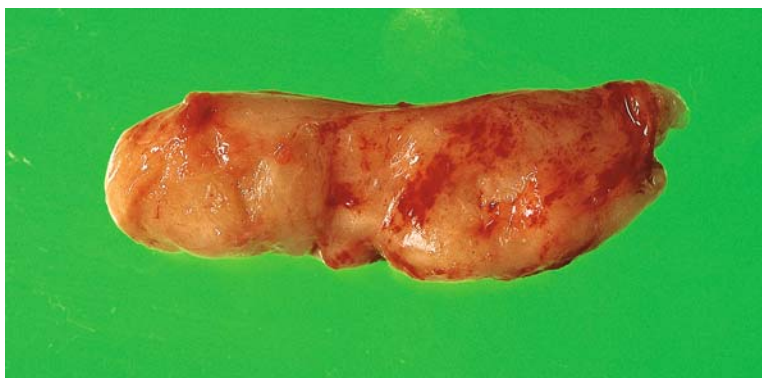


Fig. 10-15. Macroscopic appearance of a leiomyoma (resection specimen)

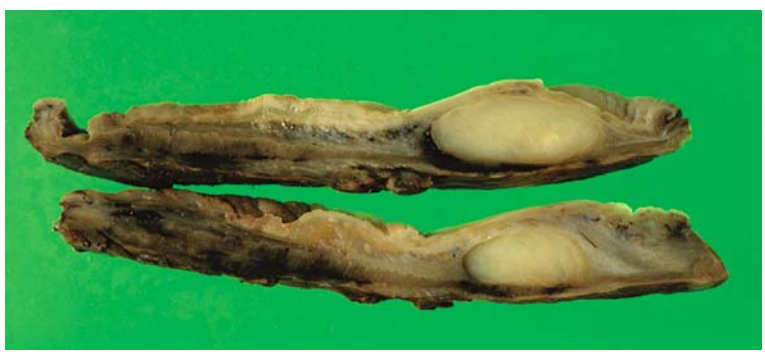


Fig. 10-16. Macroscopic appearance of a seedling leiomyoma. This leiomyoma, with a white nodular appearance, was found incidentally in the lower esophageal sphincter of a patient with an esophageal carcinoma

Histologically, they show an interlacing pattern of spindle-shaped cells with smooth muscle fibers entering from the surrounding muscle layer. There are very few mitoses (Figs. 10-17, 10-18). Calcification is occasionally found. Leiomyoma can often be distinguished from neurilemmoma by the absence of surrounding nerve tissue and by the immunohistochemical profile (desmin positive, S-100 protein negative), but leiomyomata are sometimes desmin negative, and neurilemmomas are sometimes S-100 protein negative. To differentiate gastrointestinal stromal tumor, CD34 and overexpress c-*kit* oncoprotein (CD117) should be checked.

The present author generally bases his assessment of malignancy on the number of mitotic figures (see Section 14.1. Leiomyosarcoma).

In addition to the common leiomyoma, leiomyoblastomas have also been reported in the esophagus (Cantero et al. 1993). These have a mixture of polygonal epithelioid cells, with perinuclear clear cytoplasm, and fusiform cells, and there may be benign and malignant appearing areas within the same tumor. Therefore, careful microscopic sampling is necessary. As for common smooth muscle tumors, the mitotic count allows distinction between benign and malignant tumors of this type, so this author

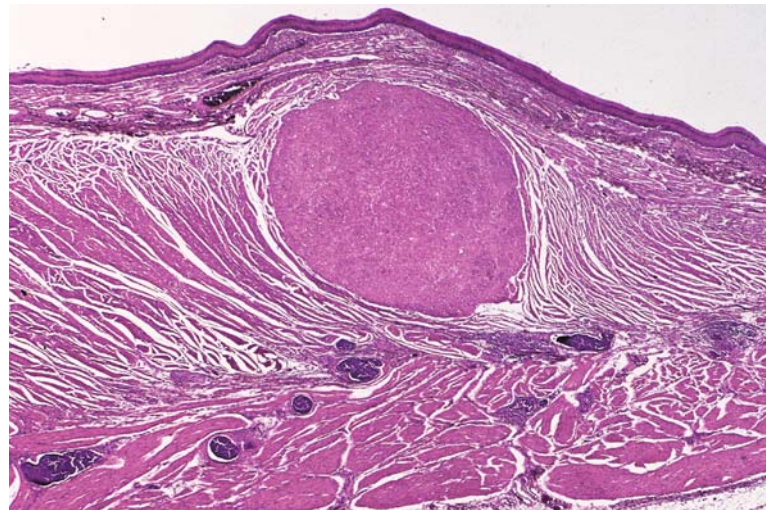


Fig. 10-17. Leiomyoma at low magnification. This tumor is arising in the inner circular muscle layer

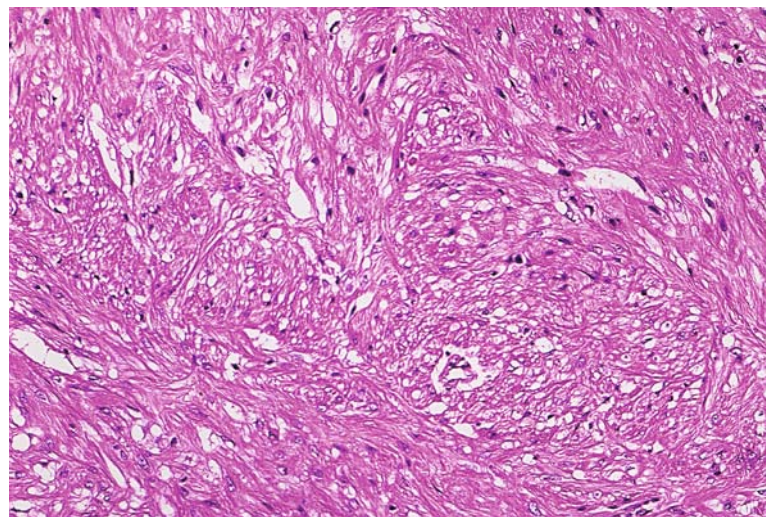


Fig. 10-18. Leiomyoma at high magnification. The tumor cells show an interlacing pattern

considers that there is no need to separately classify leiomyoblastoma from leiomyoma and leiomyosarcoma.

Cytological specimens from cases of esophageal leiomyoma, unlike leiomyosarcoma, often do not include tumor. However, when present, the tumor is seen to consist of regular, cohesive spindle cells with elongated nuclei, fine chromatin, and abundant cytoplasm (Henke et al.) (Fig. 10-19).

Electron microscopy shows features very similar to those of normal smooth muscle. There are spindle-shaped cells with long oval nuclei, and fine actin filaments with frequent areas of focal density. Although there are dense patches along the cell membranes, there are often no intercellular adhesions. The tumor cells have many micropinocytotic vesicles, and each cell is surrounded by a thin basement membrane (Fig. 10-20).

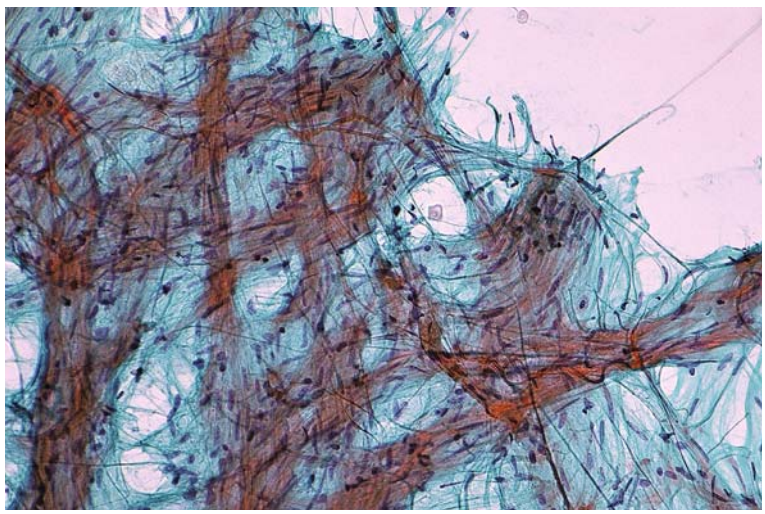


FIG. 10-19. Cytological appearance of a leiomyoma (Papanicolaou stain). The cytological appearance is similar to the histological appearance

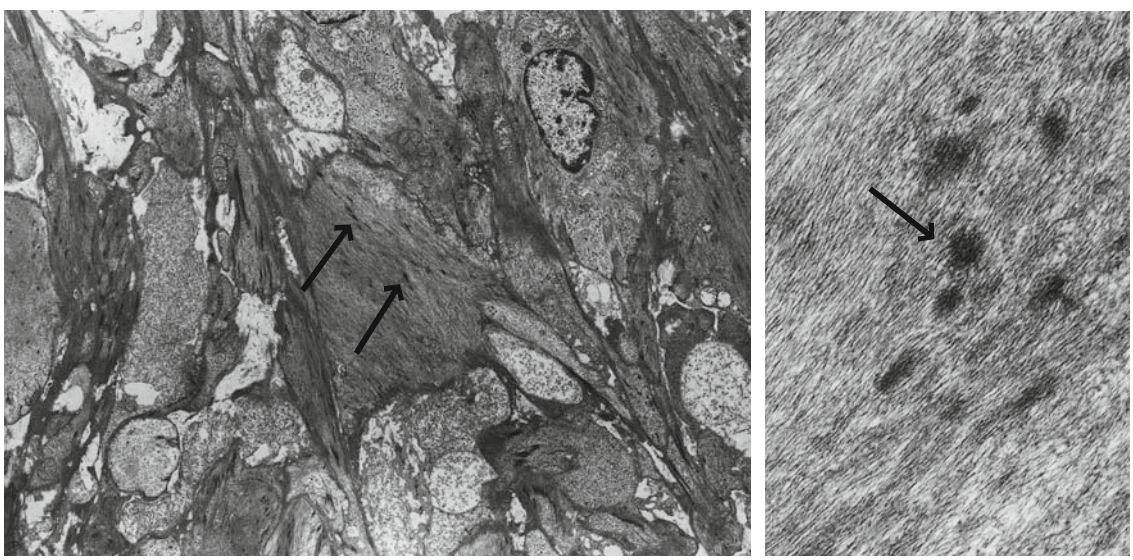


FIG. 10-20. Electron micrographs of a leiomyoma (*left, right*). Many focal densities (*arrows*) are evident in the fine filaments

10.8.1. Leiomyoma and Cancer

Several cases of squamous cell carcinoma arising in mucosal epithelium overlying and elevated by an intramural leiomyoma have been reported. A case showing carcinoma in situ and surrounding dysplasia in epithelium overlying a leiomyoma in the muscularis mucosae has also been reported (Watanabe et al.). Iizuka et al. (1984) reviewed 16 cases of leiomyoma with accompanying esophageal carcinoma that occurred in Japan. This situation is considered to be very rare, there being a similar incidence of esophageal leiomyoma in esophageal cancer patients as in the general population (Takubo et al.). In almost all reported cases, the carcinomas have been of squamous type. Six cases of early carcinoma arising in the mucosa overlying a leiomyoma were reviewed by Mafune et al. (1988). Many were located slightly proximal to the leiomyoma. On the basis of this, Mafune et al. suggested that chemical and mechanical stimulation by food may be involved in the pathogenesis.

Figure 10-21 shows a superficial carcinoma overlying a leiomyoma of the esophagus, resected from one of the patients (a 71-year-old man) reported by Mafune et al. that this author had the opportunity to study. This was a moderately differentiated squamous cell carcinoma, 3.6 cm in largest dimension, which had invaded to the muscularis mucosae. It appeared macroscopically as slightly depressed, superficial, and flat, and arose in mucosa overlying the leiomyoma. The leiomyoma was 3 cm in diameter and was derived from the inner circular muscle layer. This intramucosal carcinoma showed intraepithelial spread, beginning from a site overlying the leiomyoma and extending about 1 cm proximally (Fig. 10-22). The carcinoma had a pushing (rather than infiltrative) invasive margin (Fig. 10-23).

10.9. Diffuse Leiomyomatosis of the Esophagus and Idiopathic Muscular Hypertrophy

10.9.1. Diffuse Esophageal Leiomyomatosis

In diffuse esophageal leiomyomatosis, thickening of the esophageal wall is generally extensive and may involve all the muscle layers.

García-Torres and Guarner described an uncommon association of Alport syndrome (hereditary hematuric nephropathy, sensorineural deafness, and ocular impairment) and leiomyomatosis with a particular distribution that may include the esophagus, trachea, bronchiole, vulva, clitoris, perineum, uterus, and/or urethra (1983). Perirectal involvement has also been reported (Guillem et al. 2001). García-Torres and Orozco reviewed 38 cases of familial and sporadic Alport-leiomyomatosis syndrome (1993). The male:female ratio was 14:24. Muscular hypertrophy of the esophageal wall was observed in all 38 cases and was sometimes also seen in the gastric cardia. Many of

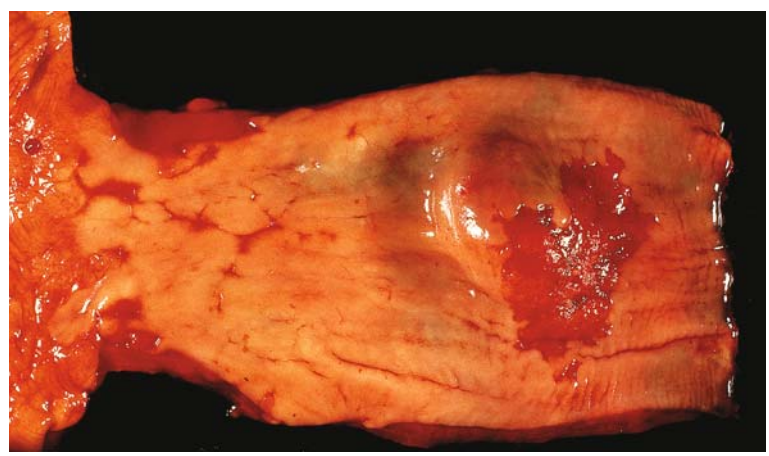


Fig. 10-21. Macroscopic appearance of an intramucosal carcinoma overlying a leiomyoma. There is a superficial carcinoma of the slightly depressed, superficial flat type just proximal to the leiomyoma

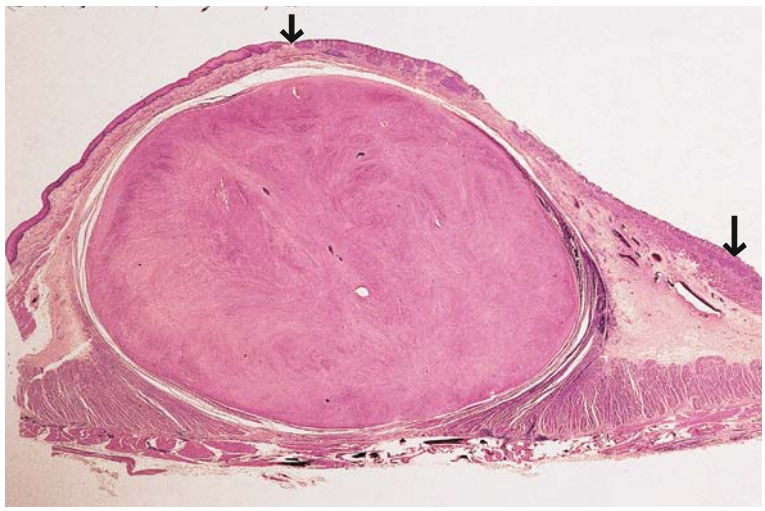


FIG. 10-22. Leiomyoma and intramucosal carcinoma at low magnification. There is a superficial carcinoma (slightly depressed, superficial flat type) overlying and just proximal to a leiomyoma that is arising in the inner circular muscle layer. The carcinoma is situated between the two *arrows*

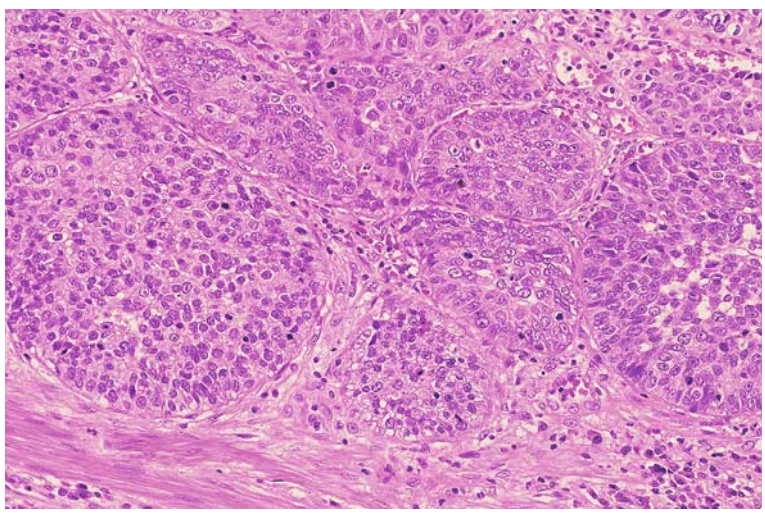


FIG. 10-23. Intramucosal carcinoma overlying a leiomyoma. The carcinoma shows expansile growth

the patients had an initial diagnosis of achalasia. Partial or total resection of the affected esophagus is the treatment of choice.

Genetic analyses of these cases have demonstrated a large deletion at the COL4A5–COL4A6 locus, which includes genes encoding for the α5 and α6 chains, respectively, of collagen IV. Cosegregation of diffuse leiomyomatosis and the X-linked Alport syndrome has been documented in most male cases.

The hypertrophy of the esophageal wall is concentric and is particularly distinct in the inner circular muscle layer of the muscularis propria (Fig. 10-24). The outer longitudinal muscle layer and muscularis mucosae are also hypertrophic in some cases (Figs. 10-25, 10-26). The mean thickness of the normal esophageal wall is 4.4 mm and that of the muscularis propria is 3.2 mm (Gocho et al.), but in this condition the wall thickness may exceed 20 mm. Figures 10-24 through 10-26 are macroscopic and histological photographs of the case reported by Matsuoka et al. in which the thickness of the esophageal wall exceeded 25 mm. In this case there was prominent hypertrophy of the inner circular muscle layer, the outer longitudinal muscle layer was also hypertrophic, and the muscularis mucosae also had a very small focus of hypertrophy.

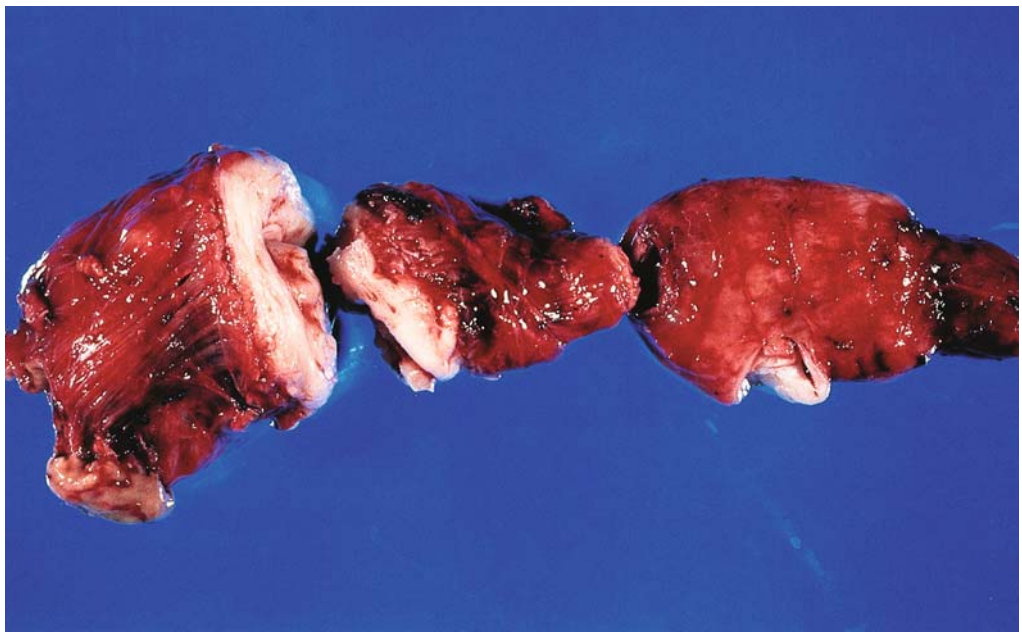


FIG. 10-24. Macroscopic appearance of diffuse esophageal leiomyomatosis. The resected unopened esophagus measured up to 8cm in diameter. The cut surface shows a markedly thickened esophageal wall

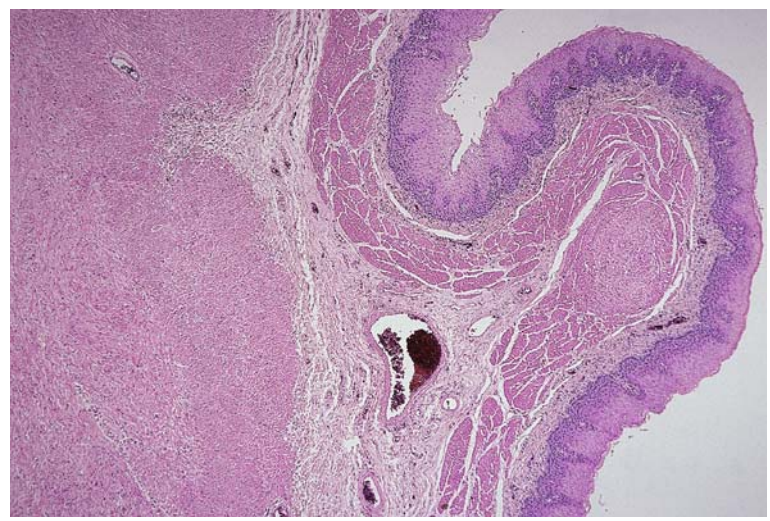


FIG. 10-25. Diffuse esophageal leiomyomatosis. There is a markedly thickened inner circular muscle layer

Because these cases usually lack macroscopic nodules they are probably better called muscular hypertrophy of the esophagus, but the condition may sometimes be nodular. There is also a view that diffuse leiomyomatosis and idiopathic muscular hypertrophy of the esophageal wall are different stages of the same condition (Lonsdale et al.). Leiomyomas may also occur in this condition.

Histologically, diffuse leiomyomatosis is characterized by benign muscular hypertrophy of the esophageal wall. An interlacing pattern of muscle fibers, often observed in leiomyomas, is not typical in the diffusely hypertrophic wall. Hyaline globules may be evident in the hypertrophic muscle (see Fig. 10-26). Necrosis, hemorrhage, fibrosis, hyalinous fibrosis, and calcification have

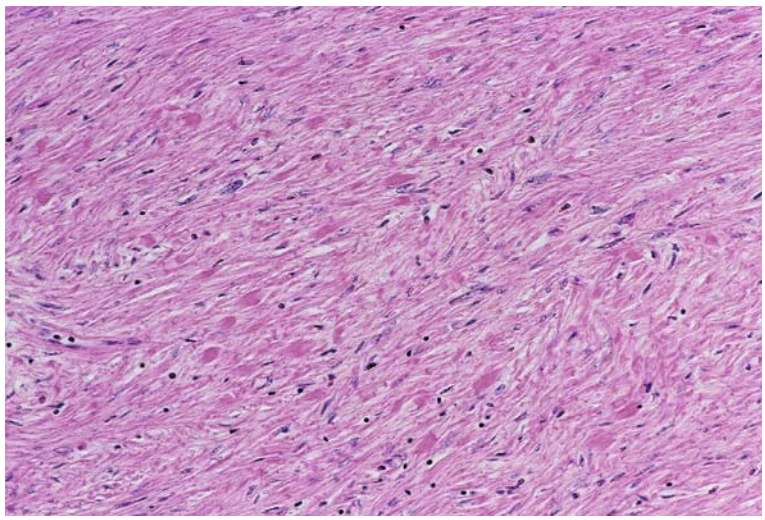


Fig. 10-26. Diffuse esophageal leiomyomatosis. There are hyaline globules in the smooth muscle cells

occasionally been reported. Although Auerbach's plexus is usually intact in this condition, a decrease in the number of ganglion cells may occasionally be seen. There is also sometimes a chronic inflammatory infiltrate in the esophageal wall.

10.9.2. Idiopathic Muscular Hypertrophy

Idiopathic muscular hypertrophy of the esophagus is a rare condition of unknown etiology, and was first described in 1839 by Albers. About 50 case reports had been published by 1990 (Kreczy et al.). It mostly occurs in male adults; only 6 cases of this condition have been reported in children (Kreczy et al.). It is characterized by excessive, diffuse hypertrophy of the esophageal wall, normal motility, and a normal appearance at esophagoscopy. In comparison to the extent of the pathological change, affected patients have only minor problems with swallowing. It is usually diagnosed at autopsy. In life it is often missed or mistaken for achalasia, diffuse spasm, or carcinoma (Iyer et al. 1986).

In one case studied by the author, the esophagus had a thickened wall throughout its entire length, more marked in the lower portion. The thickness was caused primarily by muscular hypertrophy, in which the circular layer of the muscularis propria predominated. Histologically, there were hypertrophic muscle bundles.

Cases reported in the literature as diffuse muscular hypertrophy may include various different conditions. Much remains unclear about the relationship between diffuse muscular hypertrophy and diffuse esophageal spasm. There is a view that the two disorders are identical or represent different stages of the same process. Also, the relationship between idiopathic hypertrophy and diffuse leiomyomatosis of the esophagus is controversial, and in fact the two terms have sometimes been used interchangeably.

10.10. Lipoma

Esophageal lipomas are less common than gastric, small intestinal, and large intestinal lipomas. The majority of reported esophageal lipomas have been large, pedunculated, and intraluminal (Zonderland and Ginai). Only three cases of intramural lipoma were reported (Wang et al. 2005). Suffocation resulting from a large esophageal lipoma has been reported (Allen and Talbot). Nagai et al. (2002) reported a series of 40 cases of esophageal lipoma from Japan. The male to female ratio was 27:13, and the mean age was 59 years. The lipomas in 8 of the 40 cases were resected by endoscopic polypectomy and 4 were resected by endoscopic mucosal resection. Yoshino et al. reported 19 cases of esophageal lipoma, of which 11 were located in the cervical esophagus. There was a slightly higher incidence in men than in women (ratio, 11:8) in their series. Most were pedunculated and covered by squamous

Fig. 10-27. Macroscopic appearance of an incidental lipoma in a longitudinal section of the esophagus. The tumor is yellow and nodular and is situated in the submucosa

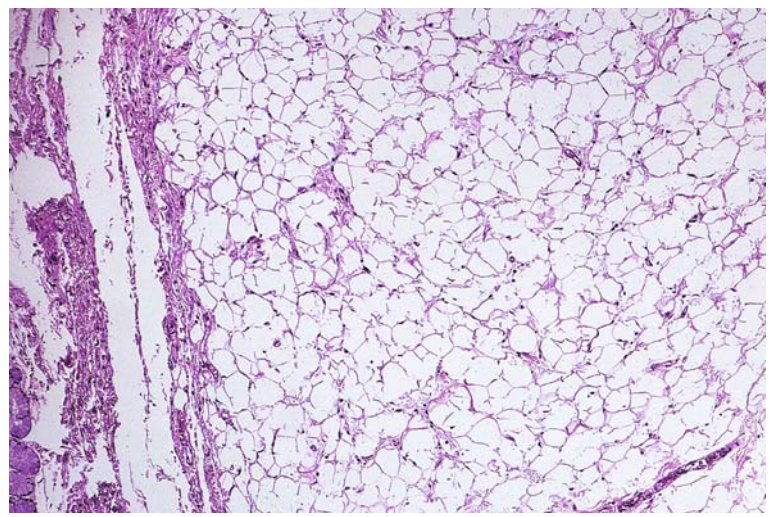


Fig. 10-28. Lipoma. The tumor is composed of mature adipocytes

epithelium, and the largest measured 22 cm in greatest dimension.

There have been two published case reports of esophageal lipoma with overlying intramucosal squamous cell carcinoma (Marcial-Rojas and Suau; Kuwano et al.).

There has been an entity described that has histological features intermediate between lipoma and fibrovascular polyp (Yoshino et al.). The relationship between lipoma and fibrovascular polyp has been previously discussed (p. 120).

This author has encountered one esophageal lipoma. This lipoma was small and was at the esophagogastric junction in an esophagus that had been resected for carcinoma. Macroscopically, the mucosa was slightly elevated and the cut surface was bright yellow in color, appearing similar to subcutaneous fat. The tumor was nodular and oblong in shape (Fig. 10-27) and was situated mainly in the submucosa. Histologically, it was encapsulated and consisted of mature adipocytes indistinguishable from those of subcutaneous fat (Fig. 10-28).

10.11. Hemangioma

Hemangiomas of the esophagus are rare, but their occurrence has been known since 1896. Hanel et al. reviewed 24 cases (1981). The patients ranged in age from neonates to age 75, with males outnumbering females by about 2 : 1. Of the 24 tumors, the majority (18) of those with available histological data were of cavernous type. Forty-five cases of esophageal hemangioma have been reported

from Japan (Yamashita et al. 1993). Another review of 344 cases of benign and malignant vascular tumors of the digestive tract stated that only 21 (6.1%) had arisen in the esophagus (Gentry et al.). Most reported esophageal hemangiomas have measured less than 5 cm in diameter, although tumors measuring more than 10 cm have occurred. No predominant site in the esophagus has been stated. In one report of patients with esophageal hemangiomas, 40% complained of dysphagia and 12% had hematemesis and/or melena (Miki et al.).

Some cases of hemangioma have been diagnosed on biopsy. A few deaths from hemangioma-related bleeding have been reported.

A case of esophageal squamous cell carcinoma in situ developing on the surface of a hemangioma has been reported (Ito et al. 2004).

There has recently been an increasing number of reports of esophageal hemangiomas being treated by endoscopic injection sclerotherapy, and 11 such cases have been reported from Japan (Nagata-Narumiya et al. 2000; Ito et al. 2004). Therefore, this type of esophageal tumor may not be resected very often in future.

Endoscopically, esophageal hemangiomas are blue and polypoid. They are soft and appear to be submucosal, but sometimes arise toward the outer aspect of the esophageal wall. On cut surface they resemble blood clots, apart from the fact they are partitioned by vessel walls (Fig. 10-29). Figure 10-30 shows a cavernous hemangioma that measured 15 mm in diameter and was submucosal. It consisted of enlarged blood-filled spaces lined by small, flat, uniform endothelial cells.

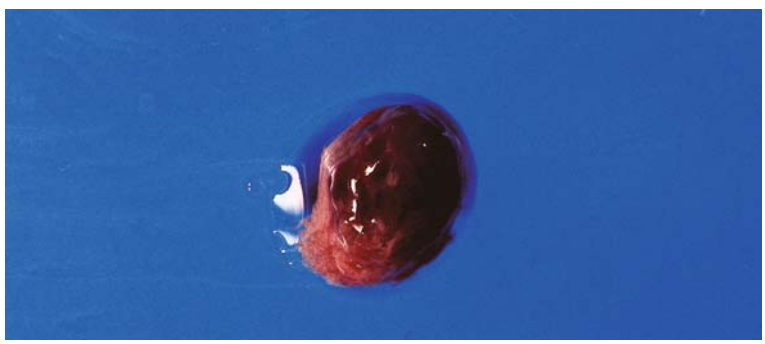


FIG. 10-29. Macroscopic appearance of a cavernous hemangioma of the esophagus. The tumor resembles a blood clot

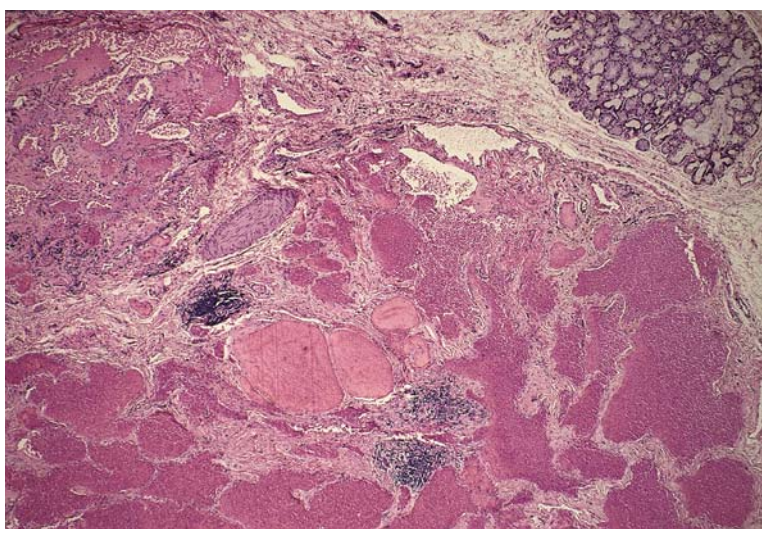


FIG. 10-30. Cavernous hemangioma. Dilated blood vessels are seen in the vicinity of an esophageal gland proper

10.12. Lymphangioma

A total of 14 cases of esophageal lymphangioma have been reported (Murata et al. 1980; Kano et al. 1985; Gerzic et al. 1996; Yoon et al. 2004; Saers et al. 2005), composed of 8 men, 5 women, and 1 of unstated sex, with an age range from 32 to 64 years. Brady and Milligan (1973) reported a case of lymphangioma that was diagnosed histologically on endoscopic biopsy specimens; in this case there was no related infection or bleeding. Armengol-Miro et al. reported a patient with a lymphangioma who was treated by polypectomy and had no recurrence postoperatively.

In the author's series of 1400 consecutive autopsy cases from the Saitama Cancer Center Hospital, only one esophageal lymphangioma was found. This tumor was rather transparent and was elevated and hemispherical in shape. It measured 7 mm in diameter (Fig. 10-31) and was located in the lower esophagus. Histologically, there were numerous dilated lymphatic vessels in the lamina propria (Fig. 10-32). The endothelial cells were flat with very small, spindle-shaped, uniform nuclei, in keeping with the benign nature of the tumor (Fig. 10-33).

10.13. Granular Cell Tumor

Granular cell tumors are relatively rare, and can arise at many different sites. The commonest sites are the skin and oral cavity. More than 1000

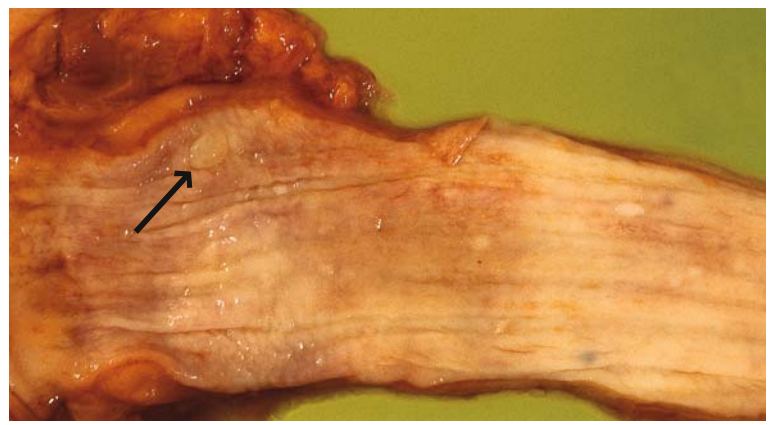


Fig. 10-31. Macroscopic appearance of a lymphangioma (*arrow*) of the esophagus. This rather transparent, hemispherical tumor was found incidentally at autopsy in a patient who had died of recurrent cervical carcinoma

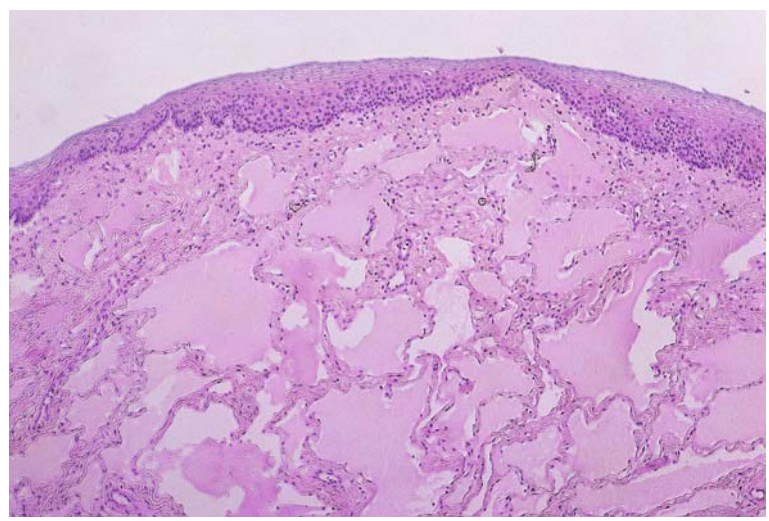


Fig. 10-32. Lymphangioma. There are many dilated lymph vessels beneath the epithelium

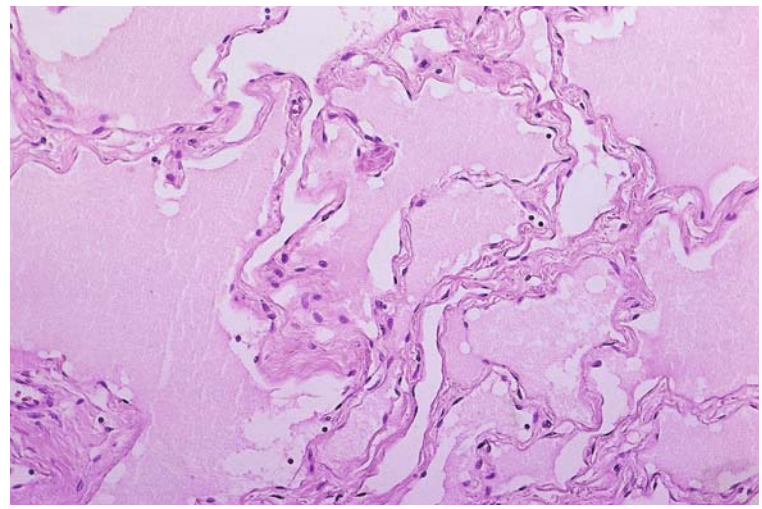


FIG. 10-33. Lymphangioma. The lining endothelial cells are flat and have small nuclei

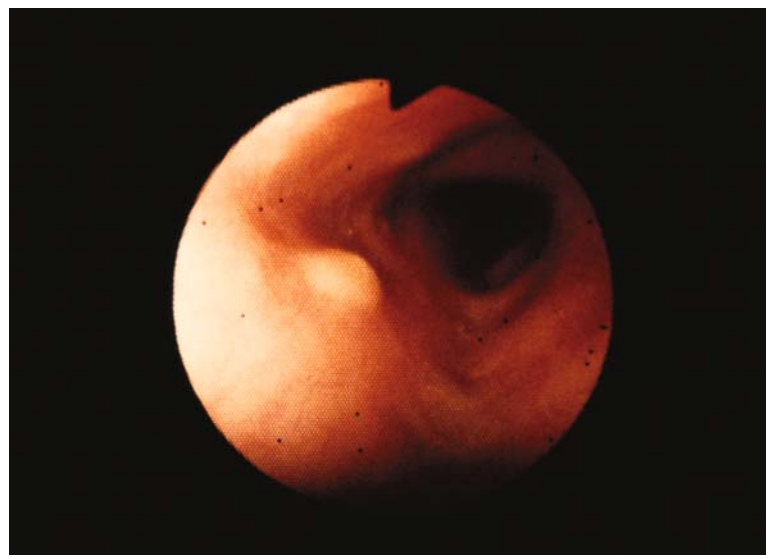


FIG. 10-34. Endoscopic appearance of a granular cell tumor of the esophagus

examples, from various sites, have been reported (Kaito et al. 1979). Although a considerable number of esophageal granular cell tumors must have been found since the first report by Abrikossoff (1926), the number of reported cases is still less than 100 (Ikeda and Abe 1984). About half of all reported cases have been asymptomatic. Males have been predominant (Shima et al.). Although some malignant esophageal granular cell tumors have been reported, most have been benign. Their growth rate is slow, showing very little change in size at endoscopy over a 2-year period (Tanaka), but even benign granular cell tumors may be invasive, so removal has been recommended (Howe and Postlethwait). The occurrence of multiple granular cell tumors of the esophagus has been reported (Cone and Wetzel; David and Jakate), and there have also been case reports of esophageal granular cell tumors with coexisting granular cell tumor(s) elsewhere, such as in the tongue, trachea, or skin (O'Connell et al.).

Endoscopically, granular cell tumors appear to be submucosal (Fig. 10-34), resembling molar teeth, and may be misdiagnosed as small leiomyomata.

Histologically, they consist of aggregates of round cells with granular cytoplasm and hyperchromatic nuclei in the lamina propria, submucosa, and muscularis propria (Fig. 10-35). Mitotic figures are usually absent. The tumor cells have small, central nuclei. The cytoplasmic granules are periodic acid–Schiff (PAS) positive (Fig. 10-36), and with immunohistochemical stains there is cytoplasmic NSE and S-100 protein positivity (Fig. 10-37) (Stefansson and Wollmann). Both pericellular tissue and tumor cells are positive for laminin and myelin basic protein.

The cytological features of granular cell tumor have not been fully documented. The present author has found the tumor cells to resemble histiocytes. They have granular and foamy, light green cytoplasm with the Papanicolaou stain, and small, oblong, or round hyperchromatic nuclei, with indistinct nucleoli (Fig. 10-38). Numerous extracellular granules, from ruptured tumor cells, are seen in cytological smears (Fig. 10-39). Recently, a detailed cytological description of an esophageal granular cell tumor was given in a case report (Hamada et al.), with the authors suggesting that this entity can be easily diagnosed cytologically.

On electron microscopy, the tumor cells have numerous cytoplasmic lysosomes, and sometimes

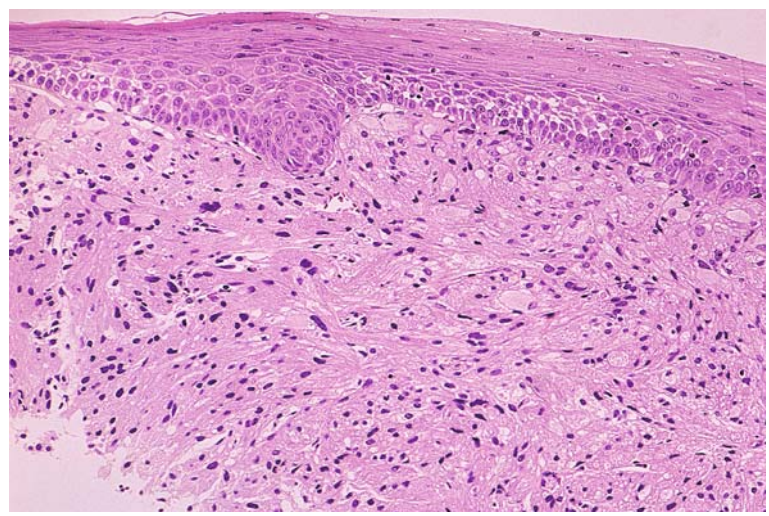


Fig. 10-35. Granular cell tumor. The tumor cells are in the lamina propria beneath the epithelium

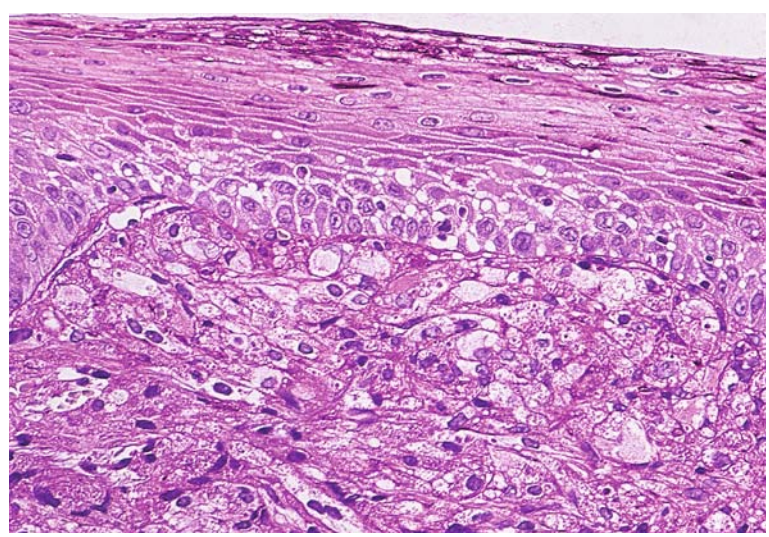


Fig. 10-36. Granular cell tumor (periodic acid-Schiff stain). Positive granules are seen in the cytoplasm of the tumor cells

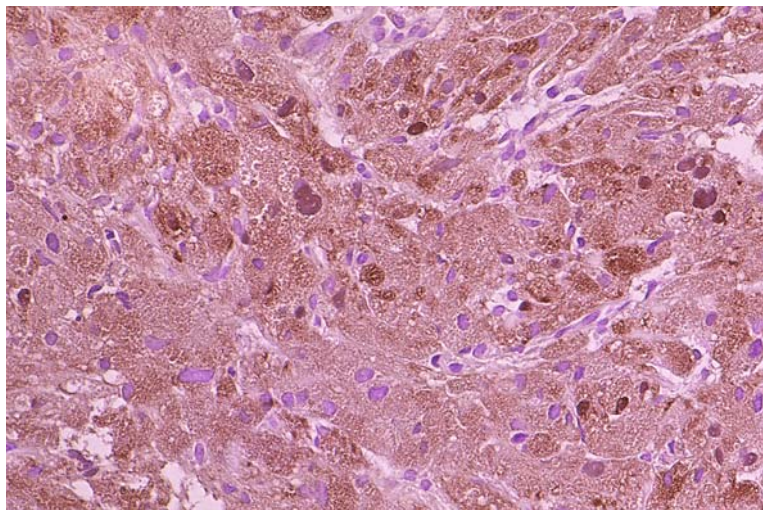


FIG. 10-37. Granular cell tumor (S-100 protein immunostain). The tumor cell cytoplasm is S-100 protein positive

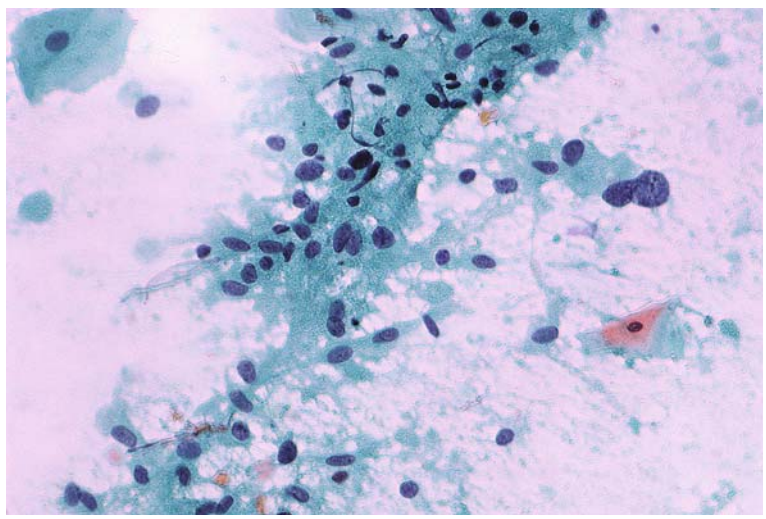


FIG. 10-38. Cytological appearance of a granular cell tumor (Papanicolaou stain). The tumor cells are aggregated

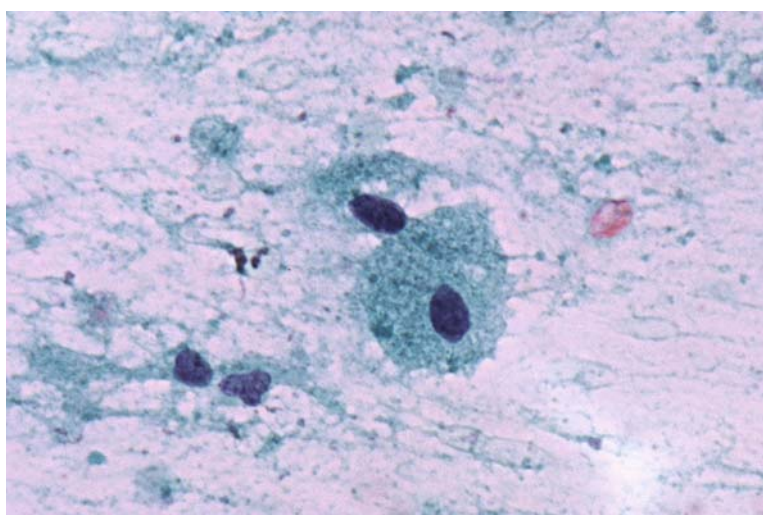


FIG. 10-39. Cytological appearance of a granular cell tumor (Papanicolaou stain). The tumor cells have small nuclei and granular cytoplasm

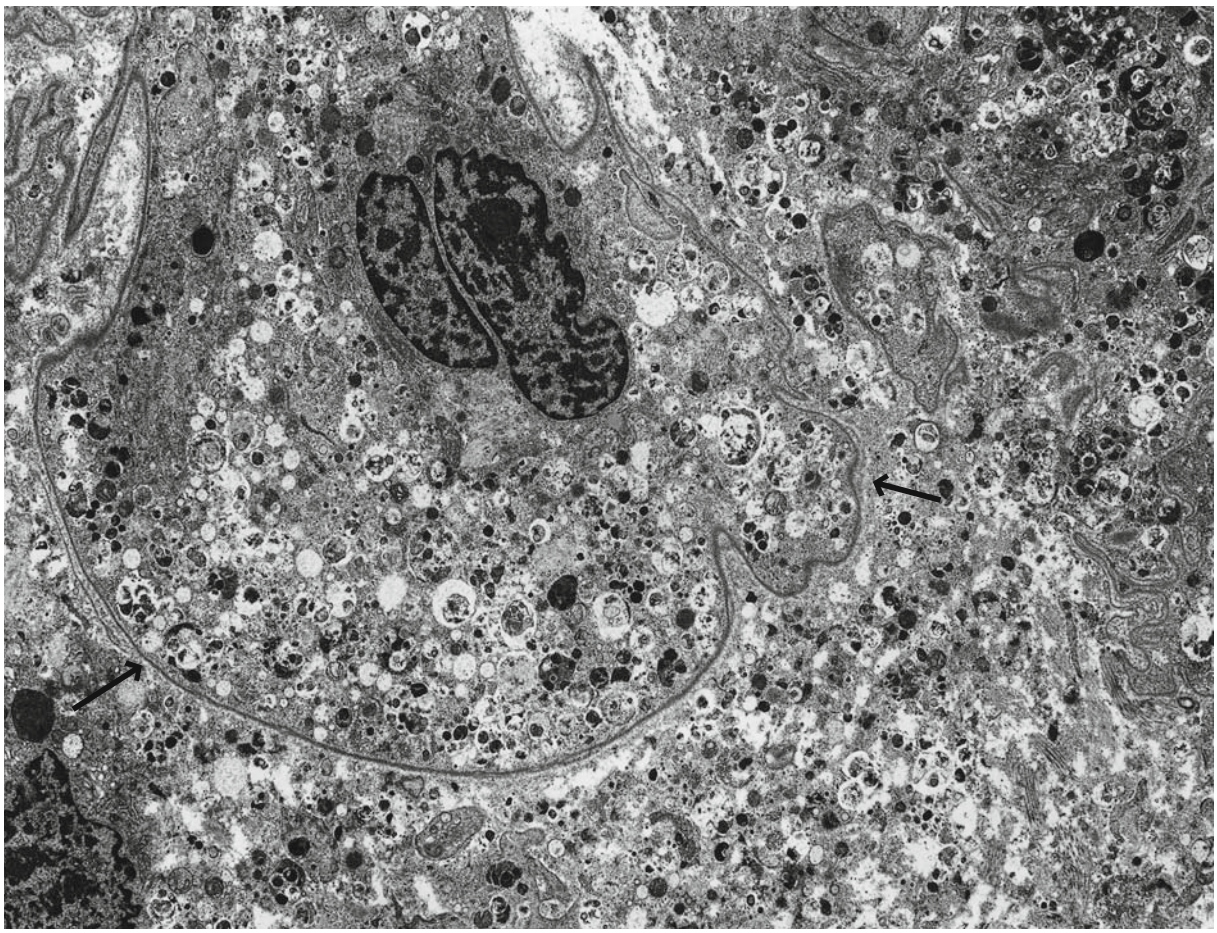


Fig. 10-40. Electron micrograph of a granular cell tumor. There are many lysosomes in the cytoplasm of tumor cells, and the cells have surrounding basement membranes (*arrows*). Cytoplasmic processes are evident

have tangled cytoplasmic processes (Fig. 10-40). They are each surrounded by a basement membrane (Fig. 10-41). The ultrastructural and immunohistochemical staining features are similar to those of perineural cells and Schwann cells, and it has been considered that granular cell tumors are derived from neural tissue, particularly Schwann cells. Recently this view has almost become the consensus of medical opinion, and it has been proposed that this entity be renamed granular cell schwannoma. The intracellular granules are generally thought to result from the autodigestion of myelin within the cells.

The epithelium overlying granular cell tumors often shows pseudoepitheliomatous (pseudocarcinomatous) hyperplasia (Fig. 10-42). The etiology of this is unknown, but it is possible that the granular cells produce a trophic factor. A similar epithelial change may also be found overlying granular cell tumors of the skin, oral mucosa, and tongue.

The malignant counterpart of this tumor is described in Chapter 14 (p. 254).

10.13.1. Pseudoepitheliomatous (Pseudocarcinomatous) Hyperplasia of the Esophagus

Extension or irregular distortion of rete pegs may produce a tumor-like appearance in surface stratified squamous epithelium, similar to cancer pearls,

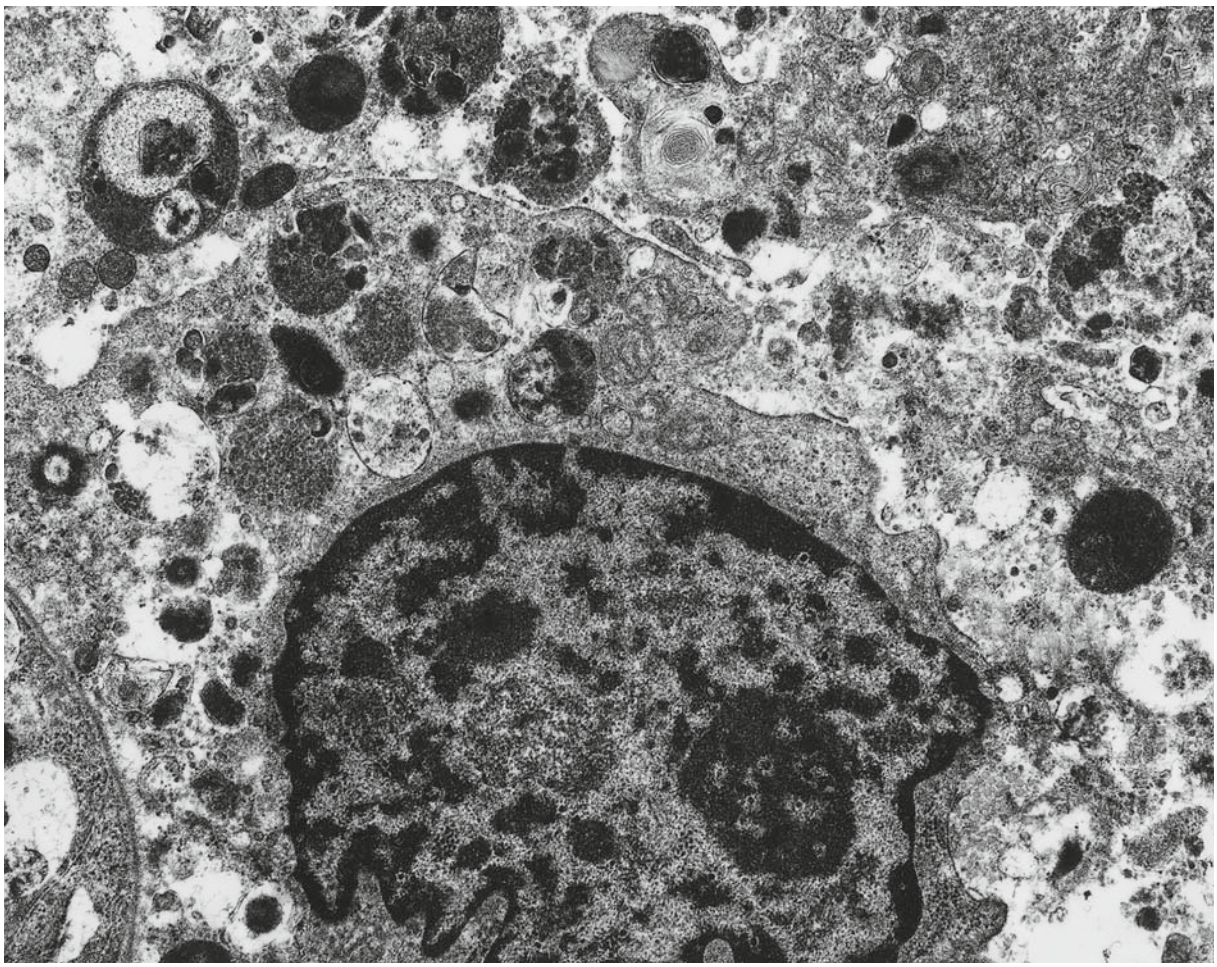


FIG. 10-41. Electron micrograph of a granular cell tumor. There are lysosomes outside as well as inside the cells because of artefactual damage at the time of sampling

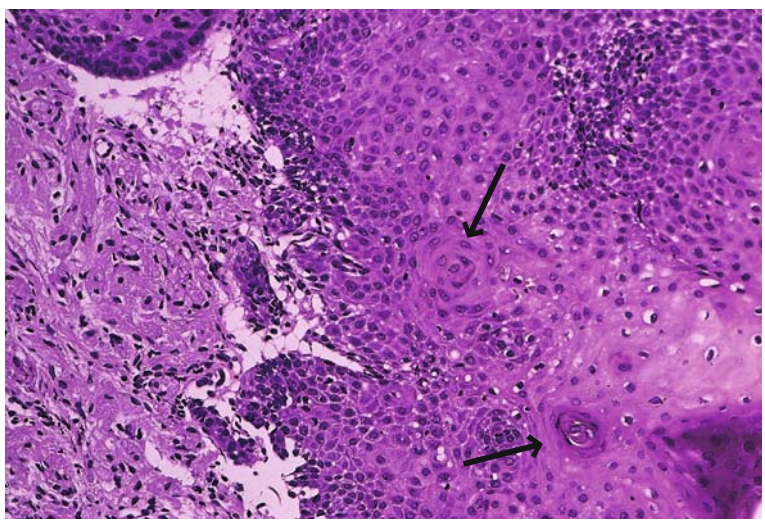


FIG. 10-42. Pseudoepitheliomatous hyperplasia of squamous epithelium overlying a granular cell tumor. Structures resembling cancer pearls (*arrows*) are evident

particularly in tangential sections (see Fig. 10-42). This condition can be distinguished from a neoplastic proliferation by the absence of atypical cells and by the examination of consecutive sections. These epithelial changes can be observed overlying granular cell tumors, at ulcer margins, or in association with chronic inflammation.

10.14. Adult Rhabdomyoma

An adult-type rhabdomyoma of the cervical esophagus has been reported in an 8-year-old boy (Pai et al. 1987). The patient had mild dysphagia. The encapsulated tumor measured 9 × 5 × 4 cm and consisted of striated muscle fibers that extended in various directions. There was no postoperative recurrence after 4 years of follow-up. Two other cases of rhabdomyoma of the esophagus have also been reported, in a 21-year-old woman and a 30-year-old man (Roberts et al. 2000). The 21-year-old woman had a 2-year history of dysphagia, and her tumor measured 9 × 3.5 × 3 cm; the 30-year-old man had a large tumor, more than 5.5 cm in size.

10.15. Osteochondroma

There has been one case report of an osteochondroma (tracheobronchial choristoma) of the esophageal wall. The patient was a 66-year-old woman and the tumor was resected surgically (Mahour and Harrison 1967). Her chief complaint was of progressive dysphagia. The tumor, measuring 5.5 cm, was covered by mucosa; it consisted mainly of cartilaginous tissue but also had some bone. Although this tumor seems to have been classified as a hamartomatous polyp (p. 124), various histogeneses have been considered.

10.16. Glomus Tumor

There have been three single case reports of esophageal glomus tumor in the English language literature, and a few case reports have also been published in Russian and German. In one of the reports, a glomus tumor occurred in the esophagus of a 62-year-old woman; the patient remained well after 2 years of follow-up postresection (Rueff and Grabiger 1967). In another, an esophageal glomus tumor, 5 cm in size, occurred in a 79-year-old woman, but the patient outcome was not described (Papla and Zielinski 2001). The case of a 41-year-old woman with synchronous esophageal and pulmonary glomus tumors has also been reported; the patient was well 3 years after diagnosis (Altorjay et al. 2003). Glomus tumors consist of large polygonal cells with oval nuclei and rather abundant cytoplasm. There is hyaline stroma among the tumor cell nests and surrounding small vessels. With immunohistochemical stains, the

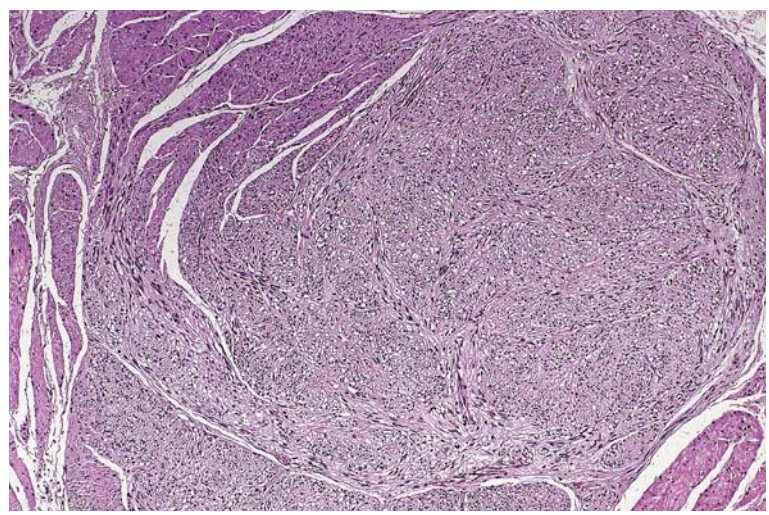


Fig. 10-43. Neurilemmoma of the esophagus. One of multiple schwannomas that arose in the esophageal wall of a patient with von Recklinghausen's disease

tumor cells are positive for vimentin and smooth muscle actin, but are negative for EMA, cytokeratin, chromogranin A, NSE, desmin, S-100 protein, and CD34 (Papla and Zielinski). On electron microscopy, the tumor cells are seen to be surrounded by a continuous basal lamina (Altorjay et al.).

10.17. Neurogenic Tumors

One case of an esophageal neurofibroma has been reported (Sturdy 1967). The patient was a 51-year-old woman, and the tumor was submucosal.

Twenty cases of esophageal neurilemmoma (schwannoma) have also been reported (Iwata et al. 1993; Arai et al. 1994; Nakamura et al. 1998; Sato et al. 2005). Eighteen of the 20 patients were Japanese, and the ratio of males to females was 4:14 in the Japanese cases (Sato et al.). The tumor size ranged from 0.5 to 10 cm.

The histological appearance of esophageal neurilemmoma is the same as that which occurs at other sites, i.e., it consists of a proliferation of fusiform cells and palisading of tumor cell nuclei is observed (Fig. 10-43). Several cases have been examined by immunohistochemistry and electron microscopy. The tumor cells are positive for S-100 protein and NSE. Electron microscopy has shown Luse's bodies, basement membranes around tumor cells, and desmosome-like structures between cells.

One case of a benign autonomic nerve tumor of the esophagus has also been reported (Lam et al. 1996), as has a case of melanotic schwannoma, with a discussion of the differential diagnosis (Brown et al. 2002).

Chapter 11
Squamous Epithelial Dysplasia and Squamous Cell Carcinoma

11.1. Squamous Epithelial Dysplasia

11.1.1. Definition of Squamous Epithelial Dysplasia

Dysplasia has been defined in the Vienna classification as intraepithelial neoplasia with no stromal invasion (Table 11-1) (Schlemper et al. 2000). However, atypical squamous epithelium is very frequently seen in resected esophagi from patients with achalasia, squamous cell carcinoma, and multiple Lugol's iodine-negative lesions seen endoscopically (see Section 11.1.4). It is often difficult to decide whether this atypical squamous epithelium is neoplastic or nonneoplastic by histological examination. On the other hand, some micrographs of squamous intraepithelial neoplasia/dysplasia published in textbooks from the United States and Europe would be called squamous cell carcinoma in situ by Japanese pathologists, even some cases that were said to be low-grade dysplasia (see Section 12.2.1.3.1). The differences in the diagnostic criteria for esophageal squamous cell carcinoma between Japanese and Western pathologists have been discussed in the literature (Schlemper et al.). Western pathologists use the term dysplasia to indicate the presence of a noninvasive neoplastic proliferation that might have the potential to become invasive. In contrast, the present author and most Japanese pathologists think that the term carcinoma in situ should be used for an intraepithelial neoplasm that is histologically similar to the intraepithelial spreading component of an invasive carcinoma, in the same way that both Japanese and Western pathologists use the terms intraductal carcinoma and lobular carcinoma in situ in the breast (Takubo et al. 2002).

In the present volume, dysplasia is defined as the appearance of an atypical squamous epithelium, similar to that which is frequently seen in resected esophagi from patients with achalasia, squamous cell carcinoma, and multiple Lugol's iodine-negative lesions seen endoscopically, and no attempt is made to distinguish whether the dysplasia is neoplastic or not. The present author uses the term squamous cell carcinoma in situ for an intraepithelial neoplasm that is histologically similar to the intraepithelial spreading component of an invasive squamous cell carcinoma.

Dysplasia can involve both architectural and cytological atypia. Dysplasia of the glandular epithelium in Barrett's esophagus, as defined in the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*, proposed by the Japanese Society for Esophageal Diseases, is

TABLE 11-1. Vienna classification of gastrointestinal epithelial neoplasia

Category 1: Negative for neoplasia/dysplasia
Category 2: Indefinite for neoplasia/dysplasia
Category 3: Noninvasive low-grade neoplasia (Low-grade adenoma/dysplasia)
Category 4: Noninvasive high-grade neoplasia
4.1: High-grade adenoma/dysplasia
4.2: Noninvasive carcinoma (carcinoma in situ)[a]
4.3: Suspicion of invasive carcinoma
Category 5: Invasive neoplasia
5.1: Intramucosal carcinoma[b]
5.2: Submucosal carcinoma or beyond

[a]Noninvasive indicates absence of evident invasion
[b]Intramucosal indicates invasion into the lamina propria or muscularis mucosae

described in Chapter 12 (p. 205). Dysplasia of both squamous and glandular epithelium is often classified as mild, moderate, and severe, according to the degree of atypia (Figs. 11-1 through 11-3).

Cytological mass screening was begun in 1959 in an area along the Yellow River in China that is known to have a very high incidence of esophageal squamous cell carcinoma. This study revealed a close relationship between squamous cell carcinoma and dysplasia and led to the conclusion that squamous cell carcinoma develops from severe dysplasia (1967, 1975). The results of this Chinese study were described in detail in a review by Yang (1980). Isono (1962) was the first author in Japan to report the atypical proliferation of esophageal mucosal epithelium, in a study of 81 esophagi resected for squamous cell carcinoma; this report preceded the series of Chinese papers on epithelial dysplasia just mentioned. Ushigome et al. (1967) reported a case of multifocal carcinoma in situ and extensive epithelial dysplasia in a black male patient. Mukada et al., from the Tohoku University School of Medicine, published a series of reports on autopsy cases of esophageal epithelial dysplasia, with and without esophageal carcinoma, seen at four different Japanese prefectures (1976, 1978). Takubo et al. (1981) also published an autopsy series of esophageal dysplasia. There has

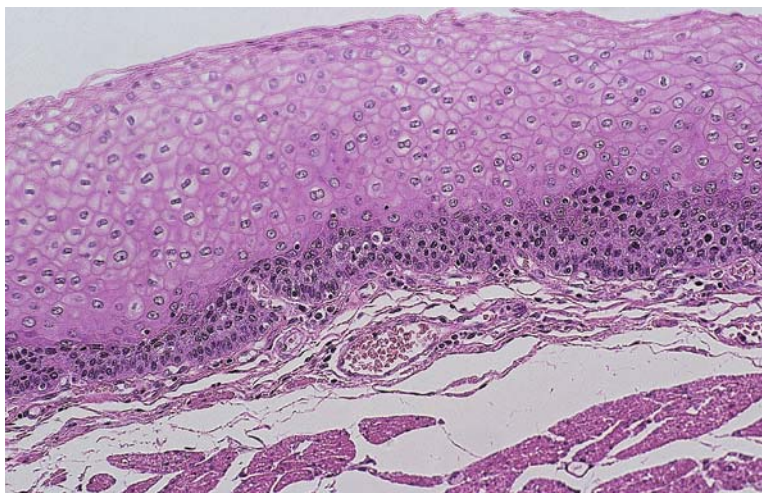


Fig. 11-1. Mild dysplasia. Atypical cells are evident in the basal and parabasal layers of the epithelium

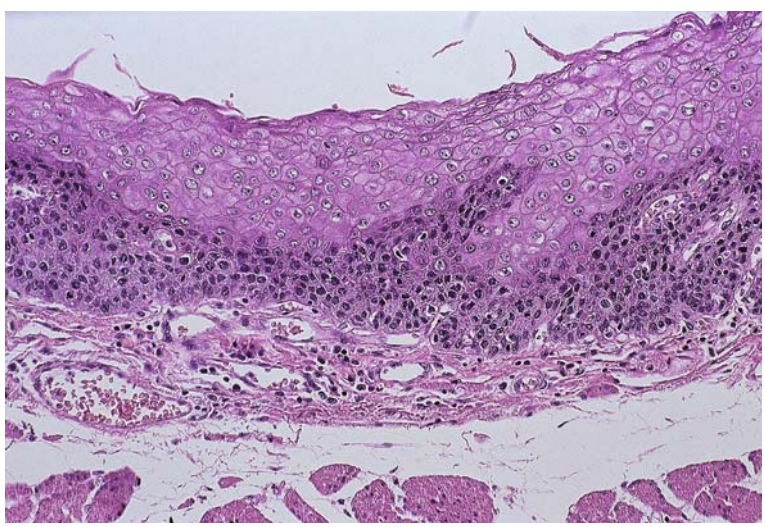


Fig. 11-2. Moderate dysplasia. There are atypical cells in the basal and parabasal layers

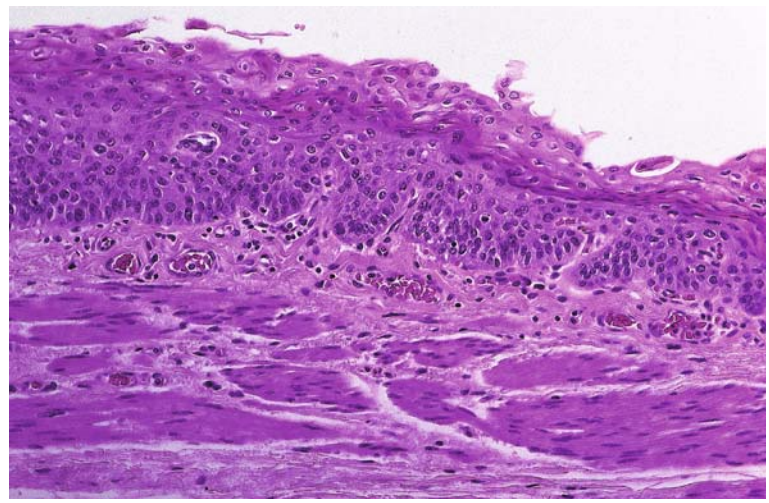


FIG. 11-3. Severe dysplasia. Atypical cells are found up to the middle and superficial layers of the epithelium, with a large number of keratinizing cells

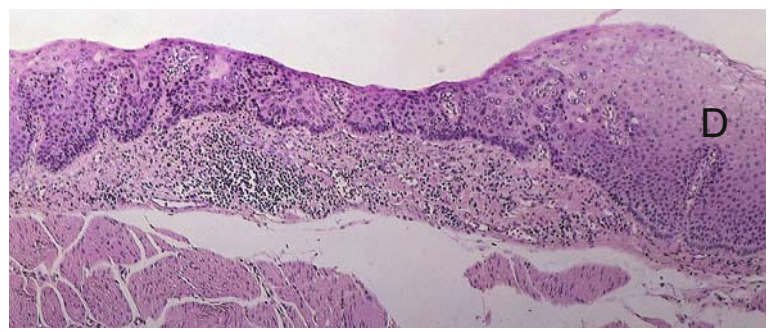


FIG. 11-4. Microcarcinoma of the esophagus. The microcarcinoma is surrounded by dysplasia (*D*)

also been a report of epithelial dysplasia in a patient with carcinosarcoma of the esophagus (Matsusaka et al.).

In the study by Mukada et al., 37% of 248 consecutive autopsy cases had epithelial dysplasia of the esophagus. Takubo et al. found epithelial dysplastic foci in 27% of 251 autopsy cases of carcinoma other than esophageal carcinoma; the combined incidence of moderate and severe dysplasia was 11%, but was 15% for males and only 3% for females. Dysplasia was more frequent in patients of advanced age, and this included some with extensive dysplasia involving almost the entire esophageal mucosa, similar to cases described by Ushigome et al. and Mukada et al. Subclinical carcinoma of the esophagus was found in 2% of all the autopsies. One of these, from a 70-year-old man, is illustrated in Figs. 11-4 and 11-5. This cancer was a minute intramucosal carcinoma, which measured less than 1 mm in diameter; there was early microinvasion and surrounding dysplasia. Five of the seven microcarcinomas found in the series had adjacent epithelial dysplasia. Although the number was small, a high likelihood of cancer arising in morphologically defined dysplasia was suggested. In the study by Mukada et al. (1976), a higher incidence of epithelial dysplasia was found in autopsy cases from the Kagoshima Prefecture than from the other three prefectures, and there was an association between dysplasia and a history of habitual alcohol drinking.

Subclinical esophageal carcinoma was found in 0.5% of 1000 autopsies in a study by Postlethwait

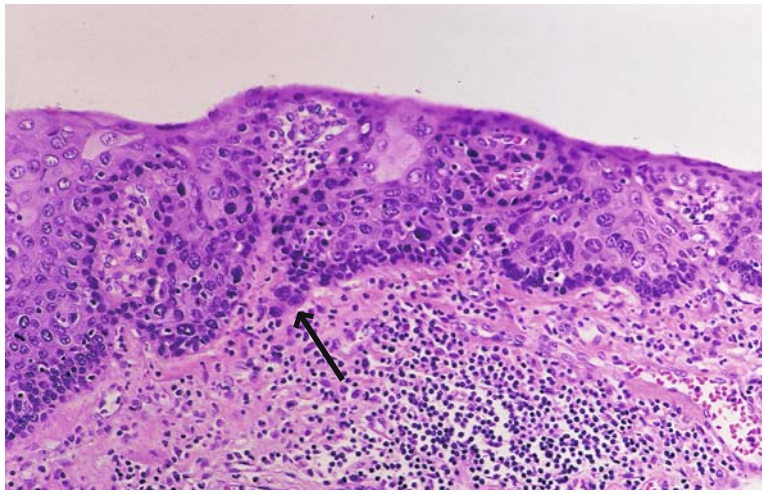


FIG. 11-5. High-magnification view of Fig. 11-4. The process of early stromal invasion (*arrow*) is seen in a bulky outgrowth type of carcinoma

and Musser; this incidence was considerably lower than that found in the series by Mukada et al. and Takubo et al.

On the other hand, there is also a view that squamous cell carcinoma does not always arise from epithelial dysplasia. The present author considers that esophageal cancer can arise both from morphologically dysplastic and nondysplastic epithelium, although the former seems more frequent, judging from data obtained from the studies of background mucosal epithelium in cases of microcarcinoma. Foci of epithelial dysplasia in these cases are usually very small, however, and the diameter of most resected esophageal microcarcinomas, usually around 10 mm, is too large to enable studies of their histogenesis. It is, therefore, difficult to assess the relationship between epithelial dysplasia and cancer from studies of resected esophagi. Endoscopic mucosal resections for mucosal carcinoma are now being very frequently performed in Japan, however, and microcarcinomas are often detected. It should thus now be possible to histologically examine a large number of very minute cancers.

The World Health Organization (WHO) histological classification of esophageal tumors, issued in 1977, stated dysplasia should be distinguished from squamous cell carcinoma in situ. The new WHO classification (1990) refers to esophageal dysplasia as being analogous to dysplasia of the uterine cervix, and points out the difficulty in distinguishing dysplasia from inflammatory and regenerative changes (Table 11-2). The *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (8th and 9th editions) describe atypical intraepithelial lesions with the term dysplasia, and classifies dysplasia as mild, moderate, and severe. This system is also used for atypical glandular epithelium.

11.1.2. High-Grade Dysplasia and Squamous Cell Carcinoma in Situ

Micrographs of examples of high-grade squamous intraepithelial neoplasia/dysplasia published in Western textbooks are regarded in Japan as examples of squamous cell carcinoma in situ. p53 protein immunostaining is positive in high grade squamous intraepithelial neoplasia/dysplasia, and a local treatment such as endoscopic mucosal resection (see Section 11.2.17.1.1) or laser ablation would be indicated. In addition, biopsy samples are limited, and there may be foci of invasion in the mucosa or in deeper layers elsewhere that have not been sampled. Also, some micrographs illustrating examples of low-grade intraepithelial neoplasia/dysplasia in Western textbooks would be regarded as examples of squamous cell carcinoma in situ in Japan.

Squamous cell carcinoma in situ can be subclassified histologically according to the appearance of the basement membrane. There is a simple

Table 11-2. World Health Organization (WHO) Histologic Classification of Oesophageal Tumours (2nd edition)

1	Epithelial tumours	
1.1	*Benign*	
1.1.1	Squamous cell papilloma	8052/0[a]
1.1.2	Viral wart	76600
1.1.3	Adenoma	8140/0
1.2	*Malignant*	
1.2.1	Squamous cell carcinoma	8070/3
1.2.2	Verrucous (squamous) carcinoma	8051/3
1.2.3	Spindle cell (squamous) carcinoma	8074/3
1.2.4	Adenocarcinoma	8140/3
1.2.5	Adenosquamous carcinoma	8560/3
1.2.6	Mucoepidermoid carcinoma	8430/3
1.2.7	Adenoid cystic carcinoma	8200/3
1.2.8	Small cell carcinoma	8041/3
1.2.9	Undifferentiated carcinoma	8020/3
1.2.10	Others	
2	Nonepithelial tumours	
2.1	*Benign*	
2.1.1	Leiomyoma	8890/0
2.1.2	Lipoma	8850/0
2.1.3	Vascular tumours	
2.1.4	Neurogenic tumours	
2.1.4.1	Granular cell tumour	9580/0
2.1.4.2	Others	
2.1.5	Others	
2.2	*Malignant*	
2.2.1	Leiomyosarcoma	8890/3
2.2.2	Kaposi sarcoma	9140/3
2.2.3	Others	
3	Miscellaneous tumours	
3.1	*Carcinosarcoma*	8980/3
3.2	*Malignant melanoma*	8720/3
3.3	*Others*	
3.3.1	Carcinoid tumour	8240/3
3.3.2	Malignant lymphoma	9590/3
4	Secondary tumours	
5	Tumour-like lesions	
5.1	*Fibrovascular (fibrous) polyp*	76806
5.2	Cysts	33400
5.2.1	Congenital cyst	26500
5.2.2	Retention cyst	33730
5.3	*Inflammatory polyp*	76820
5.4	*Glycogenic acanthosis*	
5.5	*Diffuse leiomyomatosis*	
5.6	*Gastric heterotopia*	26080
6	Epithelial abnormalities (precancerous)	
6.1	*Dysplasia and carcinoma in situ in squamous epithelium*	74000
6.2	*Barrett oesophagus*	73330
6.3	*Dysplasia in columnar epithelium (Barrett oesophagus)*	74000

[a]Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (SNOMED)

replacement type, showing a linear basement membrane pattern, and a bulky outgrowth type, showing a markedly wavy pattern, similar to the appearance of the basement membrane underlying the intraepithelial spreading component of an invasive carcinoma.

Squamous cell carcinoma in situ can also be subdivided into a total layer type, in which the whole epithelium is replaced by carcinoma cells, and a basal layer type, in which only the basal half is mostly replaced by highly atypical carcinoma cells that have a similar cytological appearance to the cells of an invasive squamous cell carcinoma. It is frequently noted in cases of minute squamous cell carcinoma that early invasion can occur directly from the basal layer type, not via the total layer type (Makuuchi; Yao et al. 2000). This finding strongly suggests that the basal layer type is not low-grade dysplasia but, rather, is squamous cell carcinoma in situ. The basal layer type is frequently called low-grade dysplasia in textbooks of surgical pathology published from Western countries, analogous to the criteria used for grading dysplasia in the uterine cervix.

11.1.3. Postirradiation Dysplasia

Dysplasia is often seen in noncancerous areas of epithelium within an irradiation field. Nuclei in the basal and/or parabasal layers are enlarged, and intercellular bridges become more distinct (Fig. 11-6). Squamous metaplasia with or without atypia can also be found in the ductal epithelium or in the terminal portions of the esophageal glands proper after radiotherapy.

The reader should also be aware of radiation-induced esophagitis (p. 94), radiation-induced changes in noncancerous tissue (p. 181), and radiation-induced carcinoma (p. 182).

11.1.4. Dysplasia After Chemotherapy

Anticancer drugs (cyclophosphamide and others) can induce atypical changes in squamous epithelium, and this phenomenon is well recognized in cytology smears. Abnormal maturation of esophageal epithelial cells may occur after anticancer chemotherapy, with squamous cells in the superficial layers having oval nuclei, and those in the

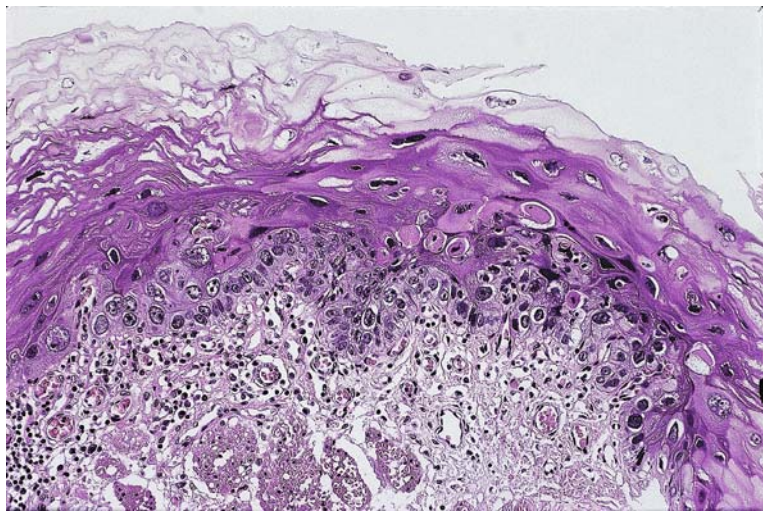


FIG. 11-6. Biopsy specimen of esophageal mucosa following radiotherapy. Atypical basal cells and dyskeratotic cells are seen in the mucosal epithelium

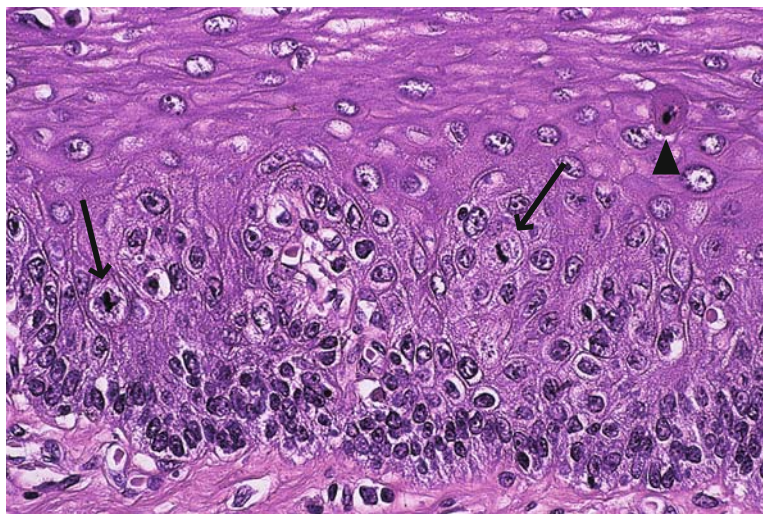


FIG. 11-7. Esophageal epithelium from an autopsy case of pulmonary small cell carcinoma treated with chemotherapy. There are many mitotic figures (*arrows*) in the parabasal layers, and there are dyskeratotic cells (*arrowhead*) in the middle layers

basal layers being abnormal in shape, occasionally spindle shaped, and having atypical nuclei. Individual cell keratinization may be seen in the middle and/or basal layers. Mitotic arrest may also be seen in the esophageal epithelium as a result of multidrug therapy or taxol administration, with very many mitotic figures seen in the parabasal layers (Fig. 11-7).

11.1.5. Benign Diseases, Epithelial Dysplasia, and Esophageal Cancer

Squamous dysplasia has been described in association with benign disorders such as benign tumors (see Section 10.8) and esophageal diverticula (Okamura et al.). Of the various benign esophageal disorders, achalasia (see Chapter 4), corrosive stenoses (see Section 7.2.1), esophageal diverticula, and benign tumors are known to have some relationship to squamous cell carcinoma. There are, however, no adequate morphological data to explain these associations. Foci of epithelial dysplasia may also be found in association with leiomyosarcomas and other malignant protruding lesions (see Fig. 14-5).

Cases of esophageal cancer developing after gastrectomy have also been reported (Kuwano et al.; Maeta et al.).

Tylosis is a hereditary autosomal dominant dyskeratosis that is characterized by severe epidermal thickening of the palms and soles. Esophageal squamous cell carcinoma has been reported in patients with tylosis (Shine and Allison 1966; Marger and Marger 1993), although changes in the noncancerous epithelium were not described in detail in these papers. In another report on tylosis and squamous cell carcinoma of the esophagus (Howel-Evans et al. 1958), there was no evidence of hyperkeratosis adjacent to the tumors but elsewhere the esophagi showed leukoplakia, hyperplasia of squamous epithelium, and subepithelial infiltration by lymphocytes. The association of tylosis and esophageal squamous cell carcinoma is known as the Howel–Evans syndrome, and the causative gene locus has been mapped to 17q23 by linkage analysis (Kelsell et al. 1996).

Dyskeratosis congenita, also known as the Zinsser–Engman–Cole syndrome, is a rare inherited disorder. There are X-linked recessive, autosomal dominant, and autosomal recessive types. It is characterized by a triad of abnormal cutaneous pigmentation, nail dystrophy, and mucosal leukoplakia (Marrone and Mason). It occurs predominantly in males, and there is a predisposition to malignancy (12% of patients). Severe pancytopenia and immunodeficiency may also occur. Squamous cell carcinoma is the most common malignancy, and it may arise from leukoplakia in the oral mucosa, pharynx, esophagus, anus, or uterine cervix (Kawaguchi et al. 1990). Fifty-nine percent of patients with dyskeratosis congenita suffer from dysphagia (Brown et al. 1993). Esophageal web has also been reported in patients with dyskeratosis congenita (Herman et al. 1997; de Roux-Serratrice et al. 2000).

11.1.6. Multiple Lugol's Iodine Negative or Weakly Positive Lesions in the Esophagus

Patients whose esophageal mucosa shows multiple small unstained or weakly stained lesions (mottles) at endoscopy, after Lugol's iodine staining, often have multifocal squamous dysplasia and squamous cell carcinoma in situ (Fig. 11-8). The lesions are irregular in size and shape. These patients often also have associated head and neck squamous cell carcinomas (Muto et al. 2002). The occurrence of multiple mucosal lesions has been related to alcohol dehydrogenase-2 (ADH2) and aldehyde dehydrogenase-2 (ALDH2) genetic polymorphisms (Yokoyama et al. 1999). The presence of the ADH2*1/2*1 or ALDH2*1/2*2 genes increases the risk of head and neck and esophageal squamous cell carcinomas (Yokoyama et al. 2001). The inactive from of ALDH2, encoded by ALDH2*1/2*2, is prevalent in Asians.

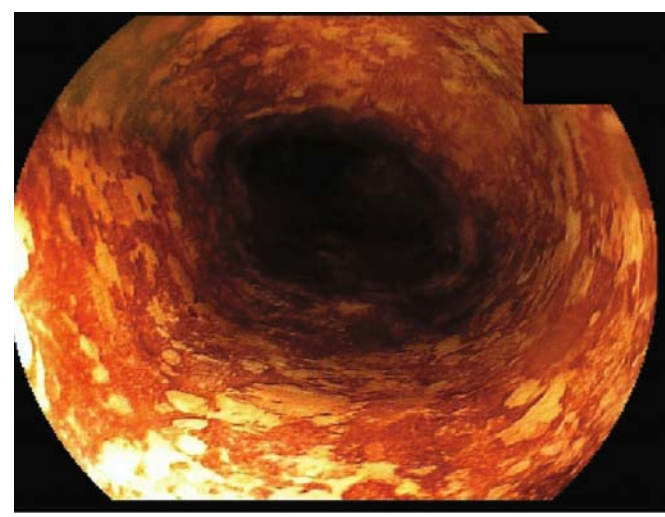


FIG. 11-8. Endoscopic appearance of multiple unstained or weakly stained lesions with Lugol's iodine. The lesions are irregular in size and shape and show a varying intensity of negative or weak staining with Lugol's iodine solution

11.2. Squamous Cell Carcinoma

11.2.1. Intraepithelial Carcinoma and Intramucosal Carcinoma

Mature squamous cells in the esophageal epithelium have many glycogen granules in their cytoplasm. Positive Lugol's iodine staining is brown in color. Negative staining occurs in squamous cell carcinoma in situ (Figs. 11-9, 11-10), ectopic gastric mucosa, gastroesophageal reflux disease (GERD), Barrett's mucosa, papilloma, granular cell tumor, and thermal burn, both at endoscopy and in resection specimens. Shimada et al. (1994) reported that 1% of unstained lesions less than 5 mm in size were carcinomas but that 10% of unstained lesions 5–10 mm in size were carcinomas.

Histologically, intraepithelial carcinoma is divided into two types, with regard to the appearance of the basement membrane: the simple replacement type, having a linear basement membrane, and the bulky outgrowth type, having a wavy basement membrane. These types often coexist. It is sometimes difficult to distinguish between intraepithelial carcinoma of bulky outgrowth type and intramucosal carcinoma with stromal invasion (see Section 11.2.8. Intraepithelial Spread and Ductal Involvement). When the

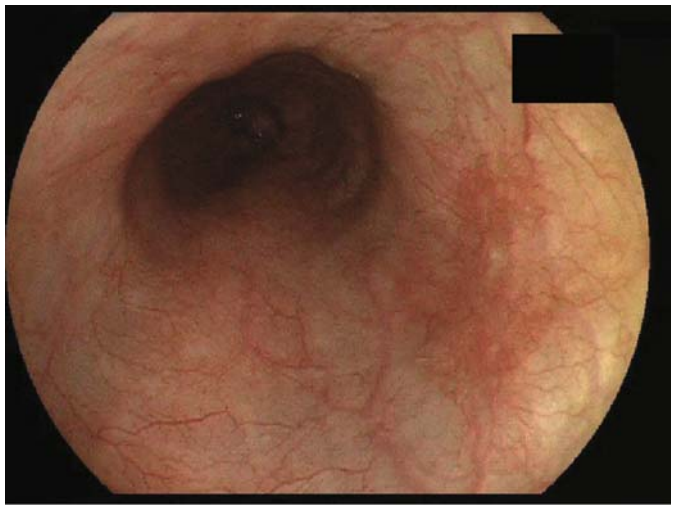


Fig. 11-9. Endoscopic appearance of intraepithelial carcinoma. There is a slightly depressed and irregular surface lesion. Histology showed squamous cell carcinoma in situ

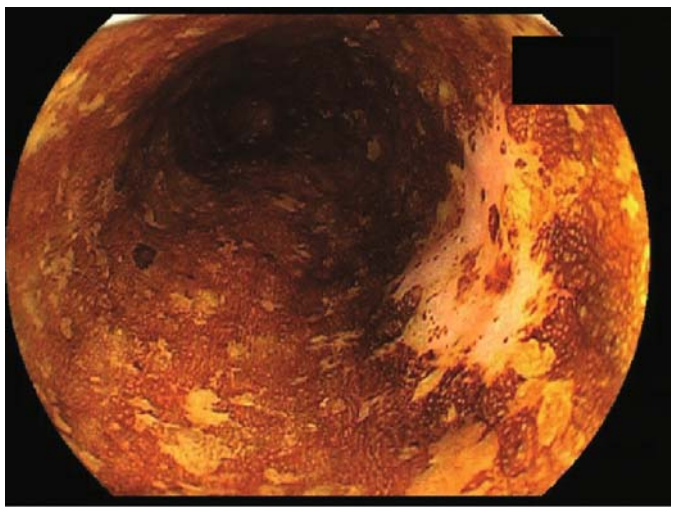


Fig. 11-10. Endoscopic appearance of an intraepithelial carcinoma after Lugol's iodine staining of Fig. 11-9. The normal mucosal epithelium stains dark brown but the carcinoma does not stain

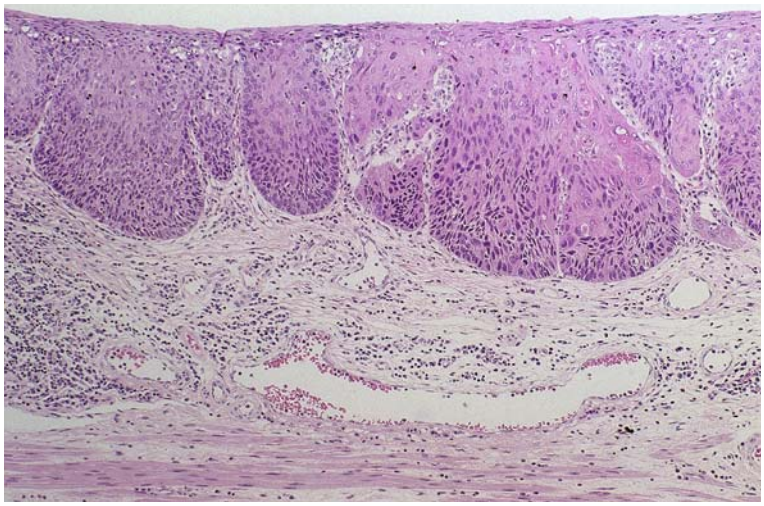


Fig. 11-11. Intramucosal squamous cell carcinoma. The carcinoma shows droplet infiltration. This is an expansive growth type of squamous cell carcinoma

Table 11-3. Histological staging of esophageal carcinoma, from the *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus* (8th edition, 1992), by the Japanese Society for Esophageal Diseases

	Depth	Lymph node metastasis	Organ metastasis	Pleural dissemination
Stage 0 (early carcinoma)	m, sm	–	–	–
Stage I	mp	–	–	–
Stage II	a1	n1	–	–
Stage III	a2	n2	–	–
Stage IV	a3	n3–n4	+	+

m, within the mucosa; sm, into the submucosa; mp, into the muscularis propria; a1, invasion reaching the adventitia; a2, definite invasion of the adventitia; a3, invasion of other structures passing through the adventitia; –, absent; +, present; n1, positive metastasis to group 1 lymph nodes; n2, positive metastasis to group 2 lymph nodes; n3–n4, positive metastasis to group 3 or 4 lymph nodes (the regional lymph nodes are divided into 4 groups depending on the location of the primary tumor)

basement membrane is wavy and cancer cells do not reach the muscularis mucosae but there is droplet, finger-like, or confluent invasion (Fig. 11-11), the lesion is regarded as an invasive carcinoma. Also, when mucosal carcinoma reaches the muscularis mucosae, even without droplet or finger-like invasion, the lesion is regarded as invasive.

11.2.2. Early, Superficial, and Advanced Carcinoma

Superficial carcinoma, defined as carcinoma in situ or carcinoma involving mucosa or submucosa regardless of the presence of lymph node metastasis, can usually be distinguished from advanced carcinoma (invading the muscularis propria) by macroscopic observation of cut surfaces of the tumor or by determining whether a superficial tumor is fixed to the muscularis propria; if not fixed, the tumor will slide over the muscularis propria when a slight force is applied parallel to the mucosa.

Early carcinoma (Stage 0 carcinoma) of the esophagus (Table 11-3) was previously defined as a superficial carcinoma with no nodal or distant metastases, but this definition has now been changed (Table 11-4). It suggests a high likelihood of cure (see Chapter 11, p. 187). The term "early carcinoma" is widely used in Japan, but it is not strictly correct, because the time from tumor onset is unknown. The term is mentioned in the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (8th edition, 1992) and, in

TABLE 11-4. Histological staging of esophageal carcinoma, from the *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus* (9th edition, 1999), by the Japanese Society for Esophageal Diseases

Metastasis \ Depth of invasion	pTis	pT1a	pT1b	pT2	pT3	pT4
pN0	0		I			III
pN1	–	I	II			IVa
pN2	–			III		
pN3	–					
pN4	–					
pM1	–			IVb		

pTis, carcinoma in situ; pT1a, carcinoma invading the lamina propria mucosae or lamina muscularis mucosae; pT1b, carcinoma invading the tunica submucosa; pT2, carcinoma invading the tunica muscularis propria; pT3, carcinoma invading the adventitia; pT4, carcinoma invading other structures passing through the adventitia
The lymph nodes are divided into four groups depend-ing on the location of the primary tumor; pN0, no lymph node metastasis; pN1, positive metastasis to group 1 lymph node(s); pN2, positive metastasis to group 2 lymph node(s); pN3, positive metastasis to group 3 lymph node(s); pN4, positive metastasis to group 4 lymph node(s); with 4–7 positive metastatic lymph nodes, pN number is stepped up one grade; with 8 or more positive nodes it is stepped up two grades; pM1, positive metastasis in distant structures apart from the recurrent laryngeal nerve, azygos vein, thoracic duct, or lymph nodes
Early carcinoma (Stage 0 carcinoma) of the esophagus was defined as an intramucosal carcinoma with no nodal or distant metastasis (9th edition) and will be defined as an intramucosal carcinoma with or without metastases (10th edition, 2007)

recent years, has also apparently become accepted in the medical literature in America and Europe.

Advanced carcinoma (Stage I, II, III, and IV carcinoma) of the esophagus was previously defined as a superficial carcinoma with metastasis, or a carcinoma that had invaded the muscularis propria or adventitia (see Table 11-3). This definition has also now been slightly changed, in accordance with the changes made to the definition of early carcinoma (see Table 11-4). Although the term advanced carcinoma is widely used it is not really the true opposite of the term superficial carcinoma.

In the most recent edition of the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (9th edition, 1999), early carcinoma was defined as an intramucosal carcinoma without nodal or distant metastases (see Table 11-4).

However, in the next edition (10th edition, 2007), early carcinoma will be defined as an intramucosal carcinoma with or without nodal metastases.

11.2.3. Relationship Between Macroscopic and Histological Types

It is desirable that the macroscopic classifications of both superficial and advanced carcinomas of all parts of the gastrointestinal tract are consistent. The current macroscopic classification of superficial esophageal carcinoma, prescribed in the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (8th and 9th editions), is in accordance with the classification of early gastric carcinoma established by the Japanese Research Society for Gastric Cancer (1962, 1998) (Figs. 11-12 through 11-20). Advanced carcinoma of the esophagus is classified macroscopically according to Borrmann's classification of gastric carcinoma (Table 11-5).

The macroscopic classification (see Fig. 11-12a,b) and the histological types of malignant esophageal tumors are closely related.

Polypoid types of superficial and advanced malignant tumor are usually found to be carcinosarcomas, squamous cell carcinomas, or malignant melanomas. Plateau-type superficial and advanced tumors are usually basaloid squamous carcinomas, adenoid cystic carcinomas, poorly differentiated squamous cell carcinomas, or adenocarcinomas, and in most superficial carcinomas of plateau type the tumor invades into the submucosa. Predominantly subepithelial-type superficial and advanced tumors are usually small cell carcinomas, basaloid squamous carcinomas, or adenoid cystic carcinomas. Cauliflower-type lesions of advanced carci-

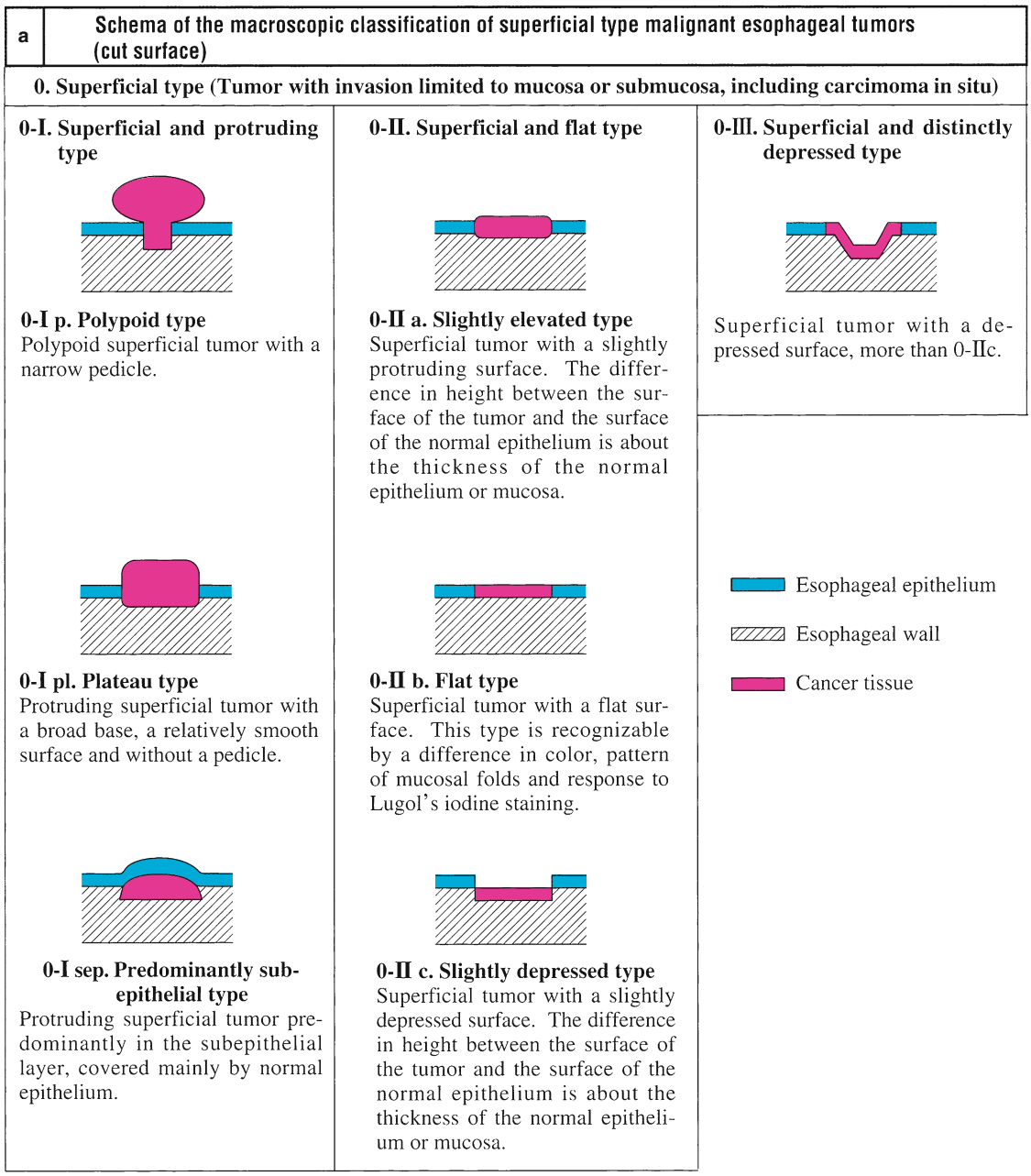


FIG. 11-12. Schema of the macroscopic classification of malignant esophageal tumors (cut surface) based on the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (9th edition, 1999) by the Japanese Esophageal Society. **a** Schema of the macroscopic classification of superficial type malignant esophageal tumors (cut surface). **b** Schema of the macroscopic classification of advanced type malignant esophageal tumors (cut surface)

noma are often well- to moderately differentiated squamous cell carcinomas. Superficial and flat-type lesions, including slightly elevated, flat, and slightly depressed types, are usually squamous cell carcinomas and are often confined to the mucosa. Most superficial and ulcerative-type malignant tumors are squamous cell carcinomas, and these usually invade the submucosa.

b Schema of the macroscopic classification of advanced type malignant esophageal tumors (cut surface)

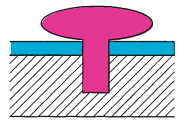
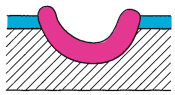
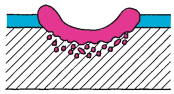
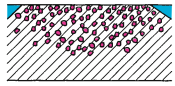
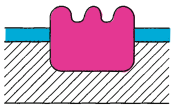
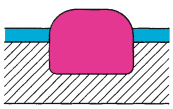
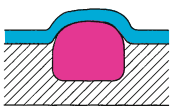
1. Protruding type	2. Ulcerative and localized type	3. Ulcerative and infiltrating type	4. Diffusely infiltrating type
			
1p. Polypoid type Polypoid advanced tumor with a narrow pedicle.	Ulcerated advanced tumor with a clear border between tumor and surrounding tissues.	Ulcerated advanced tumor with an indistinct border between tumor and surrounding tissues.	Advanced tumor with a flat surface, without clear distinction from the normal mucosal surface, and invading diffusely in the esophageal wall. This is divided into scirrhous and non-scirrhous types.
			
1c. Cauliflower type Protruding advanced tumor with a broad base and an uneven surface.			
			
1pl. Plateau type Protruding advanced tumor with a broad base and a relatively smooth surface without a pedicle.			
			
1sep. Predominantly subepithelial type Protruding advanced tumor predominantly in the subepithelial layer, covered mainly by normal epithelium.			

FIG. 11-12. *Continued*

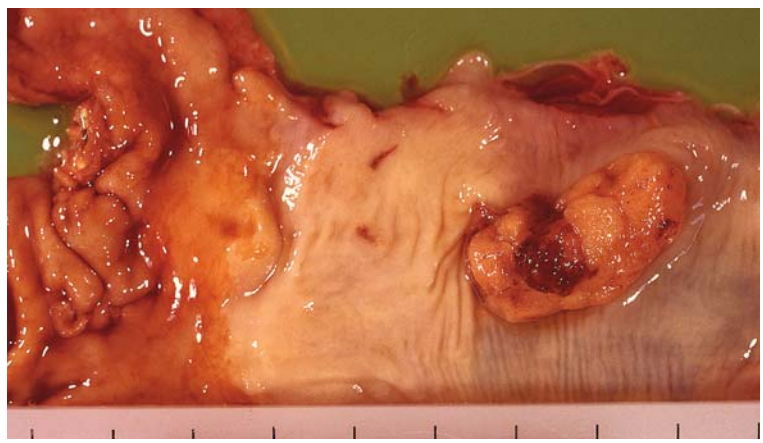


FIG. 11-13. Macroscopic appearance of a polypoid type, superficial and protruding carcinoma. Histologically, this was a moderately differentiated squamous cell carcinoma

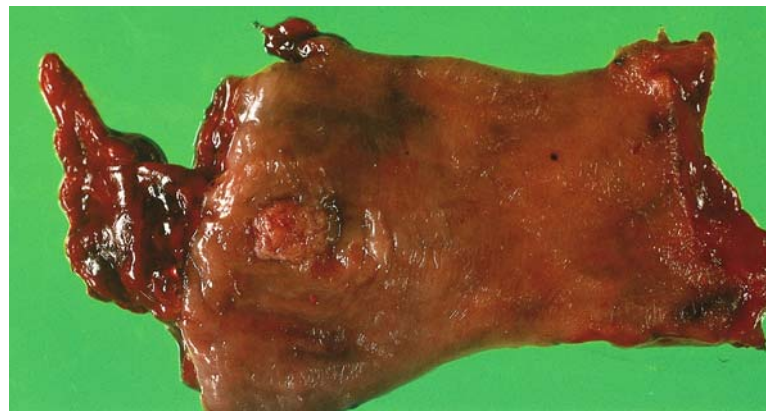


Fig. 11-14. Macroscopic appearance of a plateau-type, superficial and protruding carcinoma

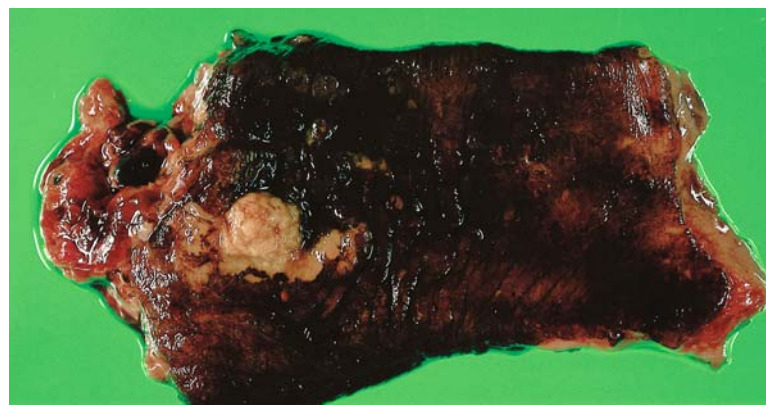


Fig. 11-15. Plateau-type, superficial and protruding carcinoma stained with Lugol's iodine solution. The normal mucosal epithelium stains dark brown but the carcinoma does not stain

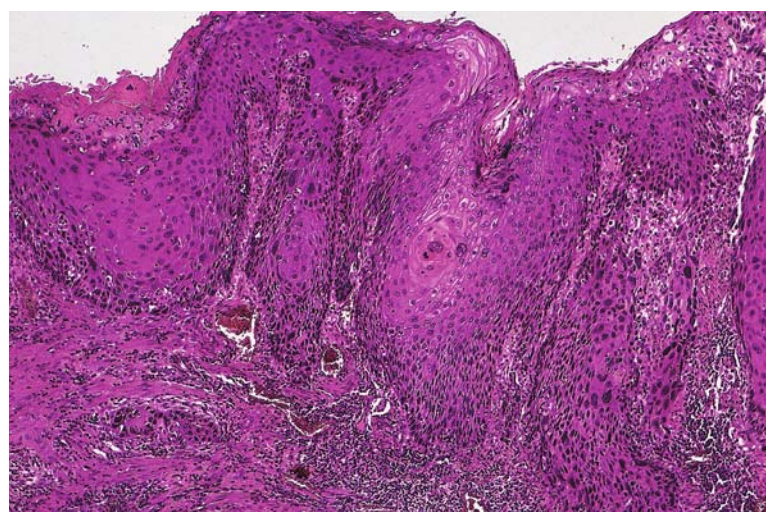


Fig. 11-16. Histological appearance of the carcinoma shown in Figs. 11-14 and 11-15. A moderately differentiated squamous cell carcinoma is invading the submucosa with an expansive growth pattern

Ulcerative and localized types of advanced malignant tumor are usually squamous cell carcinomas. Ulcerative and infiltrating types of advanced tumor are usually squamous cell carcinomas, adenosquamous carcinomas, or mucoepidermoid carcinomas. Diffusely infiltrating types of advanced tumor, with sclerosis, are often adenosquamous or mucoepidermoid carcinomas (Mafune et al.).

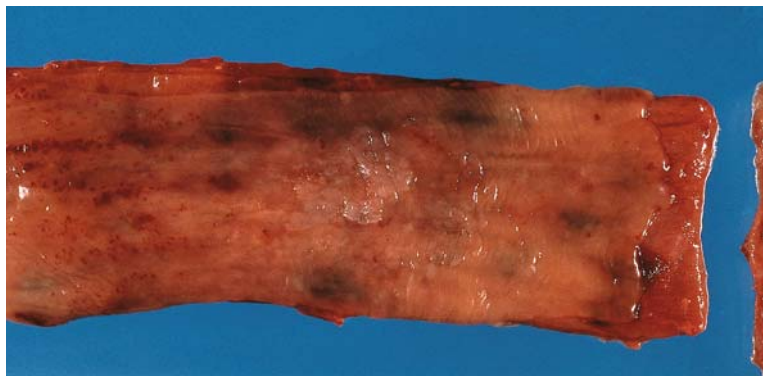


Fig. 11-17. Macroscopic appearance of a slightly elevated type, superficial and flat carcinoma

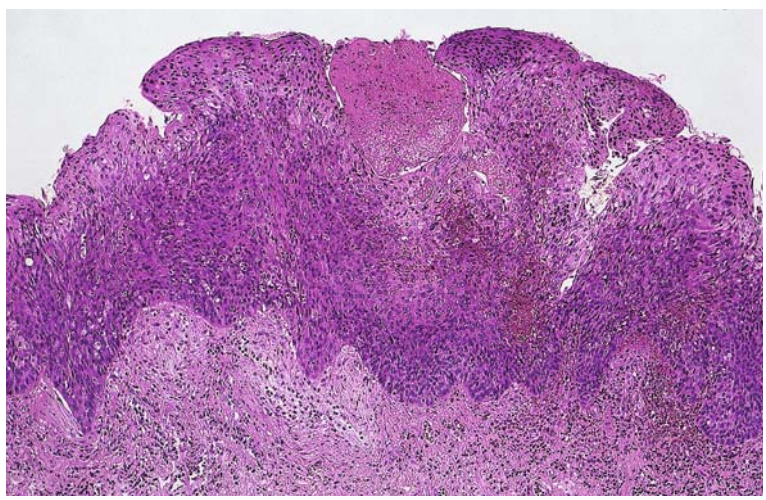


Fig. 11-18. Histological appearance of the carcinoma shown in Fig. 11-17. This section shows a moderately differentiated squamous cell carcinoma within the mucosa

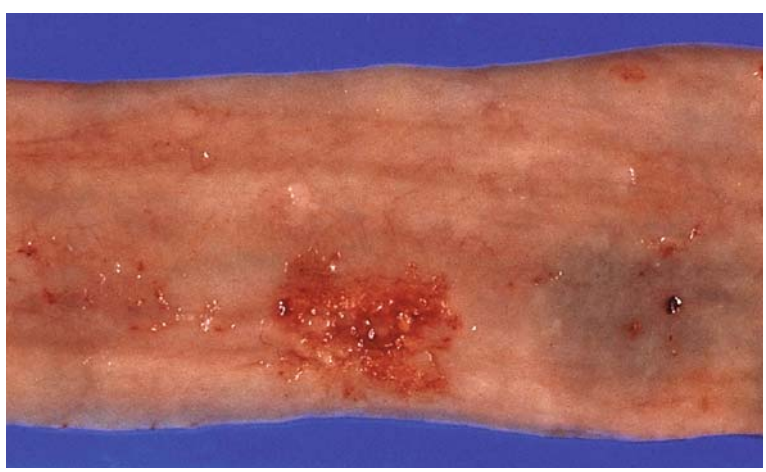


Fig. 11-19. Macroscopic appearance of a slightly depressed type, superficial and flat carcinoma. This lesion was a squamous cell carcinoma in situ that was thinner than the normal epithelium

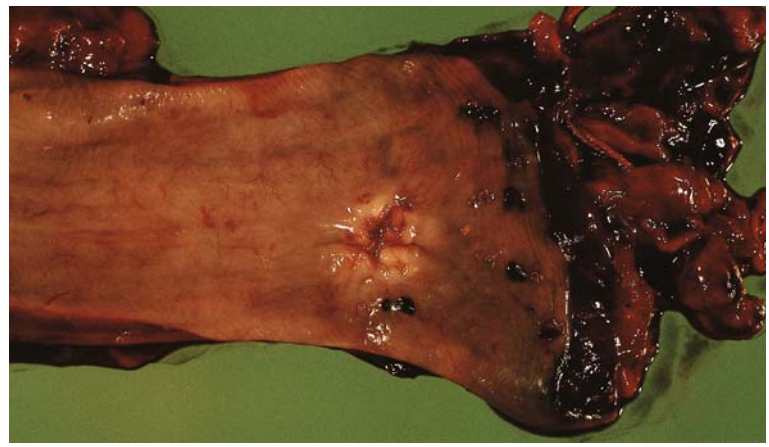


Fig. 11-20. Macroscopic appearance of a superficial and distinctly depressed type of carcinoma. This lesion was a squamous cell carcinoma with submucosal invasion

Table 11-5. The macroscopic classification of esophageal carcinoma, from the *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus* (8th and 9th editions), by the Japanese Society for Esophageal Diseases

0. Superficial type
   - I. Superficial and protruding type
     - p. Polypoid type [Papillary type]
     - pl. Plateau type
     - sep. Predominantly subepithelial type
   - II. Superficial and flat type
     - a. Slightly elevated type
     - b. Flat type
     - c. Slightly depressed type
   - III. Superficial and distinctly depressed type

1. Protruding type
   - p. Polypoid type
   - c. Cauliflower type
   - pl. Plateau type
   - sep. Predominantly subepithelial type

2. Ulcerative and localized type
3. Ulcerative and infiltrating type
4. Diffusely infiltrating type
   - s. Scirrhous type
   - ns. Non-scirrhous type

5. Miscellaneous type
   - c. Combined type
   - s. Other specific type
   - u. Unclassifiable type

11.2.4. Histological Features and Subclassification of Squamous Cell Carcinoma

Squamous cell carcinomas form solid nests and show squamous differentiation, characterized by the presence of keratinization and intercellular bridges. Conventional squamous cell carcinomas of the esophagus occasionally have a minor component of adenocarcinoma or basaloid squamous carcinoma (Kuwano et al.; Takubo et al.). Electron microscopy of squamous cell carcinomas also occasionally shows morphological features of adenocarcinoma (Newman et al.). Despite the presence of minor adenocarcinomatous or basaloid components the lesion should still be classified as a squamous cell carcinoma, with a supplementary note given about the presence of the other component. There is, however, no established upper limit for the percentage of another component allowed for a lesion to still be classified as a squamous cell carcinoma.

Squamous cell carcinomas are subclassified into well (Figs. 11-21, 11-22), moderately, and poorly differentiated types (Figs. 11-23, 11-24), depending on the amount of keratinization.

The superficial keratinizing layer of differentiated squamous cell carcinoma in situ tends to exfoliate. It is therefore often difficult to recognize well-differentiated squamous cell carcinoma in situ applying the criterion of the degree of keratinization. For this reason, the *Guidelines* do not subclassify carcinoma in situ. In addition, many believe that the term "keratinized" is preferable to "differentiated" because the esophageal epithelium is essentially nonkeratinizing.

Cytologically, esophageal squamous cell carcinomas show clusters of highly atypical cells, often stainable with Orange G (Figs. 11-25, 11-26).

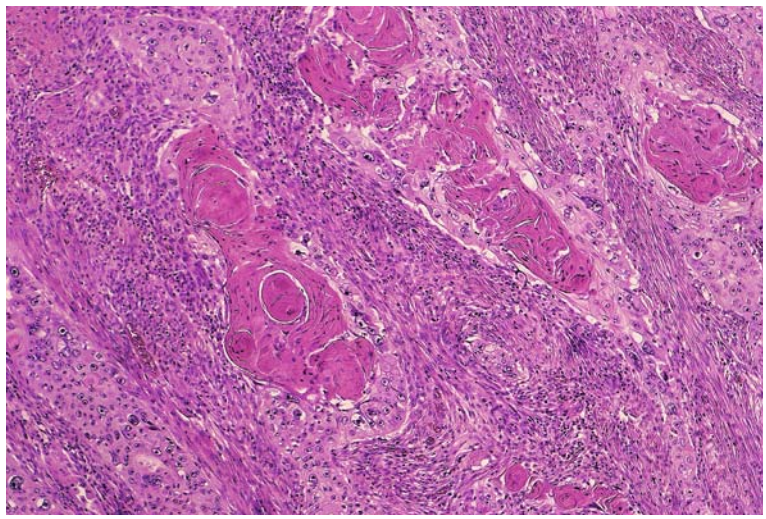


FIG. 11-21. Well-differentiated squamous cell carcinoma. The tumor has large areas of keratinization

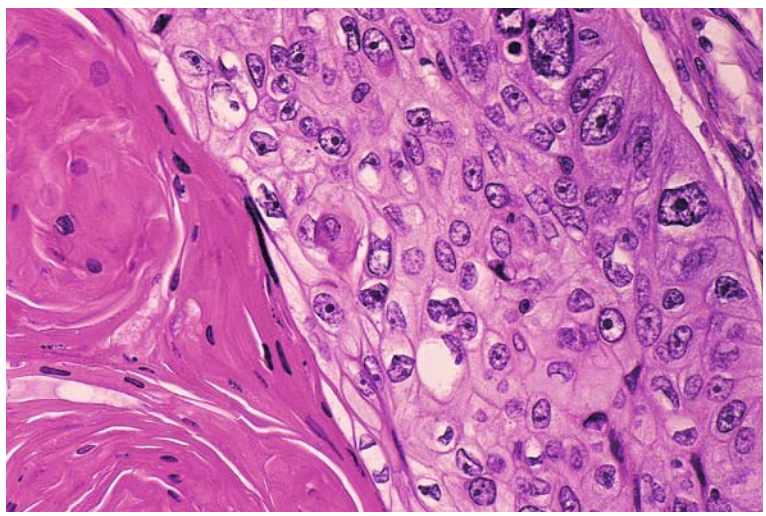


FIG. 11-22. Well-differentiated squamous cell carcinoma. The tumor consists of large cells and shows keratinization

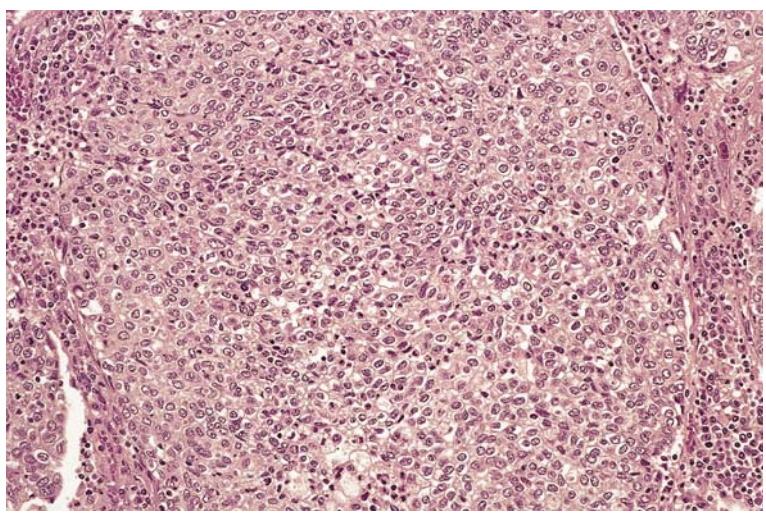


FIG. 11-23. Poorly differentiated squamous cell carcinoma. The tumor is composed of large cells

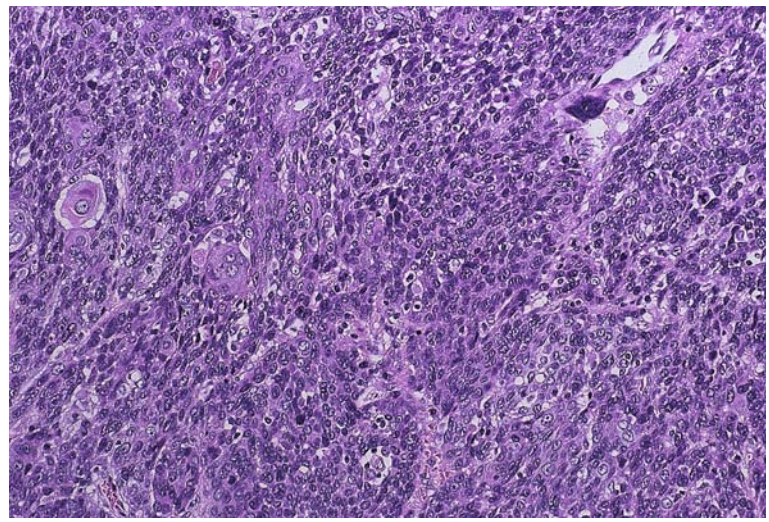


Fig. 11-24. Poorly differentiated squamous cell carcinoma. The tumor is composed of small cells

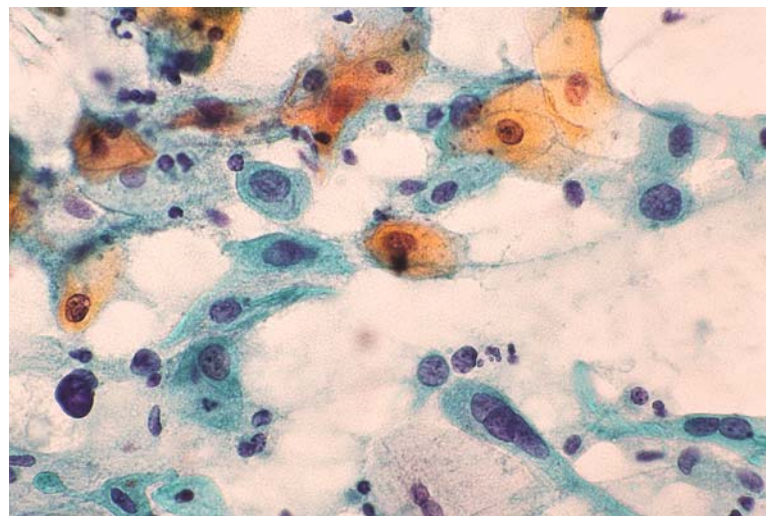


Fig. 11-25. Cytological smear of a well-differentiated squamous cell carcinoma (Papanicolaou stain). Large keratinizing and nonkeratinizing tumor cells are seen

Keratinizing cells are occasionally found even in cases of poorly differentiated squamous cell carcinoma (Figs. 11-27, 11-28), in contrast to a lack of keratinizing cells in basaloid squamous carcinoma. The nuclei of carcinoma cells are large and show membrane thickening and prominent nucleoli. There is a distinct increase in chromatin content, the nuclei staining deeply with hematoxylin and sometimes being described as India ink like.

11.2.4.1. Verrucous Carcinoma of the Esophagus

The *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* do not specify verrucous carcinoma, which is a less-invasive form of squamous cell carcinoma than conventional squamous cell carcinoma and has relatively little cellular atypia. Rather, the *Guidelines* classify it as a type of well-differentiated squamous cell

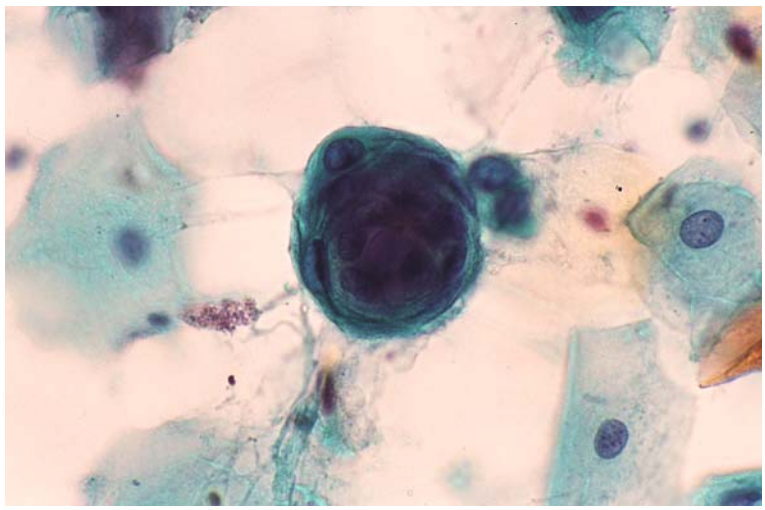


Fig. 11-26. Cytological smear of a well-differentiated squamous cell carcinoma (Papanicolaou stain). A squamous pearl is evident

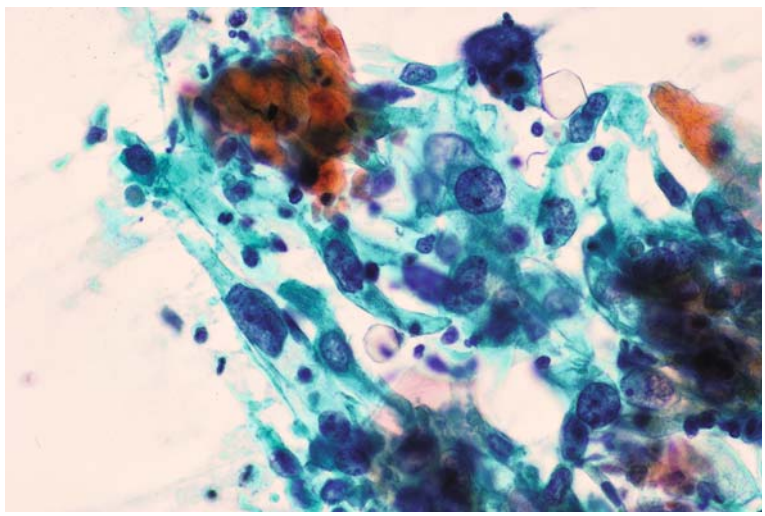


Fig. 11-27. Cytological smear of a poorly differentiated squamous cell carcinoma (Papanicolaou stain). There are occasional dyskeratotic cells that stain positively with Orange G

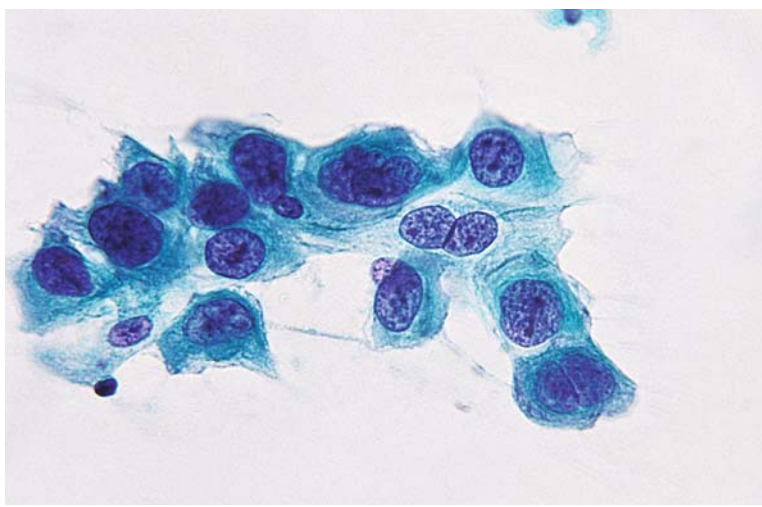


Fig. 11-28. Cytological smear of a poorly differentiated squamous cell carcinoma (Papanicolaou stain). Small tumor cells with a high nuclear to cytoplasmic ratio are evident

carcinoma, regardless of whether there is any keratinization, but the WHO histological classification of esophageal carcinoma (see Table 11-2) classifies verrucous carcinoma separately. Verrucous carcinoma is occasionally seen in association with achalasia (Minielly et al. 1967; Roach and Barr 1993).

The present author has never seen an example of verrucous carcinoma of the esophagus in routine practice, but he has had the good fortune to see two cases in consultation, kindly provided from Japan and Germany. The incidence of verrucous carcinoma of the esophagus would seem to be very low and, in fact, having reviewed histological micrographs published in the literature, the present author considers that very few published examples of verrucous carcinoma of the esophagus actually exhibit the typical features of the entity as seen, for example, in the uterine cervix. Around 13 cases of esophageal verrucous carcinoma have been reported (Tajiri et al. 2000). Human papillomavirus (HPV) has not been detected in esophageal verrucous carcinoma (Malik et al. 1996).

Macroscopically, verrucous carcinoma of the esophagus has a white or reddish, rough surface (Fig. 11-29).

Histologically it is a very well differentiated squamous cell carcinoma, with or without keratinization. Verrucous carcinoma shows expansive growth. Prominent acanthotic squamous epithelium and atypical basal cells abutting stroma are characteristic (Fig. 11-30). Two or more nucleoli are often seen in basal cell nuclei (Fig. 11-31). Mitotic figures and dyskeratosis are relatively frequent. Keratinization, with or without a granular layer, is occasionally seen. In deeply invasive portions, the cancer nests may show keratinization that abuts stromal tissue.

11.2.4.2. Esophageal Carcinoma with Lymphoid Stroma

As at other sites such as the breast, uterus, and stomach, carcinomas accompanied by many lymphoid follicles and a prominent infiltrate of lymphocytes and plasma cells in cancerous and stromal tissue have been reported in the esophagus. The first case reports were by Amano et al. (1988) and Mori et al. (1989). There have been a few reviews and other recent reports of such tumors in the literature (Sashiyama et al. 1999; Takubo and Lambie 2001; Chen et al. 2003; Angulo-Pernett and Smythe

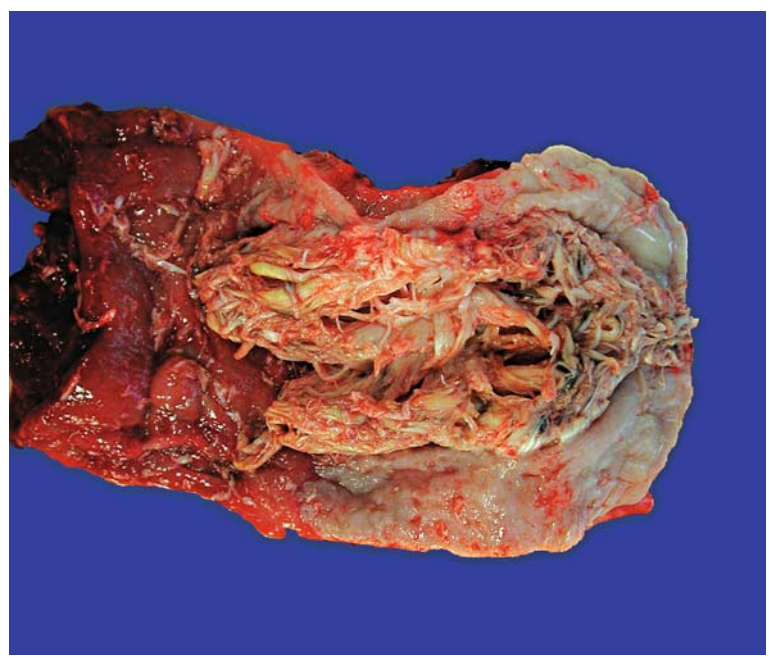


FIG. 11-29. Macroscopic appearance of a verrucous carcinoma of the esophagus. The tumor has a white, roughened surface resembling a cauliflower

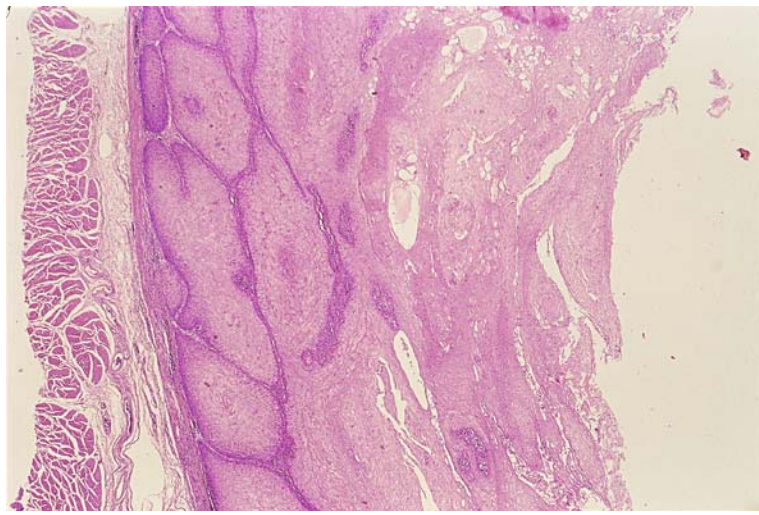


FIG. 11-30. Verrucous carcinoma of the esophagus. There is prominent acanthotic squamous epithelium showing expansive growth into the lamina propria

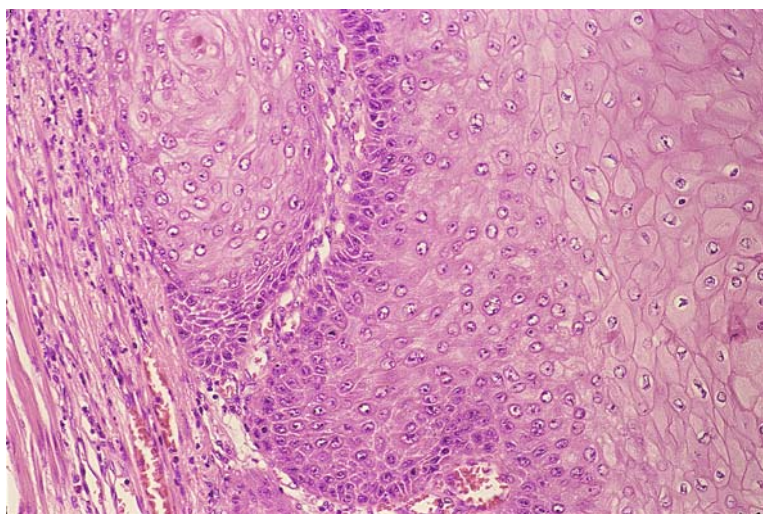


FIG. 11-31. Verrucous carcinoma of the esophagus. There are atypical basal cells in the squamous nests. The basal cell nuclei each have two or more nucleoli. Mitotic figures and dyskeratosis are relatively frequent. There is also some focal keratinization

2003), and a total of 15 cases of esophageal carcinoma of this type have been reported.

Macroscopically, these tumors have mainly been of the predominantly subepithelial type (see Table 11-5), with growth beneath the epithelium (Fig. 11-32), occasionally with associated intraepithelial spread. Histologically, they have been classified as poorly differentiated squamous cell carcinoma (Figs. 11-33, 11-34) in 12 of the reported cases, non-small cell-type undifferentiated carcinoma in 2, and Barrett's adenocarcinoma (Takubo and Lambie) in 1 case.

Metastases to lymph nodes at the time of esophagectomy have been noted in several of the reported cases. The prominent lymphoid infiltrate would be expected to give this type of carcinoma a favorable prognosis, as is the case for medullary carcinoma of the breast and for gastric carcinoma with lymphoid stroma. Some tumors of this type have been associated with Epstein–Barr virus infection.

No specific description of this entity has been given in either the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* or in the WHO classification of esophageal tumors. Figures 11-32 through 11-34 show the macroscopic and histological appearances of the case reported by Murata et al. (1995). This carcinoma was of superficial type and invaded the submucosa.

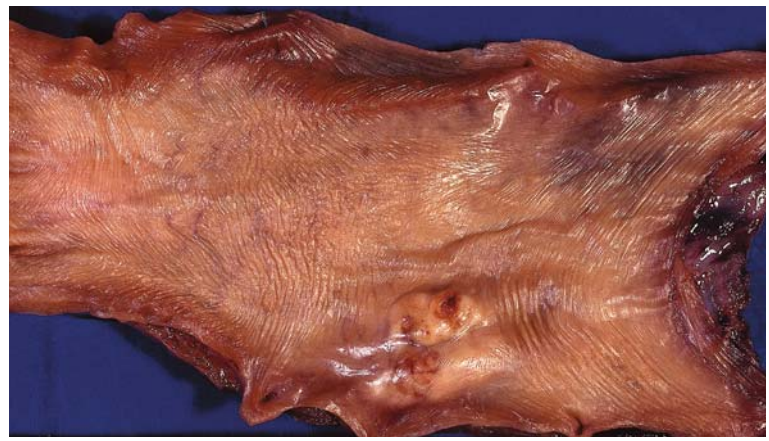


Fig. 11-32. Macroscopic appearance of an esophageal carcinoma with lymphoid stroma. The tumor has the macroscopic appearance characteristic of a predominantly subepithelial type of carcinoma and is covered mainly by nonneoplastic epithelium. The superficial erosion on the tumor is the result of a preoperative biopsy procedure

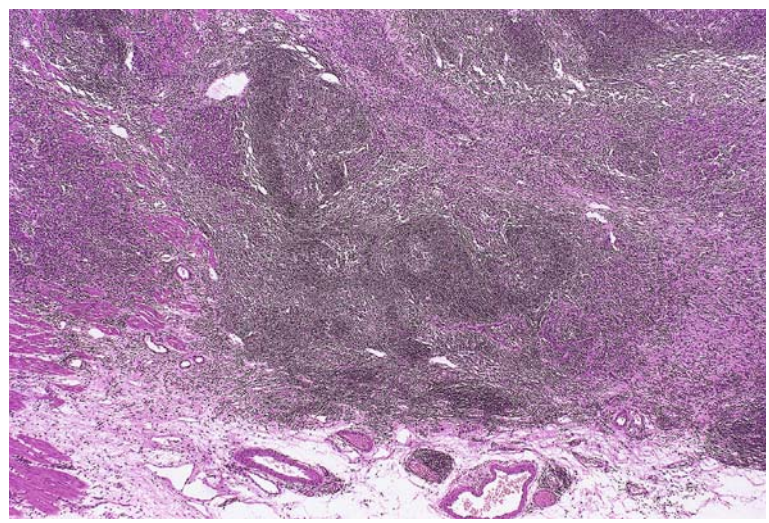


Fig. 11-33. Esophageal carcinoma with lymphoid stroma. The tumor is heavily infiltrated by lymphocytes and plasma cells. Lymphoid follicles are also present

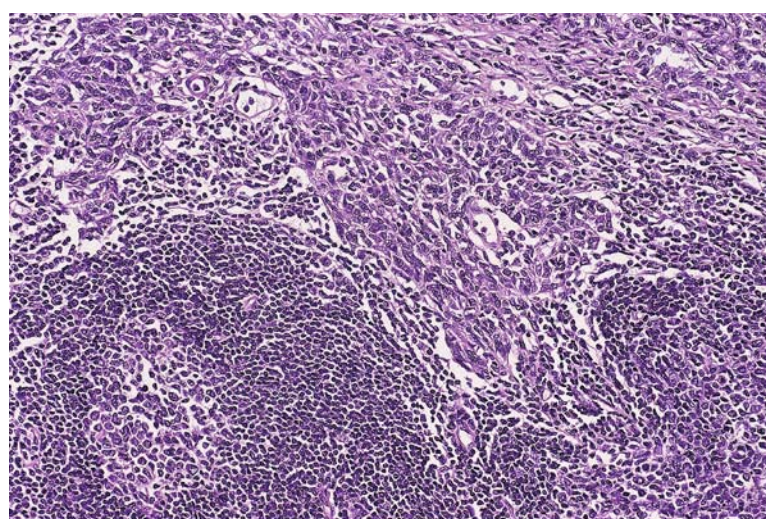


Fig. 11-34. Esophageal carcinoma with lymphoid stroma. High magnification of Fig. 11-33, showing a nonkeratinizing carcinoma and associated lymphoid follicle. The tumor and stromal tissue are infiltrated by lymphocytes

11.2.5. Histological Growth Pattern

The histological growth pattern at the advancing edge of esophageal carcinomas (not just squamous cell carcinomas) is usually divided into three types. In the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*, invasion as large cell nests is called the expansive type (Fig. 11-35), whereas invasion as small nests, each consisting of several tumor cells, is termed the markedly infiltrative type (Fig. 11-36). An intermediate form between these two is termed the moderately infiltrative type. The invasive pattern often varies in different parts of a tumor, however, making it difficult in routine practice to classify some cases.

11.2.6. Growth Rate

It is said that esophageal squamous cell carcinomas grow faster than cancers of other parts of the gastrointestinal tract. The doubling time of squamous cell carcinoma, which accounts for the majority of esophageal cancers in Japan, has been reported to range from 0.54 to 25.4 months, with a mean of 6.3 months, based on consecutive radiologic examinations (Nabeya et al.). The doubling times of other types of esophageal carcinoma are discussed in the sections describing these tumors.

11.2.7. Venous and Lymphatic Permeation

Elastic fibers are present in the walls of large lymphatic vessels, more than 40 μm in diameter, as in

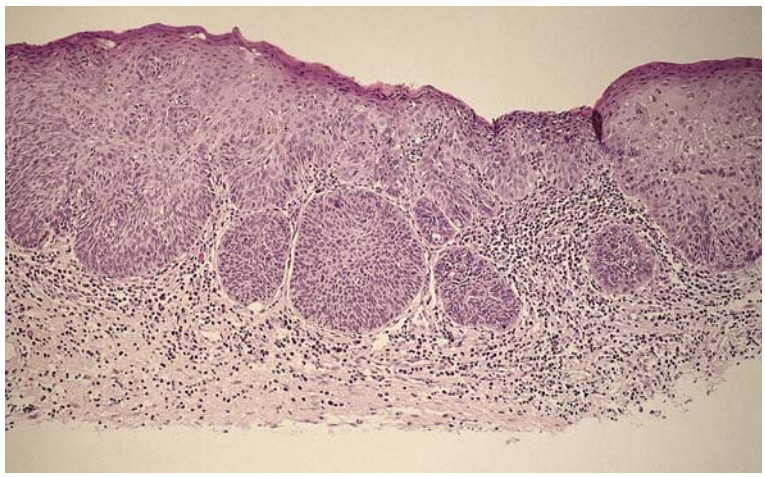


Fig. 11-35. Expansive growth of squamous cell carcinoma. Expansive growth of a poorly differentiated squamous cell carcinoma

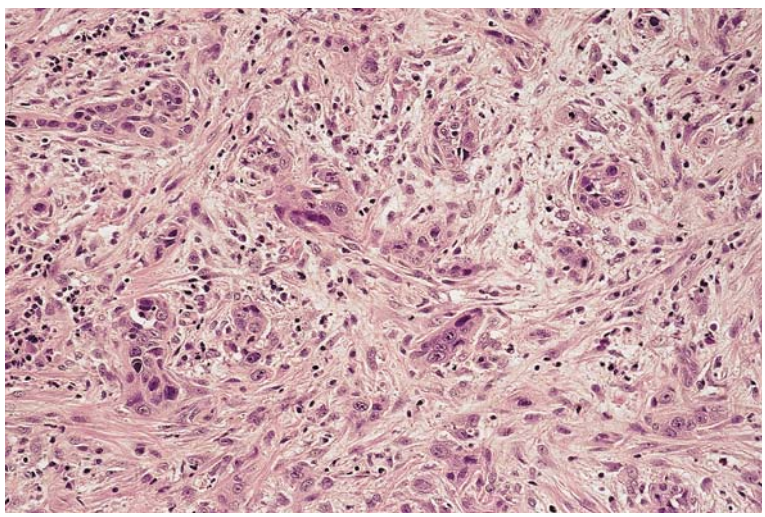


Fig. 11-36. Markedly infiltrative growth of squamous cell carcinoma. Small nests of tumor cells are seen in the fibrous tissue

vein walls, so it is difficult with elastic stains to distinguish lymphatic permeation from venous permeation by carcinoma (Figs. 11-37 through 11-39). It has been reported that larger lymphatic vessels, measuring more than 100–200 μm in diameter, have a muscular layer. The presence of erythrocytes in the lumen does not rule out the possibility that a vessel is lymphatic because a lymphatic vessel may convey erythrocytes from a site of bleeding. One attempt to distinguish between veins and lymphatics used an antibody to stain the basement membrane (Barsky et al.), and it has been said that immunostaining for factor VIII stains almost all endothelial cells in blood vessels but only a small proportion of endothelial cells in lymph vessels, and that the latter staining is weak (Martin et al.) (Fig. 11-40). Also, it has been reported that immunostaining for CD 31 stains almost all endothelial cells in blood vessels whereas immunostaining for D2-40 stains all lymphatic endothelial cells (Inayama et al. 2005). Generally, however, the two vessel types are distinguished by routine hematoxylin and eosin stains and by elastic stains, but this is probably not always accurate.

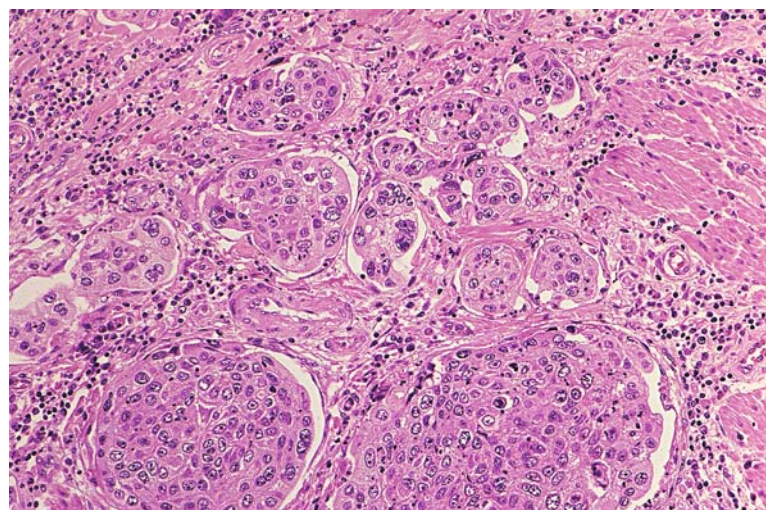


Fig. 11-37. Lymphatic permeation by squamous cell carcinoma. There are multiple tumor emboli in lymphatic vessels

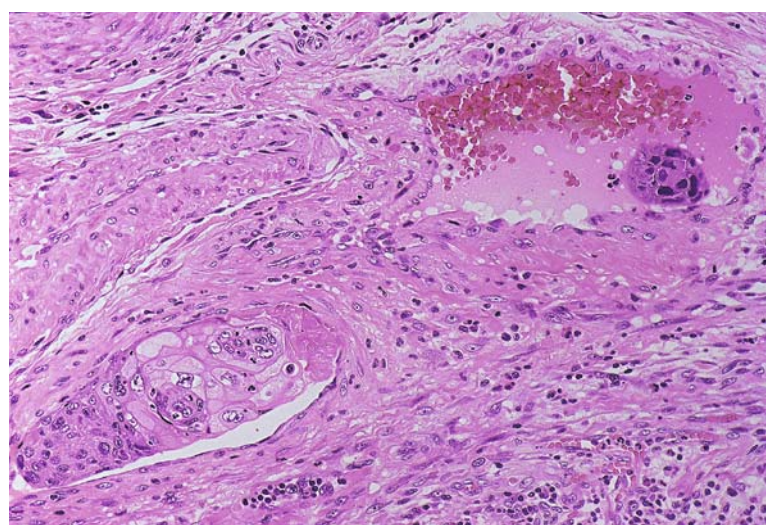


Fig. 11-38. Venous permeation by squamous cell carcinoma. Two tumor emboli are seen in veins, which also contain red blood cells

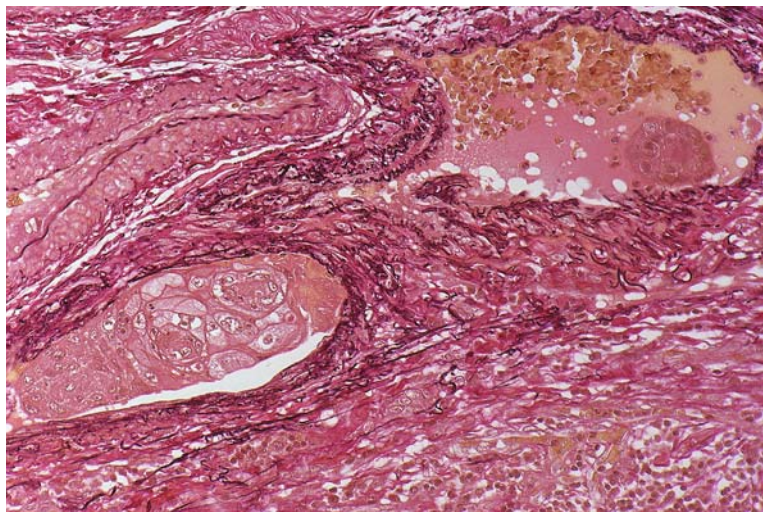


FIG. 11-39. Venous permeation by squamous cell carcinoma (elastica van Gieson stain). A serial section of the specimen shown in Fig. 11-38

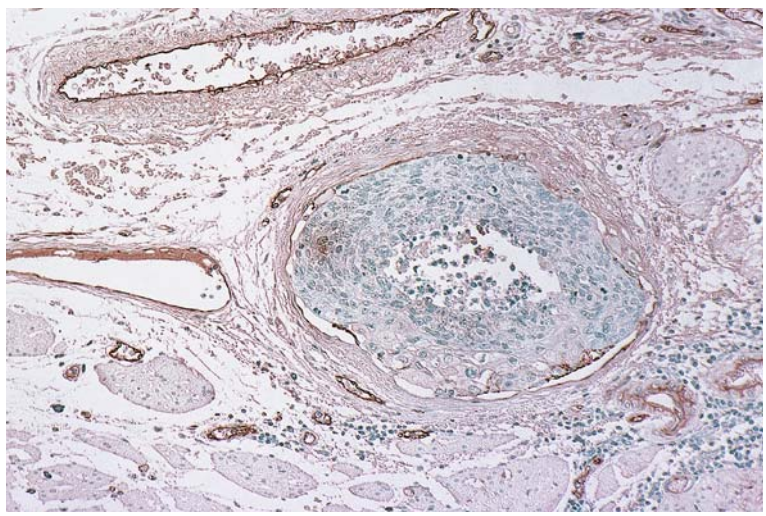


FIG. 11-40. Venous permeation by squamous cell carcinoma (factor VIII immunostain). A tumor embolus is surrounded by factor VIII-positive endothelial cells

Theoretically, there should not be any lymphatic permeation in cases of intraepithelial carcinoma. Vascular permeation was found in 29% of cases of mucosal carcinoma that had invaded the lamina propria and muscularis mucosae in one of the author's studies (Takubo et al.). Elastic stains demonstrate vascular permeation in about 80% of cases of advanced carcinoma of the esophagus. In routine practice, a few tissue blocks containing carcinoma should always be examined with elastic stains.

Venous and lymphatic permeation are each divided into three grades in the 8th and 9th editions of the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*. Permeation is judged to be severe when lymphatic or venous tumor emboli can be easily found in each section of tumor, mild when only a few emboli are found throughout the entire tumor, and moderate between these two. There is likely to be wide interobserver variability in this assessment, however, which is why earlier editions of the *Guidelines* said that only the presence or absence of venous and lymphatic permeation should be assessed. Sasaki et al. have investigated vessel permeation by esophageal carcinoma, but they did not distinguish lymphatic from venous permeation.

Electron microscopy has revealed that squamous carcinoma cells within vessels are larger, and have less uneven cell membranes, than do those outside vessels. Also, their microvilli are shorter and rather thicker than those of cells outside vessels (Fig. 11-41).

11.2.8. Intraepithelial Spread and Ductal Involvement

11.2.8.1. Intraepithelial Spread in Esophageal Mucosa

Intraepithelial spread is infiltration by tumor cells within the mucosal surface epithelium, without extending into deeper layers of the wall. This pattern of spread is often seen in squamous cell carcinomas of the uterine cervix. In the esophagus, histological examination may show that intraepithelial spread, recognized macroscopically, may not necessarily remain confined to the epithelium but may infiltrate into the stroma in some places. This author found intraepithelial spread of 2 mm or more in 63% of a series of esophageal carcinomas (Takubo et al. 1987). Such intraepithelial spread is histological evidence that a tumor is an esophageal primary, allowing distinction from an intramural metastasis from either an esophageal carcinoma elsewhere or from a carcinoma of

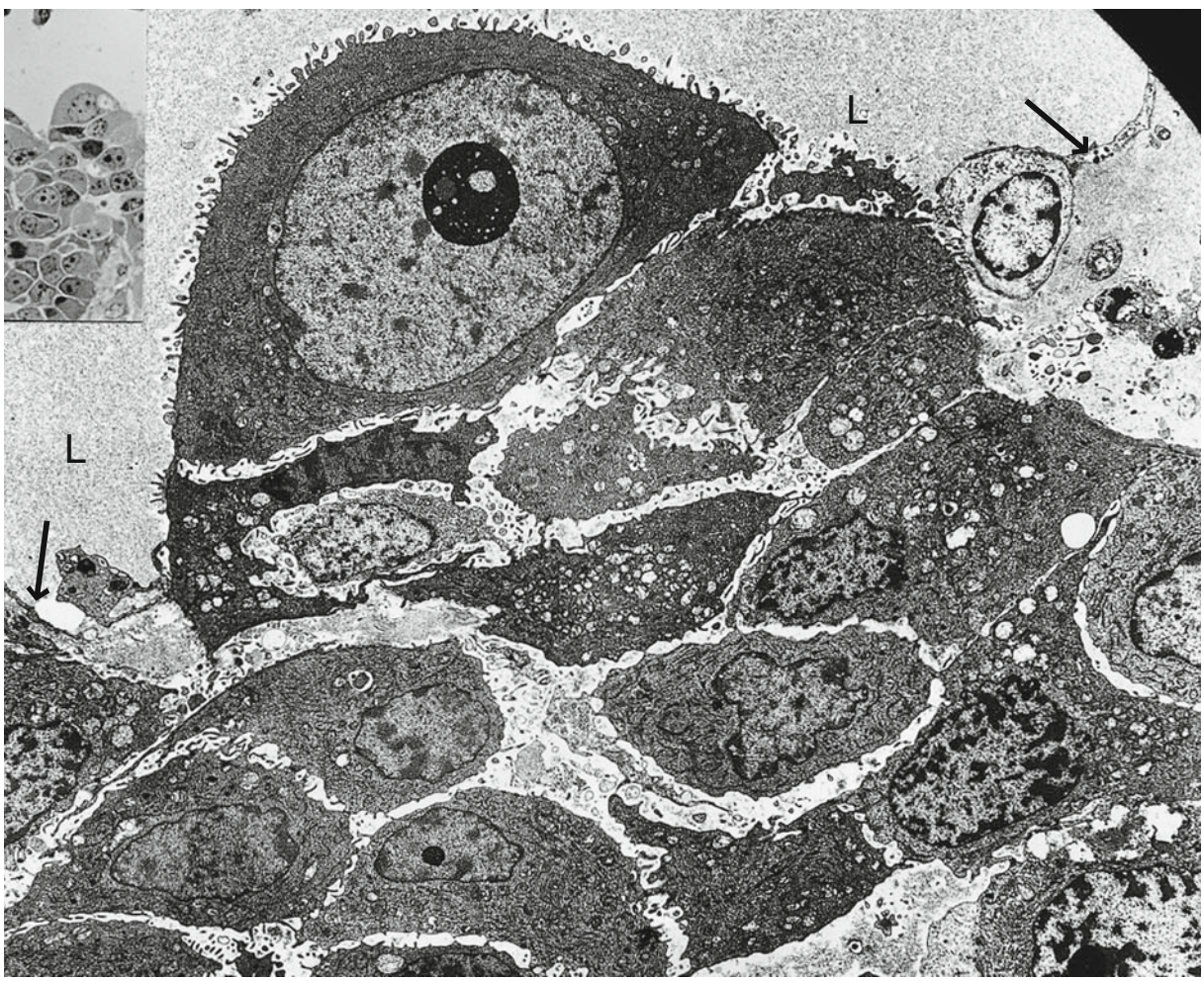


Fig. 11-41. Electron micrograph of lymphatic permeation by cancer cells. The cell membranes of tumor cells facing the lymphatic lumen are less uneven than elsewhere. *L*, lumen of the lymph vessel; *arrows*, endothelium; *inset*, semithin section

another primary site. The absence of intraepithelial spread, however, does not rule out the possibility that the tumor is primary esophageal.

Macroscopically, mucosa involved by intraepithelial spread is brownish, so is often readily distinguishable from the normal white epithelium of the esophagus. Well-differentiated intraepithelial squamous cell carcinomas occasionally show a pearl-like white luster. Lugol's iodine solution stains the uninvolved epithelium dark brown (Voegeli 1966), allowing easier recognition of intraepithelial spread (see Fig. 11-15).

Intraepithelial spread can be histologically subdivided by the appearance of the basement membrane into a simple replacement type, showing a linear basement membrane pattern (Fig. 11-42), and a bulky outgrowth type, showing a markedly wavy pattern (Fig. 11-43), similar to the appearances of the basement membrane in squamous carcinoma in situ. Intraepithelial spread may also be classified into a total layer type, in which the total epithelium is replaced by tumor cells, a basal layer type, in which the basal half is predominantly replaced (Fig. 11-44), and a mixed type, showing a combination of the two. It is common for there to be a large number of lymphoid follicles in the lamina propria beneath areas of intraepithelial spread.

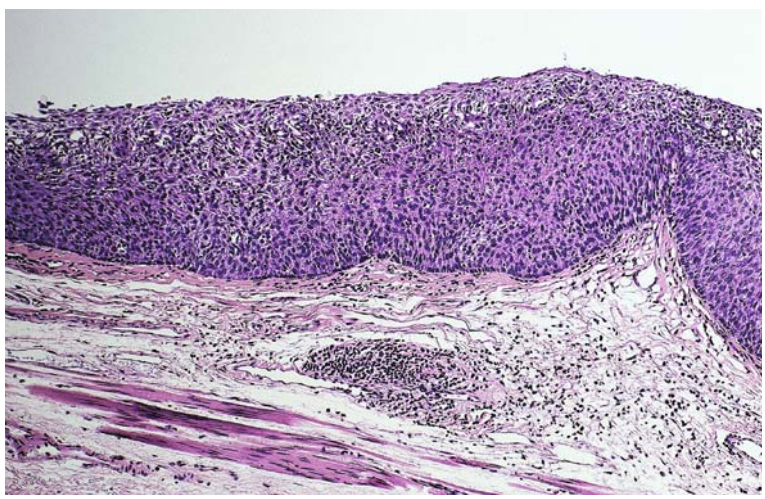


Fig. 11-42. Simple replacement type of intraepithelial spread. This is the total layer simple replacement type of spread. The basement membrane is almost linear. The epithelium is completely replaced by carcinoma cells

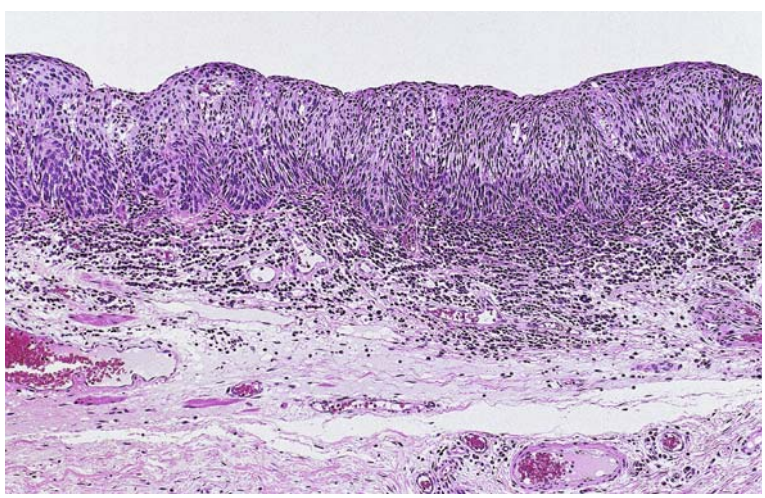


Fig. 11-43. Bulky outgrowth type of intraepithelial spread. The total layer bulky outgrowth type of spread. The basement membrane has a wavy appearance. The epithelium is completely replaced by carcinoma cells

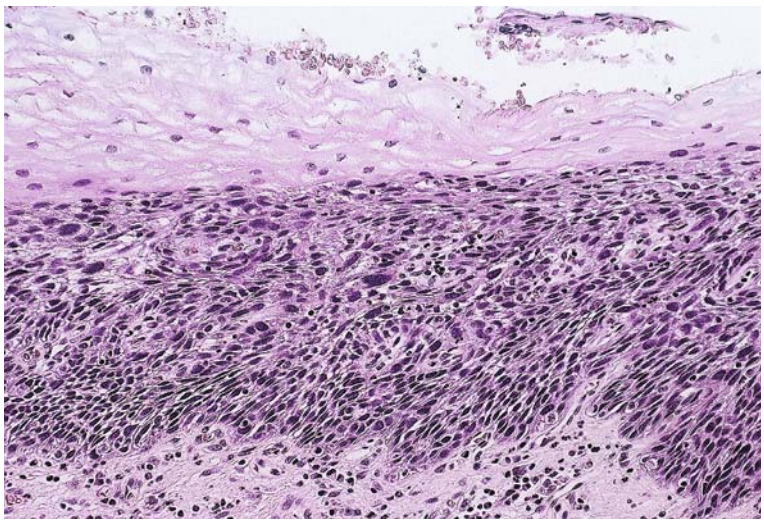


Fig. 11-44. Basal layer type of intraepithelial spread. The basal half of the epithelium is replaced by carcinoma cells

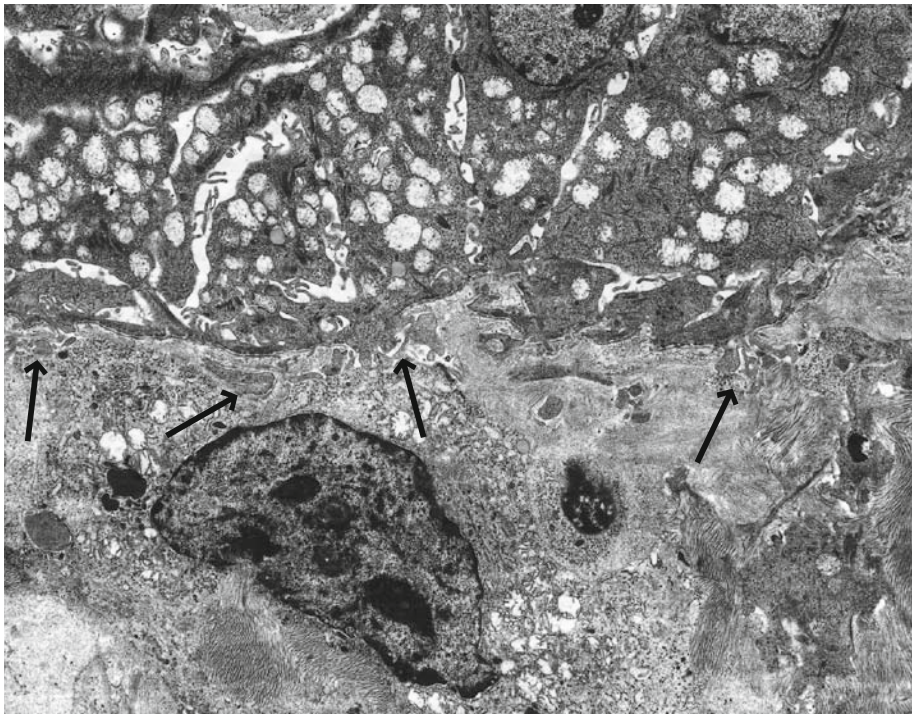


Fig. 11-45. Electron micrograph of intraepithelial spread of the bulky outgrowth type. Many pseudopodial projections (*arrows*) protrude into the lamina propria from the carcinoma cells on the basement membrane. The basement membrane is interrupted by the pseudopodial projections

Electron microscopy often shows the basement membrane to be interrupted in intraepithelial spread of bulky outgrowth type, with tumor cells having many pseudopodial projections that protrude through the basement membrane toward the lamina propria (Fig. 11-45). Lysosomes are often seen in the pseudopodial projections. In the simple replacement type, the basement membrane is continuous. The bulky outgrowth pattern is thus considered to be a little more advanced than the simple replacement pattern. In other words, on the basis of these ultrastructural features, a lesion showing the bulky outgrowth pattern is considered to be at the very first stage of invasion.

Tumor cells infiltrate between the basement membrane and the epithelium at the interface between normal epithelium and epithelium involved by intraepithelial spreading carcinoma. Also, there are often degenerate epithelial cells and inflammatory cells at the interface (Fig. 11-46). Tumor cells are sometimes directly attached to normal epithelial cells by desmosomes (Fig. 11-47), providing evidence that benign and malignant cells can form desmosomes cooperatively (Takubo et al. 1984).

11.2.8.2. Intraepithelial Spread in Gastric Mucosa

It is rare to find intraepithelial spread from esophageal carcinomas into gastric mucosa and, if present, it usually only involves a small area. Figure 11-48 is a micrograph of the largest area of intraepithelial spread into gastric mucosa seen in a series examined by the present author, where extension into the columnar epithelium of the gastric mucosa measured up to 24 mm from the esophagogastric junction.

11.2.8.3. Ductal Involvement

Intraepithelial spreading carcinoma involving the excretory ducts of the esophageal glands proper, without accompanying stromal invasion, is called ductal or intraductal involvement (Fig. 11-49). Such intraductal involvement has also been described in uterine cervical, mammary, and prostate cancers. Involvement of ducts of the esophageal glands proper had only been described in a few case reports since 1955 (O'Gara and Horn; Yagasaki et al.), so the present author carried out a systemic study of this issue and reported the results in 1987. This author defines positive ductal spread in esophageal carcinoma as spread of tumor cells into ducts in the submucosa. According to this definition, ductal spread was found in 19% of the cases examined. The current editions (8th and 9th) of the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* prescribe that involvement of ducts in the submucosa by spread from intramucosal carcinoma should not be regarded as submucosal invasion, provided there is no invasion into the stroma of the submucosa. There remains the question, however, as to whether ductal spread forming an extremely large cyst, which occasionally occurs, should also follow this definition.

Lesions in which tumor cells have reached the terminal portions of the esophageal glands proper are considered to have glandular involvement (Fig. 11-50); this was found in 36% of tumors that showed ductal spread.

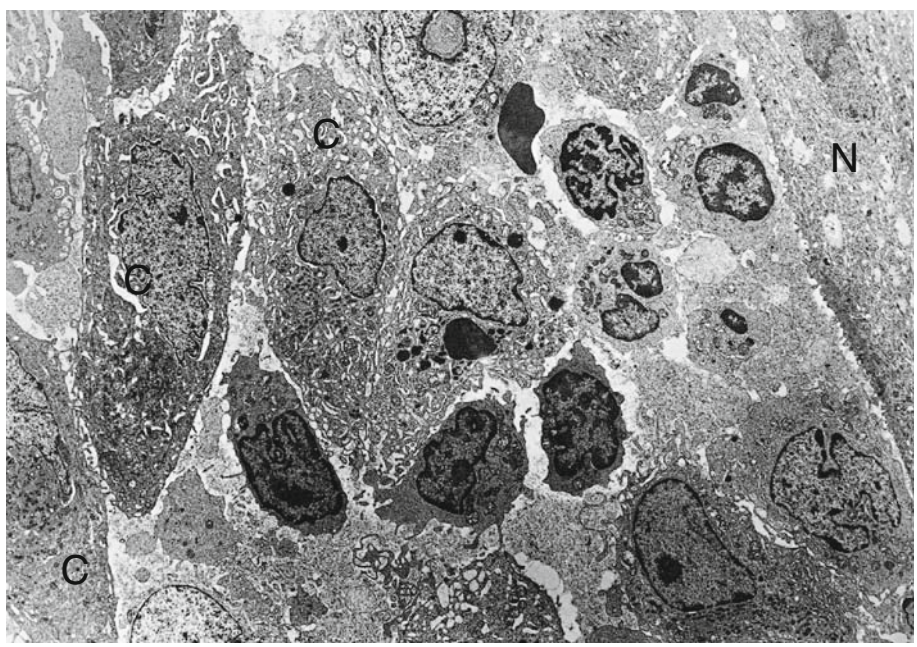


FIG. 11-46. The interface between a squamous cell carcinoma and normal mucosal epithelium. There are degenerate epithelial cells and mesenchymal cells at the interface between the intraepithelial carcinoma (*C*) and the normal mucosal epithelium (*N*)

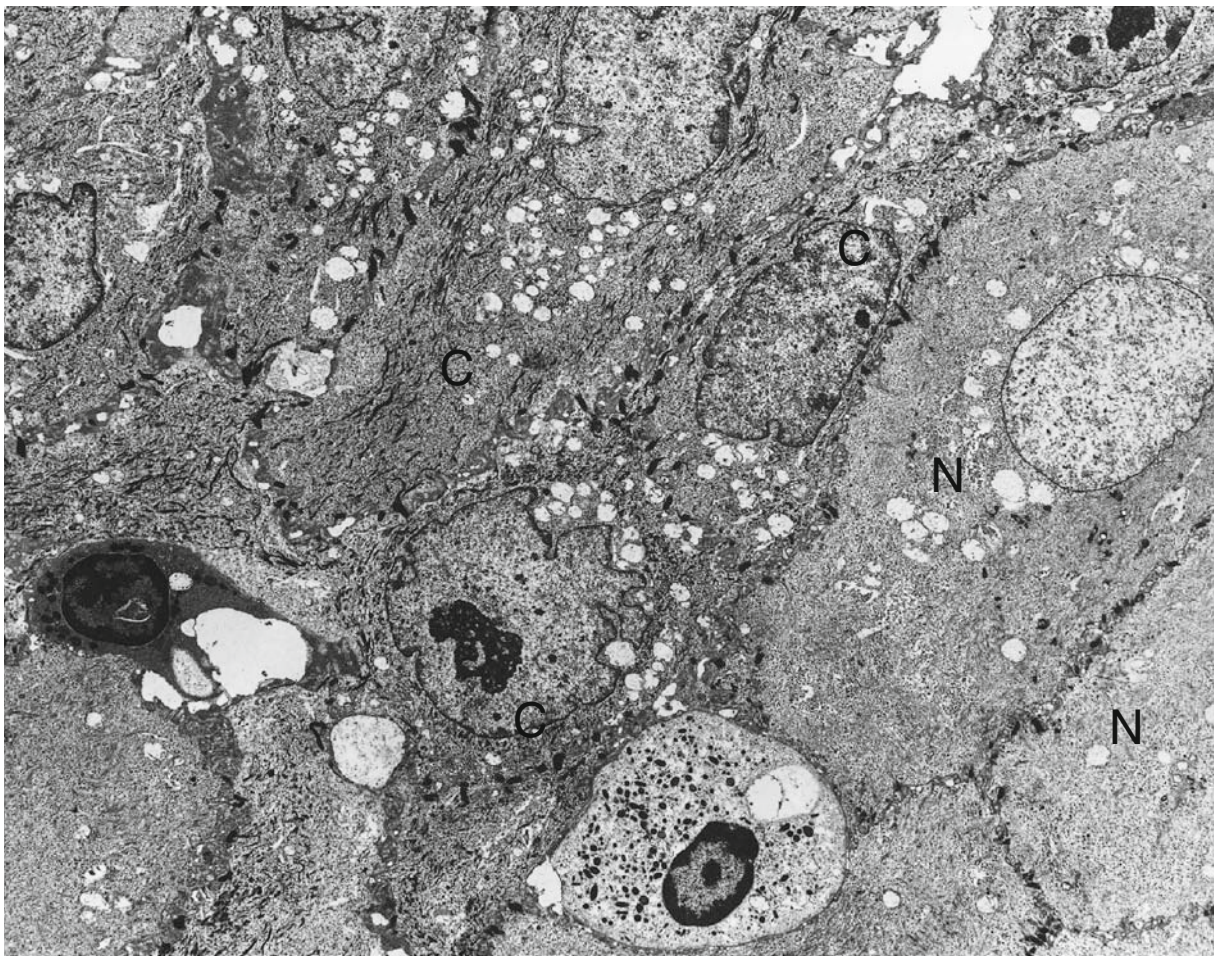


Fig. 11-47. Interface between an intraepithelial carcinoma and normal mucosal epithelium. The carcinoma cells (*C*) are directly attached to the normal epithelial cells (*N*). Desmosomes between malignant and nonmalignant cells are evident

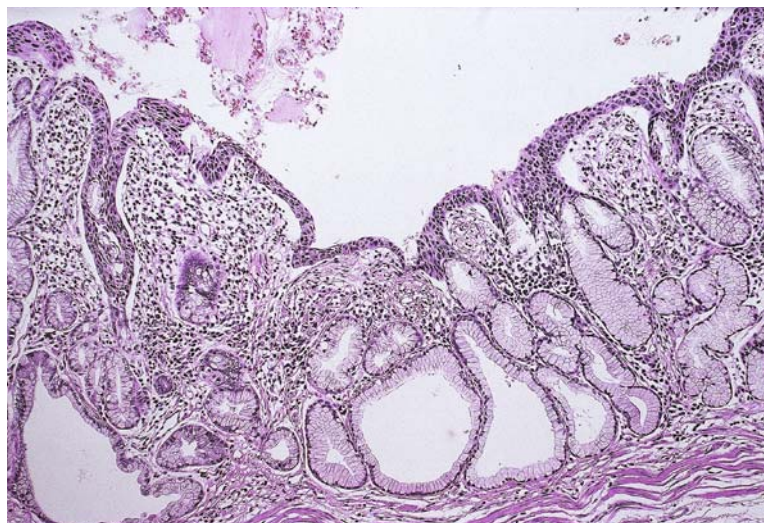


Fig. 11-48. Intraepithelial spread of esophageal squamous cell carcinoma in gastric mucosa. The superficial epithelium of the gastric cardiac mucosa is replaced by thin squamous cell carcinoma in situ

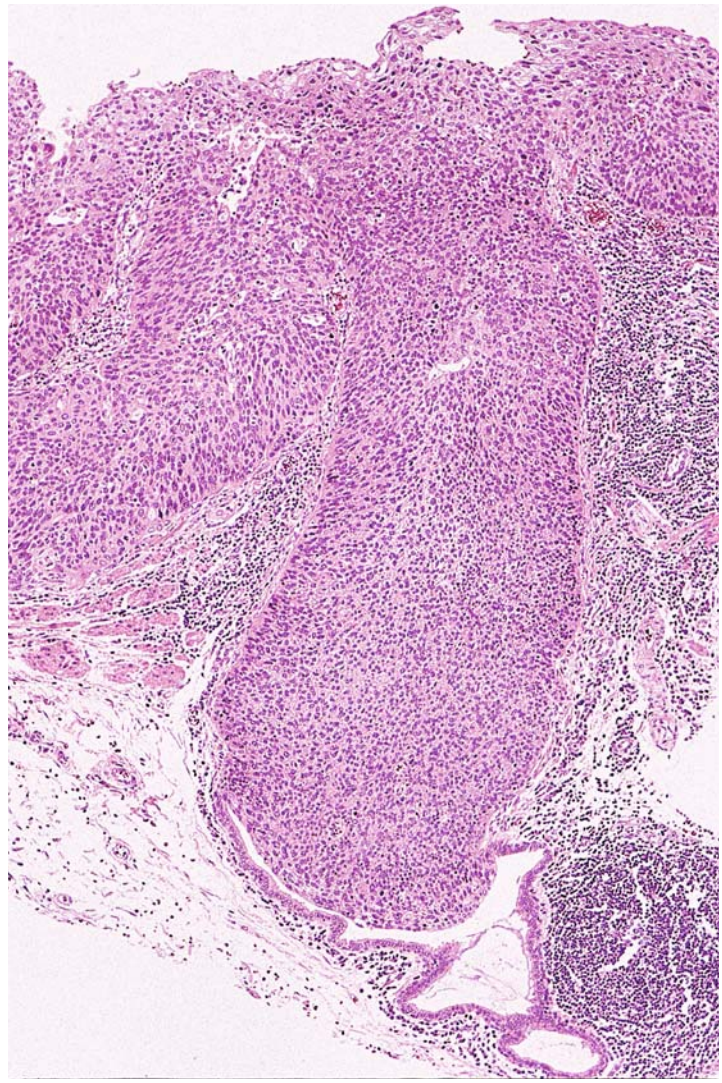


FIG. 11-49. Ductal involvement of an esophageal gland proper. Intraepithelial squamous cell carcinoma extends into the submucosa within the duct, without stromal invasion

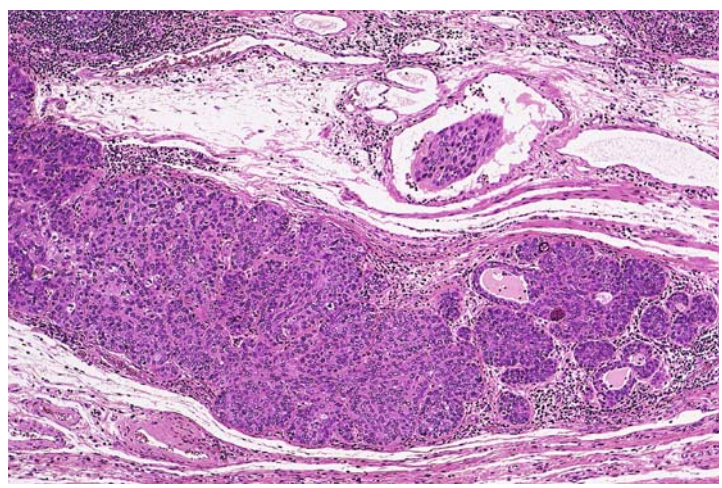


FIG. 11-50. Glandular involvement of an esophageal gland proper. There is stromal invasion by cancer cells, via ductal involvement. The cancer cells also involve the terminal portion of the esophageal gland proper

In this author's series ductal spread was found in one of eight cases of in situ carcinoma and in three of nine cases of mucosal carcinoma with stromal invasion. A minute intramucosal carcinoma, measuring 7 mm in diameter, which had reached the submucosa along the duct of an esophageal gland proper, was also found. These findings suggested that ductal involvement of the esophageal glands proper may be an important pathway of early tumor spread into deeper tissue.

The ultrastructural features of ductal involvement are similar to those of mucosal intraepithelial spread. Degenerate epithelial cells and inflammatory cells are found at the interface between intraductal carcinoma and normal ductal epithelium, with the tumor cells sometimes attached directly to normal ductal epithelial cells by desmosomes (Fig. 11-51). The tumor cells infiltrate between the basement membrane and the ductal epithelial cells. These observations suggest that ductal spread progresses via a mechanism similar to that which occurs in the mucosal intraepithelial spread of carcinoma.

11.2.9. Perineural Invasion and Spread

Cross sections of peripheral nerves invaded by tumor occasionally show circumferential involvement (Figs. 11-52, 11-53). Pathologists often see this pattern of spread in carcinomas from various body sites. According to Kitano (1989), the first description of perineural sheath invasion by a malignant tumor was made in 1842. There have been detailed reports of perineural infiltration by carcinomas of the prostate, gallbladder, pancreas, and oral cavity, and many related reports are available in the literature.

There had not been any reports on perineural invasion by esophageal cancer until this author described its histological and ultrastructural features (1985). Perineural invasion was formerly believed to be invasion of perineural lymphatics, but electron microscopic studies have shown that peripheral nerves are not surrounded by lymphatic vessels. This author's data, from the electron microscopic examination of esophageal carcinomas, suggest that carcinoma cells reach a peripheral nerve and partly destroy the perineural sheath, thereby inducing total degeneration of the perineurium even before tumor invasion occurs. Subsequent infiltration of tumor cells along the degenerate perineurium, which is the path of least resistance, results in a pattern of circumferential involvement (Fig. 11-54).

Perineural invasion was evident histologically in 23% of this author's series of primary esophageal carcinomas (Takubo et al.). It was particularly frequent in cases of deeply invasive carcinoma that had gone through the adventitia into other structures, being seen in 46% of this group. In contrast, no perineural invasion was found in cases of superficial carcinoma confined to the mucosa or submucosa. The incidence of perineural invasion was related to the depth of invasion, ranging from 13% for tumors invading the muscularis propria to 22% for those invading the adventitia (Takubo et al.).

The length of perineural invasion by esophageal carcinoma, determined by the examination of serial sections, ranged in one series from 2.4 to 11.0 mm, with a mean of 6.8 mm (Takai). In contrast, it has been reported that the length of perineural invasion in squamous cell carcinomas of the oral cavity may reach several centimeters, although it is rare for it to exceed 2 cm. Tumor invasion into the endoneurium from the perineum is known as neural invasion. Well-differentiated squamous cell carcinomas of the head and neck have been found to show perineural invasion more often than poorly differentiated carcinomas (Kitano). There have not been any reports of a relationship, if any, between the frequency of perineural invasion and the degree of differentiation of esophageal carcinomas, however.

Also, it remains unclear whether there is any relationship between perineural invasion and esophageal pain in cases of esophageal cancer.

11.2.10. Intramural Metastasis

Metastasis from an esophageal carcinoma to the esophagus or stomach is termed intramural metastasis, and this has been considered an important pathway of tumor spread (Fig. 11-55). Intramural metastasis was first reported by Watson in 1933, and this report has been cited frequently in subsequent publications. Intramural metastasis has

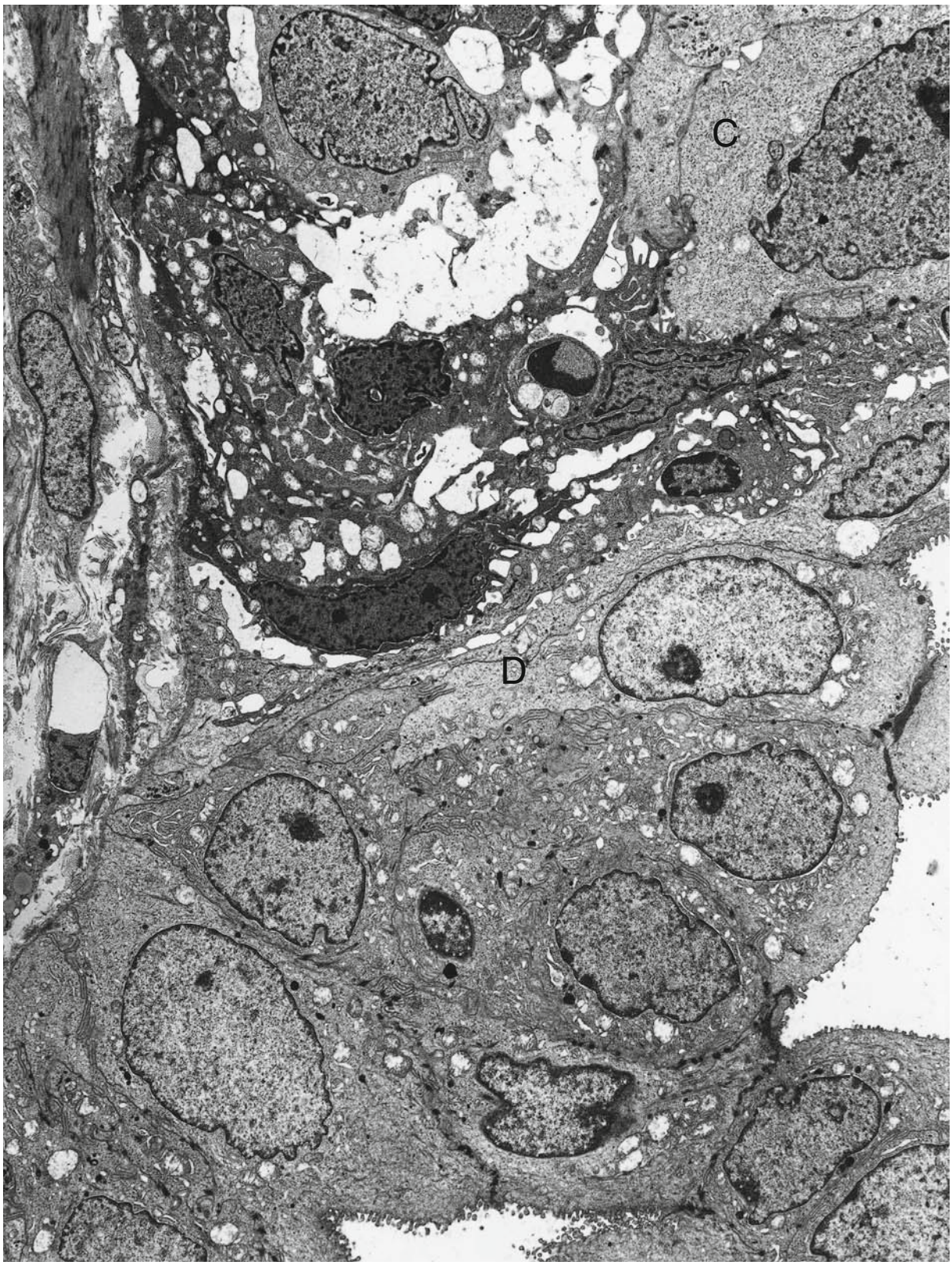


FIG. 11-51. Electron micrograph showing ductal involvement of an esophageal gland proper. There are degenerate epithelial cells and mesenchymal cells at the interface between the carcinoma cells (*C*) and the nonneoplastic ductal cells (*D*)

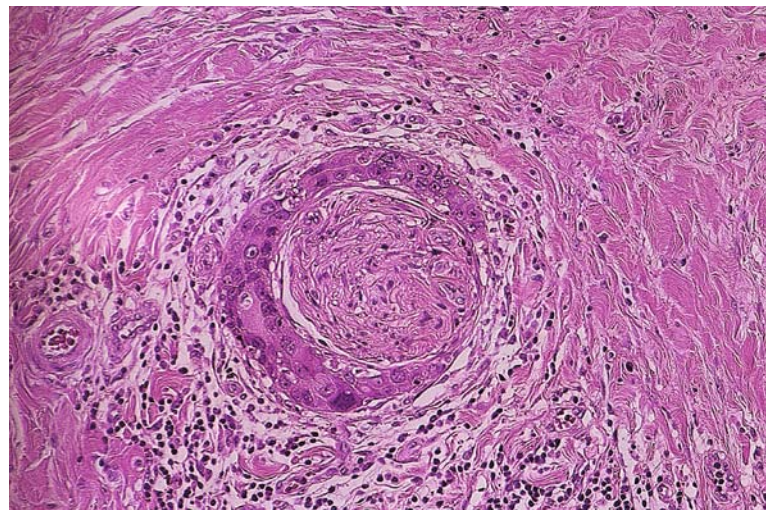


FIG. 11-52. Perineural invasion. Cancer tissue surrounds the nerve circumferentially

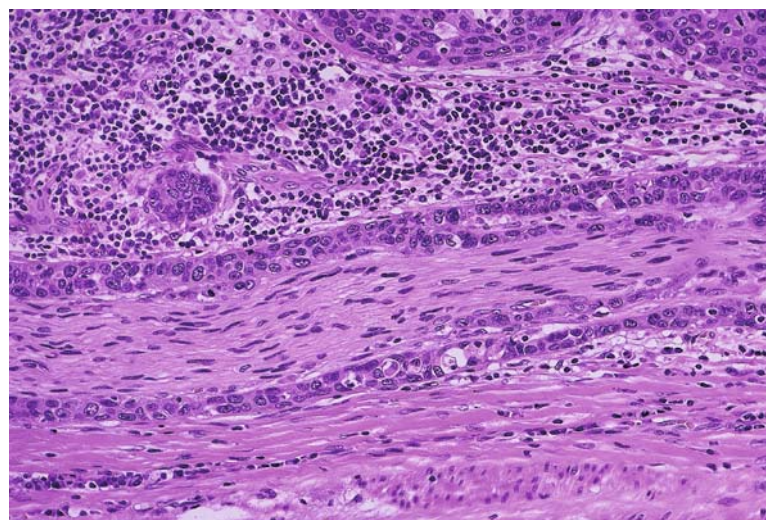


FIG. 11-53. Perineural invasion. Cancer tissue extending along a nerve in longitudinal section

been intensively studied in Japan, with many reports having been published.

In five papers written by Japanese authors, the incidence of intramural metastasis found in surgical specimens has ranged from 7.0% to 14.3% (Tanaka et al.). In this author's series of surgical specimens, the incidence of intramural metastasis, defined as a tumor deposit 5 mm or more away from the primary lesion, was 11.9%. The definition of intramural metastasis has varied in different studies, however, and different studies have also included cases with diverse patient characteristics and diverse tumor stages. Therefore, a simple comparison of these figures seems uninformative. Watanabe et al. (1979) defined intramural metastasis as a tumor deposit 2 cm or more away from the primary lesion and noted an incidence of 7.0%. Kato et al. (1992) reported that intramural metastasis was found in 60 (15%) of a series of 393 cases of carcinoma of the thoracic esophagus.

In all the published reports, the greatest distance between a primary tumor and a focus of intramural metastasis has been 16.3 cm.

The respective incidences of intramural metastasis of esophageal carcinoma to the gastric wall were 5.5% in this author's series (1990), 1.7% in

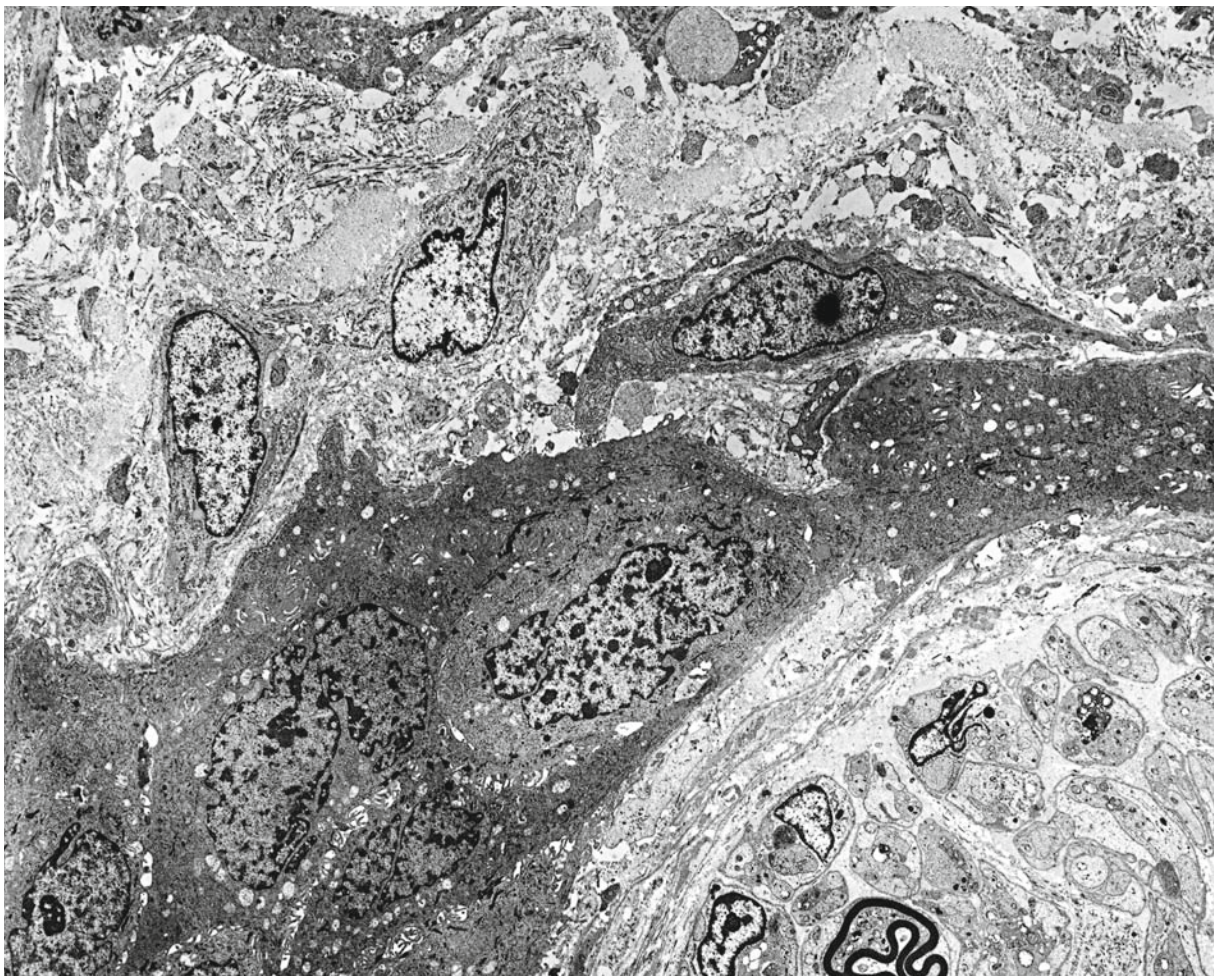


Fig. 11-54. Electron micrograph of perineural invasion. Cancer cells are present in the degenerate perineurium

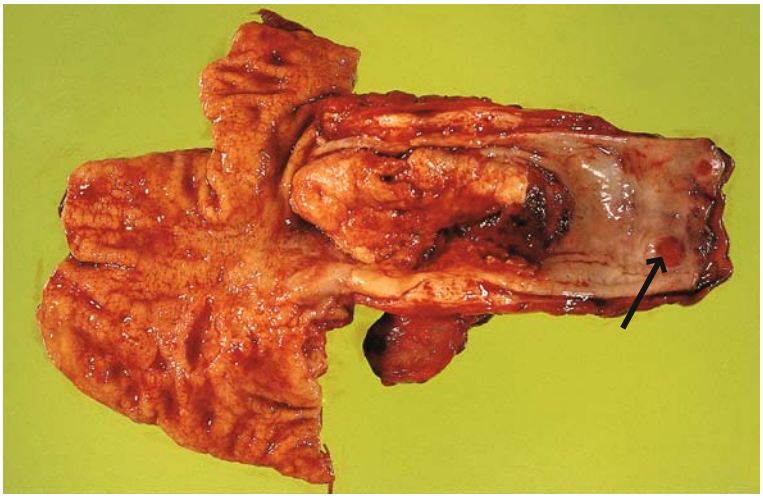


Fig. 11-55. Macroscopic appearance of intramural metastases. There are two metastatic foci (*arrow*) proximal to the primary tumor and there are two ulcerated metastases in the stomach. A lymph node containing metastatic tumor can also be seen, under the esophagus

the series of Saito et al. (1985), 10% in that of Seki (1991), 2.7% in that of Kuwano et al. (1992), and 4.6% in that of Kato et al. (1992).

This author found that intramural metastasis more frequently occurred distal than proximal to the primary tumor. Watanabe et al. also found this, and noted that most patients with metastasis proximal to the primary tumor had been given preoperative radiotherapy. This author reviewed the data relating to the location of intramural metastasis from six Japanese studies. Four of these found that the incidence of intramural metastasis proximal and distal to the primary tumor was almost the same; of the remaining two studies, one reported that intramural metastasis was more frequent proximally whereas the other reported the opposite.

Seki (1991) reported that lymphatic permeation more than 5 mm away from the primary tumor (defined as distant lymphatic invasion) was much more often seen in patients with intramural metastasis than in those without.

Almost all the reported cases of esophageal carcinoma with intramural metastasis have also had lymph node metastasis at surgery. Also, distant organ metastasis is significantly more frequent in patients with intramural metastasis than in those without. The incidence of distant metastasis, as defined in the *TNM Classification of Malignant Tumors* by the International Union Against Cancer (UICC), was 29.2% in this author's group of esophageal cancers with intramural metastasis. Erosion or ulceration was found in 42.9% of foci of intramural metastasis. Of all cases of intramural metastasis, 54.2% were recognizable at preoperative esophagography and/or esophagoscopy. If the metastasis was proximal to the primary tumor, the rate of preoperative detection was 70.0%.

There was an obvious difference in outcome between patient groups with and without intramural metastasis, the former showing an unfavorable outcome.

Fujita (1984) reported an autopsy series in which the incidence of intramural metastasis following resection was 13%.

11.2.10.1. Differences Between Intramural Metastasis and Multiple Primary Carcinomas

Although the incidence of multiple carcinoma of the esophagus is high (10%–20% of cases of esophageal carcinoma), the prognosis of multiple carcinoma is similar to that of a single carcinoma; however, but the prognosis of a carcinoma with intramural metastasis is much poorer than that of a carcinoma without intramural metastasis, as mentioned earlier. Therefore, it is important to distinguish between multiple primary carcinomas and intramural metastasis. The distinction is not difficult. When tumor deposits have accompanying intraepithelial spread, they are judged to be multiple primary carcinomas, but when there is no contact with the surface epithelium, a tumor is regarded as an intramural metastasis (Fig. 11-56). It has been shown by electron microscopy that

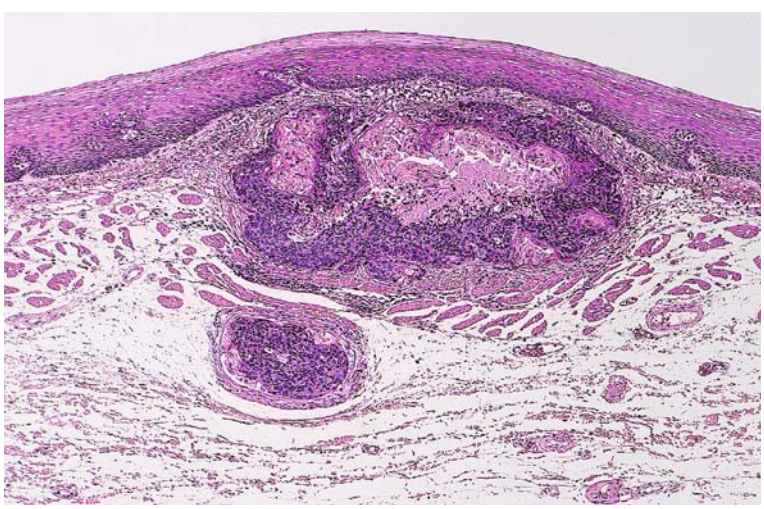


FIG. 11-56. Intramural metastasis. There is a focus of intramural metastasis involving the lamina propria and muscularis mucosae

malignant and nonmalignant epithelial cells may form desmosomes by cooperation, so close contact between tumor cells and normal epithelial cells cannot on its own serve as evidence of multiple carcinoma; in these cases, multiplicity versus intramural metastasis is judged by the pattern of invasion of tumor cells in the esophageal wall.

11.2.10.2. Primary Intramural Carcinoma

Aside from intramural metastasis, already mentioned, a few cases of primary esophageal cancer, including some squamous cell carcinomas and adenoid cystic carcinomas, thought to have arisen from intramural epithelial tissue in the esophagus (cyst, esophageal gland proper, etc.), have been reported (McGregor et al.). The present author has not seen any such cases. As these tumors were located within the wall, even multiple biopsies sometimes failed to detect them. It may sometimes be necessary to consider the possibility that a carcinoma has arisen in the esophageal glands proper or their excretory ducts if a tumor is located mainly in the wall, with only a small mucosal lesion.

11.2.11. Histological Description of the Effects of Therapy

Of the various guidelines for clinical and pathologic studies established for different carcinomas in Japan, the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* was the first to stipulate histological criteria for judging the efficacy of therapy. The *General Rules for Gastric Cancer Study in Surgery and Pathology*, proposed by the Japanese Research Society for Gastric Cancer, have now also prescribed criteria for judging the effects of therapy. These histological criteria have all been based on a paper by Shimosato (1969), but whereas the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* state that efficacy should be judged on the amount of remaining viable tumor, the *General Rules for Gastric Cancer* state that the judgment should be based on the amount of degenerate or necrotic tumor present.

In the esophagus, the amount of remaining viable tumor, estimated at the time of resection, is graded 0–3. Nonviable cells are defined as cells showing loss or pyknosis of nuclei and cytoplasm that is deeply eosinophilic, whereas cells having eosinophilic cytoplasm with vacuoles and swollen nuclei are considered to be viable. Therapeutic efficacy is rated as grade 0 when there has been almost no effect on cancer cells, and grade 1a, 1b, or 2 when presumed viable cells account for more than 2/3, 1/3–2/3, and less than 1/3, respectively, of the area of each histological section examined (Fig. 11-57). Absence of viable cancer cells corresponds to grade 3 (Fig. 11-58a).

It may sometimes be difficult to distinguish necrosis resulting from preoperative therapy from

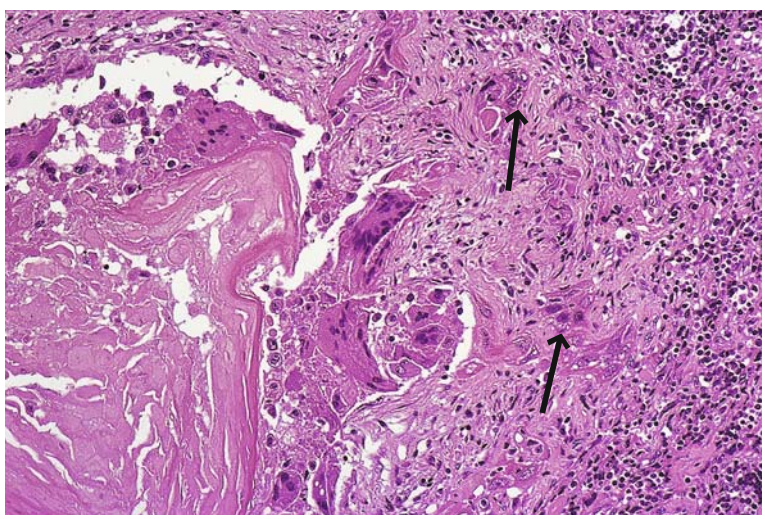
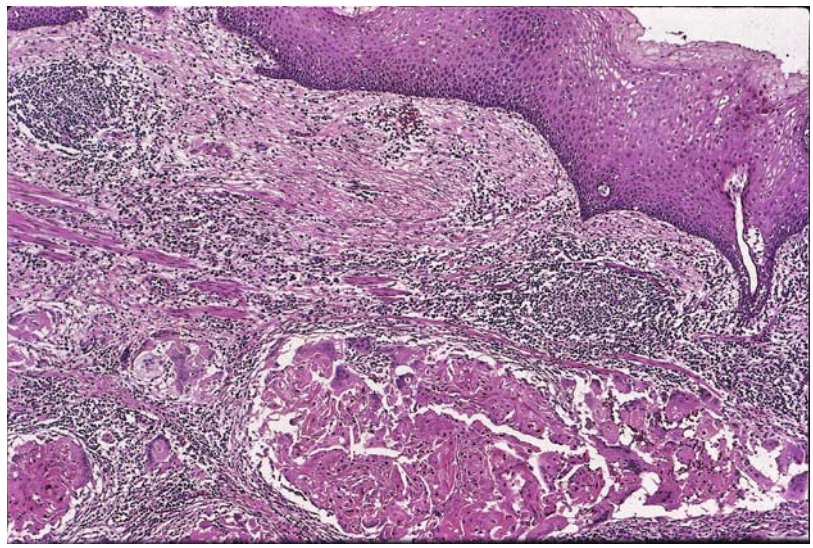
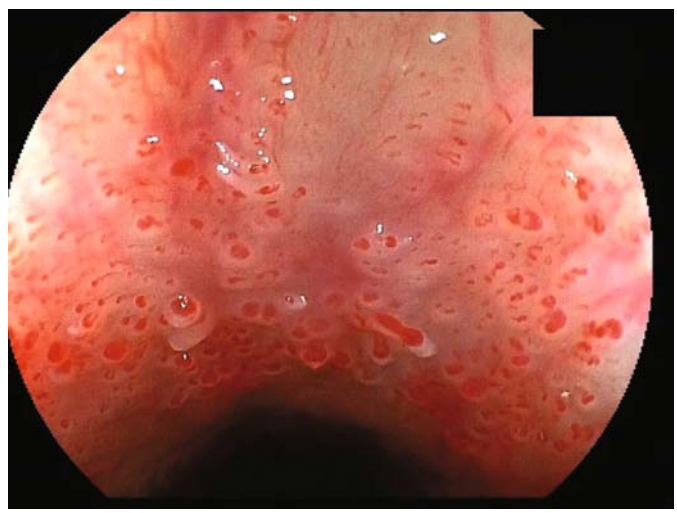


Fig. 11-57. Esophageal carcinoma following radiotherapy. Foreign-body giant cells and viable tumor cells (*arrows*) are seen, with associated fibrosis (effect of therapy: grade 2)



a



b

Fig. 11-58. **a** Esophageal carcinoma following radiotherapy. There are foreign-body giant cells and necrotic tissue. No viable tumor is seen (effect of therapy: grade 3). **b** Endoscopic appearance of esophageal mucosa following radiotherapy. Multiple intrapapillary vessel dilatations are often seen

necrotic material that is often seen in association with keratinization in the center of tumor nests in squamous cell carcinoma. It seems, however, that necrosis is usually attributable to therapy when it is seen at the advancing edge of a tumor, in direct contact with the stroma. Foreign-body granulomata, consisting of foreign-body giant cells, histiocytes, lymphocytes, and fibrotic tissue, surround necrotic tumor and keratinous debris after preoperative therapy of squamous cell carcinomas. The present author judges the depth of invasion of esophageal carcinomas after therapy by assessing the depth of the granulomatous tissue, foreign-body giant cells, or fibrotic foci, even when there are no viable cancer cells present.

Keratinization in squamous cell carcinomas seems to accelerate following radiotherapy. It is therefore common for the degree of histological differentiation seen in a postradiotherapy surgical resection specimen to differ from that of the previous biopsy specimen.

11.2.11.1. Radiation Injury to Normal Esophageal Tissue

The normal esophageal epithelium shows acute changes with atypia following radiation treatment (see Fig. 11-6), and mitosis of basal cells is inhibited. The epithelial cells have prominent nucleoli. Marked edema is found in the lamina propria, submucosa, and adventitia, and enlarged

fibroblasts (radiation fibroblasts) are often seen. Endoscopically, multiple intrapapillary vessel dilatations are often seen for a long time after radiation (Fig. 11-58b). Vascular endothelial cells are also often enlarged and have a histiocytoid appearance. Atypical epithelium may persist for a very long time, and over time the edema changes to fibrosis.

11.2.11.2. Radiation Carcinogenesis in the Esophagus

It is well known that carcinomas sometimes develop in tissues within the radiation field after radiotherapy for benign or malignant disorders at a nearby site. Of cancers that may occur after radiotherapy for benign disorders, skin cancer is the most frequent, followed by carcinomas of the hypopharynx, larynx, esophagus, and thyroid (Sakai et al.). Esophageal ulcers and carcinomas have been reported following radiation for the treatment of breast cancer, mediastinal tumors (Fékété et al.), laryngeal cancer, lung cancer (Okazaki et al.), and cervical tuberculous lymphadenitis. The incidence of esophageal cancer in patients who have undergone radiotherapy for these disorders is reported to be less than 1%. Ueda et al. (1991) found an incidence of esophageal carcinoma of 0.4% in patients with breast cancer who had undergone radiotherapy using a linear accelerator.

The diagnostic criteria for a radiation-induced carcinoma should include development within the radiation field and a certain latent period between radiation exposure and tumor development. There is controversy about the length of the latent period, however, and other criteria have also varied; histological features suggesting radiation-induced carcinoma, or a history of radiotherapy to another organ (with the esophageal tumor not necessarily in the radiation field), have sometimes been included as diagnostic criteria, for example.

Seventeen cases of radiation-induced esophageal cancer were reviewed by Goffman et al. (1983). These patients with radiation-induced esophageal carcinoma included nonsmokers and nondrinkers. Eight (47%) of the 17 patients had had radiotherapy for breast carcinoma. In a series published by Fékété et al., the esophageal carcinomas developed within the radiation field a minimum of 8 years after mediastinal radiotherapy. Histological examination of the resected esophagi showed mural fibrosis as a result of the previous irradiation. Metastasis of radiation-induced esophageal cancers to mediastinal lymph nodes within the radiation field has been reported to be rare (Fékété et al.), but Ueda et al. (1991) observed metastases to paratracheal and paraesophageal lymph nodes in 4 of 8 patients with radiation-induced esophageal carcinomas who had been treated surgically. It has been reported that there is no difference in prognosis between radiation-induced esophageal carcinoma and esophageal squamous cell carcinoma that arise de novo.

A case of radiation-induced gastrointestinal stroma tumor (GIST) of the esophagus has also been reported (Miller et al. 2000; see Section 14.14).

Esophagitis and esophageal ulcer caused by radiation therapy are described in Chapter 7 (p. 94).

11.2.12. Multiple Carcinoma of the Esophagus and Synchronous Primary Carcinoma of the Esophagus and Other Sites

11.2.12.1. Multiple Carcinoma of the Esophagus

The highest reported incidence of multiple esophageal carcinoma in Japan has been 36%. In this author's series of resection specimens examined by subserial microscopic sections, the incidence of multiple carcinoma was less than 20%, and the incidence in another recent Japanese study was 18.8% (Mizobuchi et al.). Hosokawa and Koizumi (1997) reviewed 5005 cases of esophageal carcinoma from 31 hospitals for the Japanese Research Society for Early Esophageal Cancer and Chromoendoscopy. Of the 5005 cases, 2159 (43%) were superficial carcinomas and, of these, 445 (21%) were cases of multiple carcinoma. In comparison to patients with a single cancer, there was a predominance of men over women and smokers over nonsmokers. It has also been reported that multiple esophageal carcinomas are often accompanied by epithelial dysplasia and that the prognosis of esophageal carcinoma is similar regardless of whether the patient has a single tumor or multiple primary tumors.

11.2.12.2. Synchronous and Metachronous Primary Carcinoma of the Esophagus and Other Sites

Ikeda et al. (1979) studied 327 patients with esophageal carcinoma, looking for the presence of a second primary carcinoma at another site, excluding latent cancer detected incidentally at autopsy. Of the 327 patients, 36 (11%) had, or developed, a synchronous or metachronous carcinoma at another site; pharyngeal carcinoma was the most frequent (14 cases), followed by laryngeal (7 cases), gastric (6 cases), lingual (5 cases), and oral (3 cases) carcinoma. Ikuta et al. (1996) studied 288 patients with esophageal carcinoma; they reported that 17 (5.9%) had a synchronous primary malignancy at another site and 16 (5.6%) had a metachronous primary malignancy at another site.

11.2.12.3. Head and Neck Carcinoma and Esophageal Carcinoma

The results of a questionnaire survey undertaken by Sato (Third Department of Surgery, Tokyo Medical University) were reported at the 45th meeting of the Japanese Research Society for Early Esophageal Cancer and Chromoendoscopy (June 2002, Hiroshima). This survey investigated a total of 317 head and neck carcinomas that had occurred in association with esophageal carcinomas. Sixty percent of the esophageal carcinomas were synchronous with the head and neck carcinoma and 37% were metachronous (3% unknown). Of the synchronous cases, the diagnosis of the esophageal carcinoma preceded that of the head and neck cancer in 11%, and the diagnosis of the head and neck cancer preceded that of the esophageal cancer in 82% (7% unknown). For the metachronous cases, the corresponding figures were 26% and 73%, respectively (1% unknown).

The occasional occurrence of dual primary carcinomas of the head and neck and esophagus has been long known, but in Japan the occurrence of dual primary carcinomas of the stomach and esophagus is also well known.

In one series, reported from the Saitama Cancer Center Hospital, 9.5% of patients who underwent resection of an esophageal carcinoma had a synchronous primary carcinoma at another site, with gastric carcinoma being the most frequent (Tanaka et al.).

11.2.13. Mode of Recurrence and Cause of Death in Patients with Esophageal Carcinoma

Detailed reports on the mode of recurrence of esophageal cancer following resection have been published from Japan as well as from the America and Europe. According to a Japanese report by Fujita (1984), who studied 113 autopsy cases of recurrent esophageal carcinoma after surgery, recurrence most commonly occurred in lymph nodes (82%), followed by distant organs (57%) and cavity dissemination (22%). The sites of metastatic carcinoma included lung (37%), liver (24%), bone (12%), adrenal (10%), skin (6%), thyroid (6%), pancreas (4%), kidney (4%), and brain (3%), in descending order of incidence. According to Anderson and Lad (1982), who studied 79 autopsy cases of esophageal cancer that had been treated in various ways, the corresponding order was lymph nodes (73%), lung (52%), liver (47%), adrenal (20%), diaphragm (19%), bronchus (17%), pleura (17%), stomach (15%), bone (14%), and kidneys (13%). Mandard et al. (1981) also studied autopsy cases in which treatment had not been consistent and reported a slightly different order of incidence, i.e., lymph node (75%), lung (31%), liver (23%), pleura (17%), bone (13%), kidney (10%), adrenal (9%), nervous system (5%), and stomach (5%). Sons and Borchard (1984) reported 171 autopsy cases; the order of incidence of metastatic involvement was lymph node (67%), lung (21%), liver (14%), bone (8%), kidney (8%), adrenal (6%), and brain (2%). In any event, there is a high incidence of metastasis to the lung and liver. Metastasis of esophageal carcinoma to the adrenal gland is also relatively frequent, despite it being a small organ, but metastasis to the brain is rare. In this author's studies of 45 autopsy cases, metastasis occurred most frequently to the lung and liver, followed by the adrenal gland. Moriwaki et al. (2001) reported that 21 (24%) of 87 cases of esophageal carcinoma examined at autopsy had bone marrow metastasis.

The cause of death in patients with esophageal carcinoma has been studied in detail by Isono

et al. (1982). In a series of 89 patients who died within 3 months of surgery (early postoperative deaths), 37% of the deaths were caused by pulmonary complications, 36% by anastomosis dehiscence, and 9% by postoperative bleeding. Of 151 patients who died between 3 months and 5 years after surgery, 79% of deaths were caused by recurrent carcinoma, 11% by respiratory diseases, and 4% by malnutrition.

11.2.14. Death Caused by Recurrence of Esophageal Carcinoma

It was reported in one series that there were no deaths from recurrence after surgery for esophageal carcinoma in situ, but that of 432 patients with esophageal mucosal carcinomas, excluding carcinoma in situ, there were 12 (2.8%) deaths caused by recurrence (Yoshii et al. 1991). In a review of 130 different studies related to the surgical treatment of esophageal carcinoma, Müller et al. (1990) found that the 5-year survival rate ranged from very low to more than 70%. According to clinicopathological studies of esophageal carcinoma, including DNA ploidy, the presence or absence of lymph node metastasis and the depth of tumor invasion are the most important prognostic factors.

11.2.15. Direct Invasion by Esophageal Carcinoma

11.2.15.1. Direct Invasion of Stomach

Invasion by esophageal cancer into stomach has been investigated in detail by Kuwano et al. (1992). According to their report, gastric involvement by esophageal carcinoma resulting from direct invasion or intraepithelial spread, excluding intramural metastasis and direct spread from metastasis in perigastric lymph nodes, was found in 4% of 402 patients who had undergone resection of an esophageal cancer.

11.2.15.2. Direct Invasion of Lung

Direct invasion by esophageal carcinoma into lung has been investigated by Kato et al. (1992). Of 1139 patients undergoing an esophagectomy for carcinoma, 63 (5.5%) had a pneumonectomy at the same time. Metastasis or direct invasion of lung was suspected before or during surgery in all 63, but cancer invasion into the lung parenchyma was demonstrated histologically in only 56% of the 63, whereas invasion close to the parenchyma was found in 33% and fibrous adhesions alone were found in the remaining 10%. The macroscopic and histological features of lung around an area of invasion by esophageal carcinoma are described in Chapter 2 (p. 39).

11.2.16. Hematogenous Spread

11.2.16.1. Hematogenous Spread at Diagnosis and Surgery

There have not been any case reports of an invasive intramucosal carcinoma of the esophagus (i.e., excluding carcinoma in situ) having hematogenous distant organ metastasis at the time of surgery. Yoshii et al. found pleural dissemination in 1 of 432 cases of mucosal carcinoma (excluding carcinoma in situ), although details of that case are not available. Thus, it seems reasonable to infer that hematogenous spread of esophageal mucosal carcinoma to distant organs virtually never occurs. According to van Overhagen et al., preoperative ultrasonography or computed tomography (CT) scanning suggested distant metastasis in 62 (46%) of 135 patients who had esophageal carcinoma with varying depths of invasion, and metastasis was confirmed cytologically in 33 (24%).

11.2.16.2. Hematogenous Spread at Autopsy

The most common site for hematogenous metastasis of esophageal carcinoma, as demonstrated at autopsy, is the lung, followed by the liver. Details are given in the section describing mode of recurrence (p. 183).

11.2.17. Lymph Node Metastasis

11.2.17.1. Depth of Tumor Invasion and Nodal Metastasis

The results of a questionnaire survey undertaken by Yoshii et al. were reported at the 25th meeting of the Japanese Research Society for Early Esophageal Cancer and Chromoendoscopy (June 1991). This survey included a total of 755 esophageal mucosal carcinomas that had been resected at 113

hospitals in Japan in the study period, including 299 carcinomas in situ and 456 mucosal invasive carcinomas (1993). The patients comprised 629 men and 125 women (1 unknown), who ranged in age from 35 to 86 years (mean, 63 years). None of the 299 patients with carcinoma in situ had lymph node metastases, but 26 (5.7%) of the 456 patients with invasive mucosal carcinoma had metastases in nodes dissected at esophagectomy. Lymphatic vessel permeation was observed in 46 (10.1%) of the 456 patients with invasive mucosal carcinoma. According to a review by Monma (1995), 29 (18%) of 161 invasive mucosal carcinomas of the esophagus had lymph node metastases, as did 44 (23%) of 195 carcinomas that had invaded into the superficial third of the submucosa.

According to a recent report by Kato et al. (1993) of 43 patients with superficial carcinomas who had undergone esophagectomy with dissection of cervical, mediastinal, and abdominal lymph nodes (three-field dissection), three patients with carcinoma in situ had no positive lymph nodes, but 1 (14.2%) of 7 patients with carcinomas that had invaded lamina propria and muscularis mucosae, and 19 (58%) of 33 patients with carcinomas that had invaded submucosa, had lymph node metastases. Nishimaki et al. also reported that lymph nodes dissected at surgery were positive in 52% of patients with esophageal carcinomas that had invaded submucosa.

Sayama et al. (1994) reported a study that found that carcinomas in situ and carcinomas which had only invaded lamina propria had not metastasized to lymph nodes, but that those which had extended to the muscularis mucosae did have lymph node metastases. Yoshida et al. (1994) reported that 1 of 17 invasive mucosal carcinomas had a lymph node metastasis and that this tumor invaded the muscularis mucosae; they proposed that the definition of early carcinoma of the esophagus should be the same as that of intramucosal carcinoma.

The results of this author's study (Takubo et al. 1987) into the relationship between depth of invasion of esophageal carcinoma and the presence of metastases in nodes dissected at surgery, in which we performed subserial histological sections, were as follows: lymph node metastases were found in 0 of 3 carcinomas in situ, 0 of 7 mucosal carcinomas other than carcinomas in situ, 1 (11%) of 9 carcinomas that had invaded submucosa, 16 (70%) of 23 carcinomas which had reached the muscularis propria, 88 (73%) of 95 carcinomas that had extended to the adventitia but showed no direct invasion of other structures, and 23 (82%) of 28 carcinomas which involved other structures by direct invasion. In a report by Tsurumaru and Akiyama, nodal metastases were present in 75% of 196 patients with esophageal carcinomas of varying depths of invasion who had undergone three-field lymph node dissection.

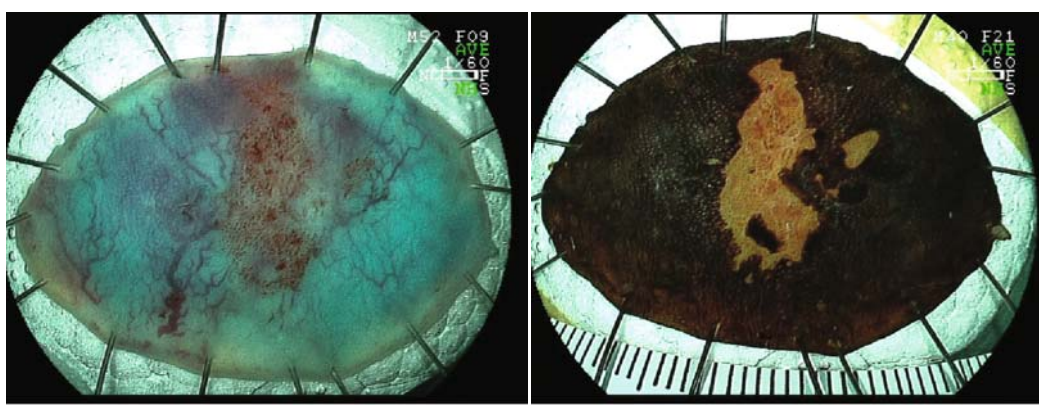


FIG. 11-59. Endoscopic resection specimen of esophageal mucosa. *Left:* There is a carcinoma, measuring 19 × 9 mm in size, with an irregular surface, slightly depressed type, superficial and flat carcinoma. *Right:* Lugol's iodine staining shows a positive reaction in nonneoplastic squamous epithelium and a negative reaction in squamous cell carcinoma. The border between the carcinoma and the noncancerous epithelium is clear. Surgical margin is free from carcinoma. The macroscopic photographs were taken by an endoscope

Aside from the absence of lymph node metastasis in cases of carcinoma in situ, the foregoing data indicate that nodal metastases are seen in a fair number (about 10%) of invasive mucosal carcinomas and in a high percentage (about 50%) of carcinomas that invade the submucosa.

11.2.17.1.1. Endoscopic Mucosal Resection, Endoscopic Submucosal Dissection, and Lymph Node Metastasis in Mucosal Carcinoma

From recent reports, cases of squamous cell carcinoma in situ and carcinoma invading the lamina propria have shown no lymph node metastasis, whereas around 10% of those invading the muscularis mucosae have shown lymph node metastasis (Fig. 11-59). Recently, in Japan, mucosal carcinomas that did not reach the muscularis mucosae have been found to be curable by endoscopic mucosal resection or endoscopic submucosal dissection. The endoscopically resected specimen should be cut into sections, 2 mm wide, and the depth of invasion and resection margins should be examined in detail histologically.

11.2.17.2. Latent Lymph Node Metastases from Cancer of Other Organs Detected at Surgery for Esophageal Cancer

In the pathological examination of 412 cases of esophageal carcinoma, Tanaka and Mafune found 3 cases (0.7%) in which lymph nodes dissected at esophagectomy contained metastatic tumor from a primary carcinoma of another site. All these metastases were from carcinomas of the thyroid gland; 2 were classified as papillary carcinomas and 1 as a follicular carcinoma.

11.2.18. Ulceration and Primary Carcinoma of the Reconstructed Esophagus After Esophagectomy

Akiyama and Nakayama (1982) reviewed cases of primary carcinoma arising in reconstructed esophagi. They collected 6519 cases of esophageal reconstruction from Japan and found 32 cases (0.04%) of carcinoma that had arisen in the reconstructed organ. Of the 6519 cases, the reconstruction had been performed using the stomach in 81.8%, the colon in 9.5%, the jejunum in 6.8%, and other tissues including skin in 1.9%. The 32 cases of carcinoma included 31 that had arisen in gastric tubes and 1 that had arisen in a skin tube.

11.2.18.1. Carcinoma Arising in the Reconstructed Skin Tube

According to a paper by Fogh-Andersen (1961), the development of a carcinoma arising in a skin tube was first described in 1957 by Petrov. Ide et al. (1970) reported two cases of squamous cell carcinoma that had arisen in skin tubes in thoracic subcutaneous tissue; in both patients these tubes had been fashioned as esophageal reconstructions for benign esophageal diseases. The squamous cell carcinomas were detected in the fistulae 33 and 25 years, respectively, after the initial surgery. In the same report, they reviewed another four cases of squamous cell carcinoma that had arisen in reconstructed skin tubes 21 to 30 years after initial surgery. Also, Horváth et al. (2000) reported two cases of squamous cell carcinoma that had arisen in reconstructed skin tubes 34 and 46 years after initial surgery. There were no detailed descriptions of the histology of the skin tubes, however, and there was no speculation on histogenesis in these reports.

11.2.18.2. Ulcer and Carcinoma of the Reconstructed Gastric Tube

In Japan, esophageal reconstruction after resection for carcinoma is most commonly undertaken using the gastric pedicle. According to Fukumoto et al. (1997), peptic ulcers had been reported in 49 Japanese patients with reconstructed gastric tubes. Food stasis within the gastric tubes, nonsteroidal antiinflammatory drugs, and irradiation therapy after surgery may all induce ulceration. Penetration of the ulcers into extraesophageal tissue was seen in 17 (35%) of the 49 patients; 5 ulcers had penetrated to the skin, 3 to the sternum, 5 to the trachea, bronchus, or lung, 6 to the pericardium, 1 to the aorta, and 1 to a brachiocephalic vein. In 1 case, the ulcer had penetrated into both the pericardium and a brachiocephalic vein. Yasumoto et al. (1990) reported a patient who developed a perforation into the aortic arch and was successfully treated.

According to Kumanohoso et al., 95 cases of carcinoma arising in reconstructed gastric tubes following esophageal resection for carcinoma had been reported from Japan before 1997. Fukushima et al. (1993) analyzed 46 patients with carcinomas that had arisen in reconstructed gastric tubes. These patients comprised 42 men and 4 women, who ranged in age from 44 to 84 years, with a

mean of 65 years. The carcinomas were detected from 13 months to 21 years (mean, 5 years and 8 months) after the esophageal resections for carcinoma. These included 10 cases of early carcinoma that had only invaded into the mucosa or submucosa.

The incidence of secondary carcinoma arising in gastric tubes has been reported to range from 0.2% to 5.1% (Nakai et al. 2002) and, recently, the incidence has been reported to be increasing because of the lengthening survival of esophageal cancer patients (Shigemitsu et al. 2002). It is not known, however, whether gastric tubes truly increase the incidence of gastric carcinoma.

11.2.18.3. Carcinoma of the Reconstructed Colon

Two cases of carcinoma arising in segments of colon used for esophageal reconstruction after resection of cancer have been reported by Goldsmith and Beattie (1968), and Altorjay et al. (1995). In the first case, the esophagus had been reconstructed using colon after resection of an esophageal squamous cell carcinoma, and a polypoid adenocarcinoma was found in the colon bypass 1 year and 9 months after the reconstruction. In the second case, a carcinoma was detected in the reconstructed colon-esophagus 1 year after the esophagectomy. There remains the possibility, however, that these colonic carcinomas might have been metachronous dual primaries because the time interval from the reconstruction to the clinical carcinoma was very short in both cases.

11.2.19. Outcome of Esophageal Carcinoma

The Registration Committee (Chairperson: H. Ide) of the Japanese Society for Esophageal Diseases (in June 2003 the Society changed its name to the Japan Esophageal Society) collects clinicopathological data on patients with esophageal carcinoma from registered hospitals every year, based on the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (1992). The report (published 1998) has data on patients from 1988 to 1997; in those years there were 1979 cases of esophageal carcinoma reported from the 127 registered institutions and hospitals. Of the 1979 patients, 1727 (87%) were male and 252 (13%) were female. Three hundred and ninety-three (20%) had been asymptomatic. One hundred and ninety (10%) of the patients had a synchronous primary carcinoma at another site and 168 (9%) had a metachronous primary carcinoma at another site. One thousand and twenty-eight (52%) of the esophageal carcinomas were located in the intrathoracic middle portion (Mt), 484 (25%) were in the intrathoracic lower portion (Lt), 212 (11%) were in the intrathoracic upper portion (Ut), 116 (6%) were in the cervical portion (Ce), and 106 (5%) were in the abdominal portion (Ae).

A total of 2123 patients (male : female ratio, 1849 : 274) with esophageal carcinoma were registered by the Committee in 1993. Of the 2131 carcinomas, 2% were in situ, 8% were mucosal invasive carcinomas, 18% showed submucosal invasion, 15% invaded into muscularis propria, 43% invaded through muscularis propria to the adventitia, and 12% invaded directly into other organs or tissues. The survival times after esophagectomy of 1655 patients who had been registered in 1993 were also published in the 1998 report (Figs. 11-60 through 11-62). The 5-year survival after esophagectomy was 41% overall (see Fig. 11-60), 39% for males and 50% for females (see Fig. 11-61). Subdivided according to stage of disease (see Table 11-3; 1992) the 5-year survival for patients with stage 0 esophageal carcinoma was 78%, for stage I, 68%, for stage II, 60%, for stage III, 34%, and for stage IV, 16% (see Fig. 11-62).

Of all the registered patients, 146 had been treated with radiation alone, and their 5-year survival was 19%; 31 had been treated with chemotherapy alone, and their 5-year survival was 3%; and 160 had been treated with both radiation and chemotherapy, with 5-year survival of 13%.

The most recent report (published in 2002 and reprinted in *Esophagus*, the official journal of the Japan Esophageal Society, in 2005) has data on patients from 1988 to 1997; in that period there were 116 421 cases of esophageal carcinoma reported from the 189 registered institutions and hospitals (Japan Esophageal Society 2005). The survival times after esophagectomy of the 11 642 patients were published in the 2002 report: these are shown in Figs. 11-62 and 11-63. The 10-year survival after esophagectomy was 26% overall (Fig. 11-63). Subdivided according to stage of

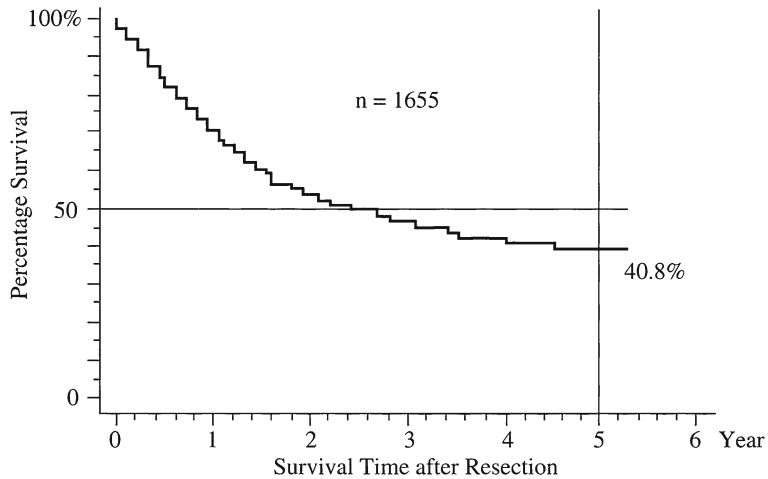


FIG. 11-60. Analysis of the crude survival following esophagectomy of 1655 patients with esophageal carcinoma [The Registration Committee (Chairperson: H. Ide) of the Japanese Society for Esophageal Diseases 1998]. Follow-up survival data were available for 1655 of the 2123 patients with esophageal carcinoma who had been registered in 1993. The 5-year survival of the 1655 patients was 40.8%

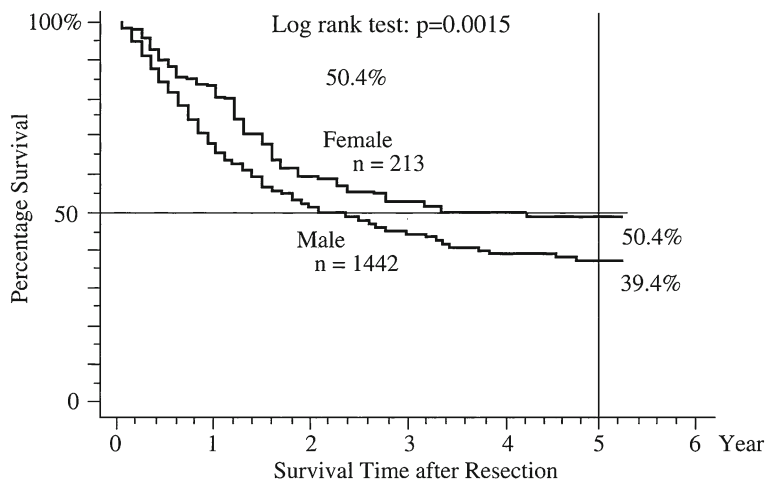


FIG. 11-61. Analysis of the crude survival following esophagectomy of 1655 of the 2123 patients with esophageal carcinoma, separated into male and female groups [The Registration Committee (Chairperson: H. Ide) of the Japanese Society for Esophageal Diseases 1998]. Of the 1655 patients for whom follow-up data were available, 1442 were male and 213 were female. The 5-year survival rate was 39.4% for males and 50.4% for females

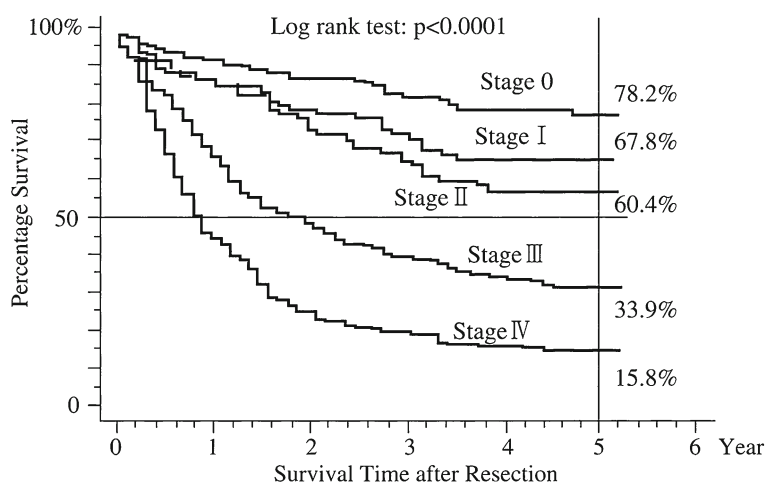


FIG. 11-62. Analysis of the crude survival following esophagectomy of 1655 of 2123 patients with esophageal carcinoma, separated according to stage of disease (see Table 11-3, 1992) into five groups [Registration Committee (Chairperson: H. Ide) of the Japanese Society for Esophageal Diseases 1998]. Of the 1655 patients for whom follow-up data were available, 255 were stage 0; 176, stage I; 145, stage II; 484, stage III; and 539, stage IV. The stage was unknown in 56 cases. The 5-year survival for stage 0 patients was 78.2%; for stage I, 67.8%; stage II, 60.4%; stage III, 33.9%; and stage IV, 15.8%

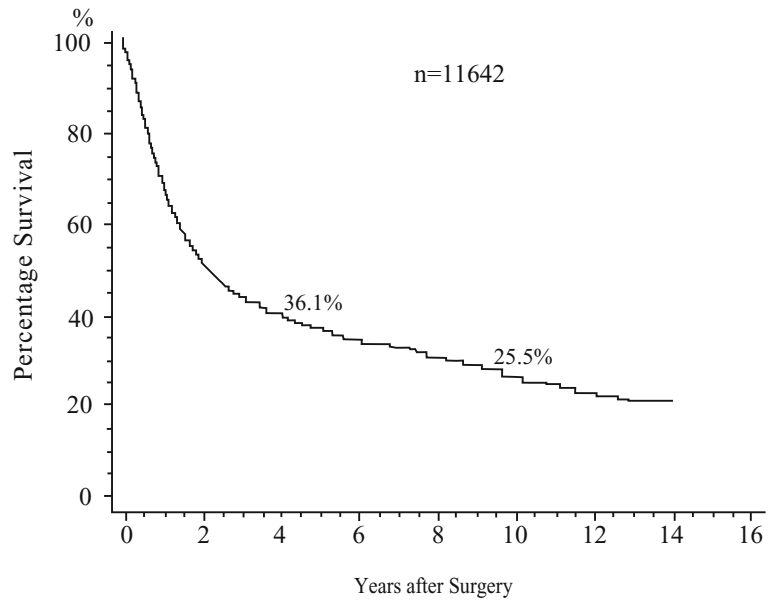


FIG. 11-63. Analysis of the crude survival following esophagectomy of 11 642 patients with esophageal carcinoma [The Registration Committee (Chairperson: H. Ide) of the Japan Esophageal Society 2002]. The 10-year survival of the 11 642 patients was 25.5%

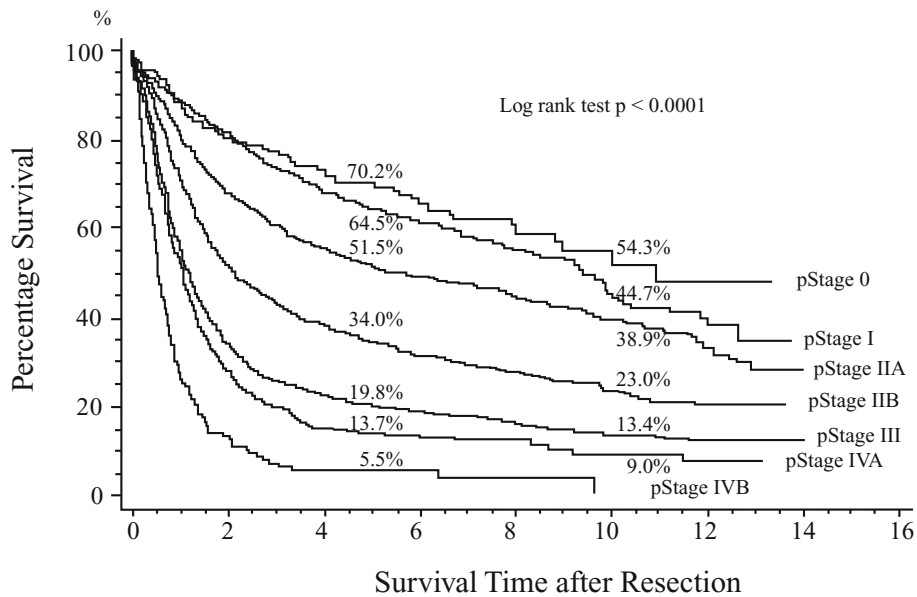


FIG. 11-64. Analysis of the crude survival following esophagectomy of 11 642 patients with esophageal carcinoma, separated according to stage of disease into seven groups [Registration Committee (Chairperson: H. Ide) of the Japan Esophageal Society 2002]. Subdivided according to stage of disease (UICC-pTNM), the 10-year survival for patients with pStage 0 esophageal carcinoma (313 patients) was 54.3%; for pStage I (2050), 44.7%, pStage IIA (2180), 38.9%, pStage IIb (1900), 23.0%, pStage III (3795), 13.4%; pStage IVA (1137), 9.0%; and pStage IV (267), 0% (see Fig. 11-63)

disease (UICC-pTNM), the 10-year survival for patients with pStage 0 esophageal carcinoma (313 patients) was 54%; for pStage I (2050 patients), it was 45%; for pStage IIA (2180 patients), 39%; for pStage IIb (1900 patients), 23%; for pStage III (3795 patients), 13%; for pStage IVA (1137 patients), 9%; and for pStage IVB (267 patients), 0% (Fig. 11-64).

11.2.20. Ectopic Production of Hormones and Hormone-Related Substances

High levels of serum parathyroid hormone-related protein (PTHrP), and hypercalcemia without bone metastasis, have been reported in a few patients with esophageal carcinoma (Mundy et al. 1984). Overall, around 20% of patients with esophageal carcinoma develop hypercalcemia.

High levels of serum granulocyte colony-stimulating factor (G-CSF), with leukocytosis, have also been reported in a small number of patients with esophageal carcinoma (Sato et al. 1979; Watanabe et al. 1999). Seven cases of esophageal squamous cell carcinoma with hypercalcemia and leukocytosis have been reported (Nakata et al. 2006).

11.2.21. Familial Carcinoma of the Esophagus

Familial carcinoma of the esophagus has been reported in some countries (Pour and Ghadirian 1974; Wu and Ruan 1979; Ghadirian 1985; Yoshimura et al. 1994).

Chapter 12
Barrett's Esophagus and Primary Adenocarcinoma of the Esophagus

12.1. Barrett's Esophagus

About 60 years ago, Barrett (1950) found instances in which the lower esophagus was lined by columnar epithelium, and reported this as a congenital anomaly. He inferred that the segment lined by columnar epithelium represented the stomach which was situated in the mediastinum, in association with a congenitally short esophagus. Allison and Johnstone (1953) regarded the columnar epithelium-lined segment as part of the esophagus, however, and Barrett later changed his view and concluded that the condition might be acquired (Mangla).

Lining of the esophagus by columnar epithelium had been known long before the reports of Barrett and Allison and Johnstone, however. In this regard Menke-Pluymers et al. (1993) cited a paper by Tileston (1906) that reported that mucosa closely resembling gastric mucosa sometimes surrounded esophageal ulcers.

Experimental data (Bremner et al.) and clinical observations (Endo et al.) have strongly suggested that this is an acquired condition, probably resulting from the long-term regurgitation of gastric contents through the esophagogastric junction zone. Goldman and Beckman (1960) first reported clinically evident proximal movement of the squamocolumnar junction. Mossberg (1966) demonstrated a case in which the junction moved about 20 cm proximally over a period of 1 year and 8 months. Endo et al. (1973) reported the process of proximal movement of Barrett's epithelium in Japan, illustrating a case, observed endoscopically, in which the squamocolumnar junction had moved 13 cm proximally over a 5-year period.

Barrett's esophagus is very often accompanied by a hiatus hernia and/or esophagitis. It is thought, however, that the development of a columnar epithelial lining is not necessarily accompanied by ulceration or erosion, and it seems possible that columnar epithelium may grow upward from the stomach in continuity, in response to the regurgitation of gastric contents. A few cases of Barrett's esophagus occurring in association with lye ingestion (Spechler et al.) and systemic sclerosis have been reported.

Barrett's esophagus has been reported in patients with familial visceral myopathies; these are rare genetic disorders characterized by degeneration and fibrous replacement of smooth muscle in the gastrointestinal tract (Mungan et al. 2003).

Some pediatric cases of Barrett's esophagus following gastroesophageal reflux (Robins et al.), frequent vomiting (Hoeffel et al.; Dessureault et al.), or antileukemic chemotherapy were also recently described, and since then there have been an increasing number of reports of Barrett's epithelium in children, especially in the cancer and gastroenterologic literature (Dahms and Rothstein). In fact, adenocarcinomas arising in Barrett's esophagus have also now been described in children (Hassall et al.).

12.1.1. Definitions of Barrett's Esophagus and Columnar-Lined Esophagus

The definition of Barrett's esophagus in Japan is the presence of a metaplastic columnar-lined esophagus (Figs. 12-1, 12-2) (Japan Esophageal Society 2000). In the United States, however, it is defined as the metaplastic replacement of any length of the esophageal epithelium that can be

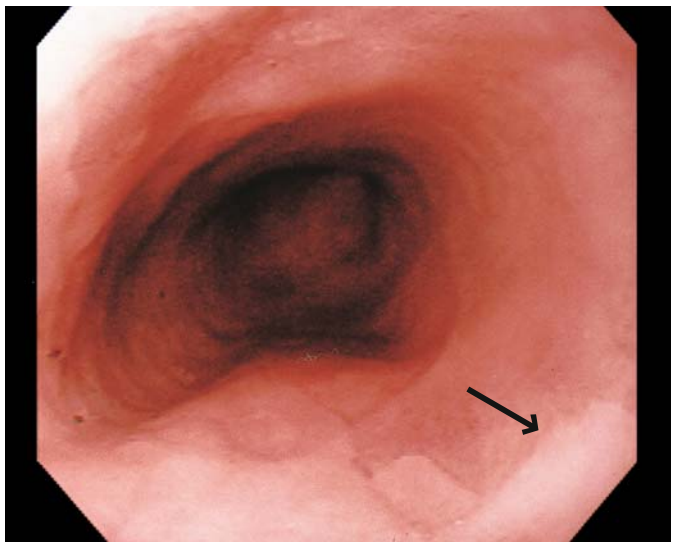


FIG. 12-1. Endoscopic appearance of Barrett's esophagus. There is a border between the white squamous and the red columnar epithelium, 22 cm from the incisor teeth (*arrow*)

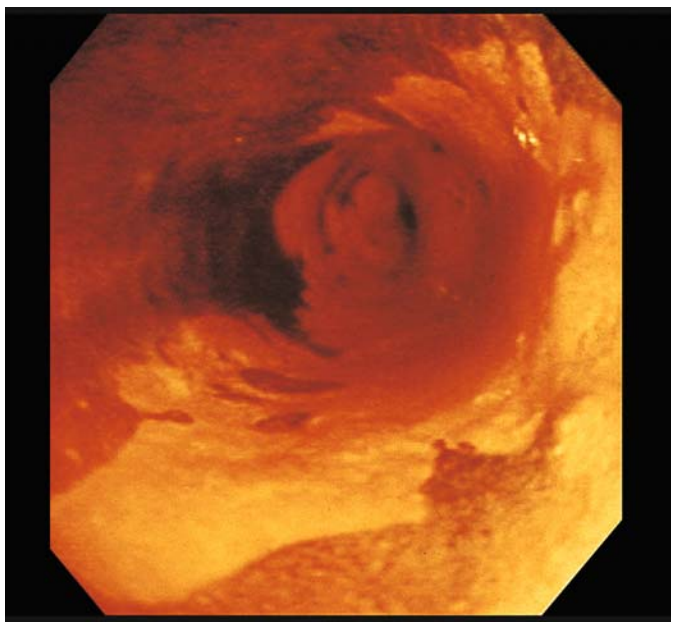


FIG. 12-2. Endoscopic appearance of Barrett's esophagus after Lugol's iodine staining. There is a border between the brown-stained squamous and the yellow columnar epithelium

recognized at endoscopy and which is confirmed by biopsy of the tubular esophagus to have intestinal metaplasia, excluding intestinal metaplasia of the cardia (The Practice Parameters Committee of the American College of Gastroenterology; Sampliner 2002).

The mucosa of columnar-lined esophagus has been classified into fundic, cardiac, and intestinal types, in what is thought to be the order of arrangement from the distal end (Paull et al. 1976). In many cases of columnar-lined esophagus (especially short-segment cases) the three types are intermixed, and biopsy specimens from Barrett's esophagus do not always demonstrate intestinal-type mucosa (Stolte and Vieth, unpublished data, 2005; Borchard 2000). Therefore, in the case of a random biopsy specimen, defining Barrett's esophagus as the presence of metaplastic columnar-lined mucosa with goblet cells is not restrictive.

The criteria commonly used in Europe and America for a diagnosis of Barrett's epithelium have been those proposed by Spechler and Goyal. They judged Barrett's esophagus to be present if the mucosal surface of the tubular esophagus was lined by columnar epithelium from the gastric end to (2–) 3 cm proximally, or if specialized columnar (intestinal-type) epithelium was found in the tubular esophagus. In a similar way, Siewert and Stein stated that Barrett's esophagus could be diagnosed if the portion of tubular esophagus lined by columnar epithelium (1) was at least 3 cm long, (2) was present in continuity from the stomach, and (3) was wholly circumferential. These criteria, however, often do not allow a histological diagnosis of Barrett's esophagus. In addition, the entity short-segment Barrett's esophagus, less than 3 cm in length, remains poorly defined. Some authors have also been of the opinion that the criterion of a 3-cm length is not critical (Kouzu et al.). In cases of Barrett's esophagus accompanied by a hiatus hernia, the esophagogastric junction of a surgically resected esophagus may only be recognizable by the difference in width between the stomach and the esophagus. Also, the definition and the location of the esophagogastric junction is controversial (see Section 12.1.2, following), and histological variations in the mucosa of this region have been reported (Section 2.2.1.2; see p. 12).

Kawano et al. reported the incidence of columnar-lined esophagus in a series of 2595 Japanese subjects (male:female ratio, 53 : 47; mean age, 56). The subjects were examined endoscopically, and the esophagogastric junction was defined as the lower limit of the longitudinal esophageal vessels. Using this definition, 0.3% of the subjects had more than 3 cm, 31% had between 1 and 3 cm, and 17.5% had less than 1 cm, of columnar-lined esophagus.

12.1.2. Definition of the Esophagogastric Junction and Longitudinal (Palisade) Vessels

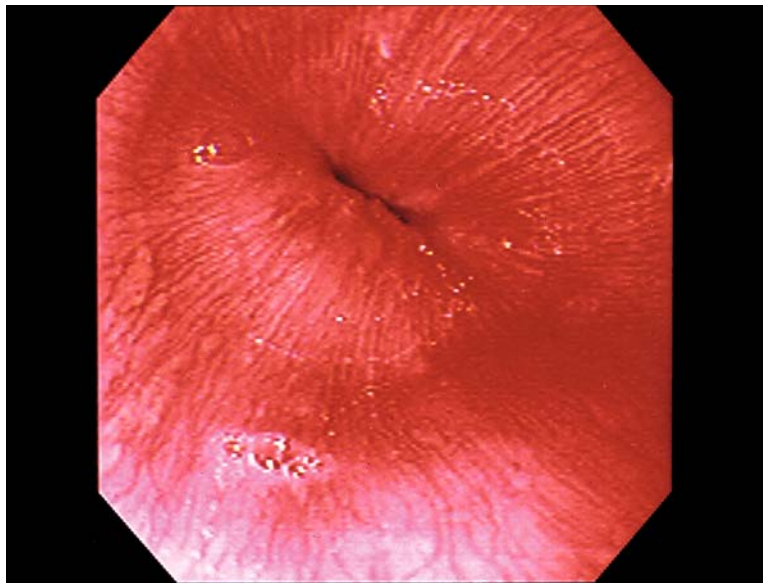
In Western countries, the esophagogastric junction (EGJ) is usually defined as the upper limit of the gastric mucosal folds.

In contrast, in Japan, the border between the esophagus and stomach (the esophagogastric junction) is considered, on endoscopic examination, to be the lower limit of the longitudinal esophageal vessels (Hoshihara et al. 1986; Takubo et al. 2003, 2005). This is the definition accepted by the Japan Esophageal Society (2000) because these longitudinal vessels have been shown, on the basis of histological studies, to always be located within the esophagus (De Carvalho 1966). The longitudinal vessels can be seen in the esophageal squamous mucosa (Fig. 12-3a,b) and in columnar-lined mucosa (Fig. 12-4). Longitudinal vessels are observed endoscopically in both the lower and upper (Fig. 12-5) esophageal sphincters whereas elsewhere a fine mesh pattern of vessels is seen; this finding suggests that the palisade vessels protect the upper and lower sphincters from ischemic damage (Makuuchi 2003). Longitudinal vessels and their endoscopic appearances have also been reported in some papers from other countries (Boyce 2000; Choi et al. 2002; Offerhaus et al. 2003; Armstrong 2004).

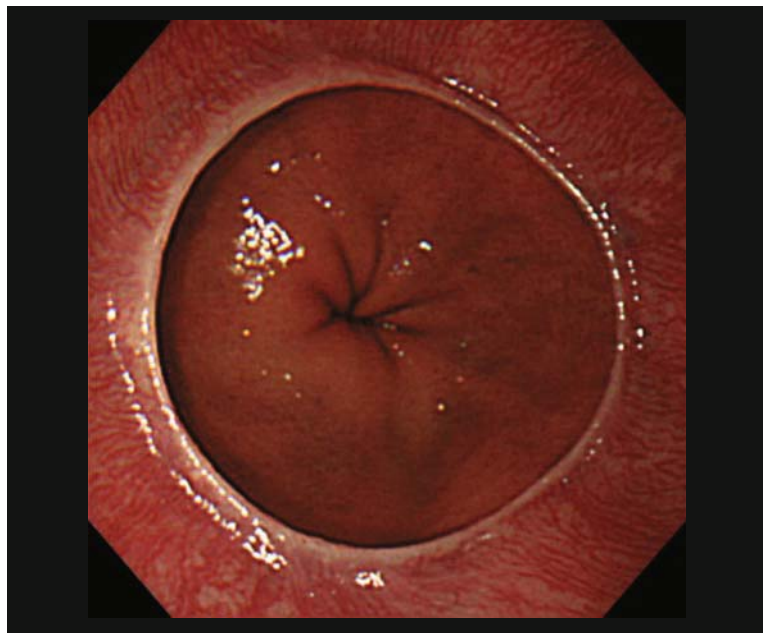
The present author considers that the criteria of Spechler and Goyal for the diagnosis of Barrett's esophagus should not be applied to resected esophagi but can be applied in cases where the esophagus remains in situ. More specifically, endoscopy and biopsy are necessary to establish a diagnosis in these cases. It is sometimes difficult to determine the precise location of the esophagogastric junction on endoscopic examination; thus, it is appropriate to make a diagnosis of Barrett's esophagus when endoscopic biopsy specimens, obtained from a site 3 cm or more proximal to the distal end of the esophagus, show columnar epithelium.

In contrast, it is absurd to claim that a 3-cm length of columnar epithelial mucosal lining in the esophagus, at least, is essential to diagnose Barrett's esophagus in resected esophagi, because the finding of openings of the esophageal glands proper into mucosa lined by columnar epithelium, a pathognomonic feature of Barrett's esophagus as already noted, serves as evidence of Barrett's epithelium (see Section 12.1.4.3. Esophageal Glands Proper and Squamous Islands in Barrett's Esophagus).

Precise analyses have been conducted on anatomical specimens to assess the distance between the squamocolumnar junction and the anatomical



a



b

FIG. 12-3. **a** Endoscopic appearance of longitudinal vessels in the squamous mucosa overlying the lower esophageal sphincter. There are many longitudinal vessels in the lower esophagus. **b** Endoscopic appearance of longitudinal vessels in the squamous mucosa in the squamocolumnar junction zone. There are many longitudinal vessels in the lower esophagus lined with squamous epithelium, not in the stomach lined with columnar epithelium. This is not lower esophageal ring (Schatzki's ring)

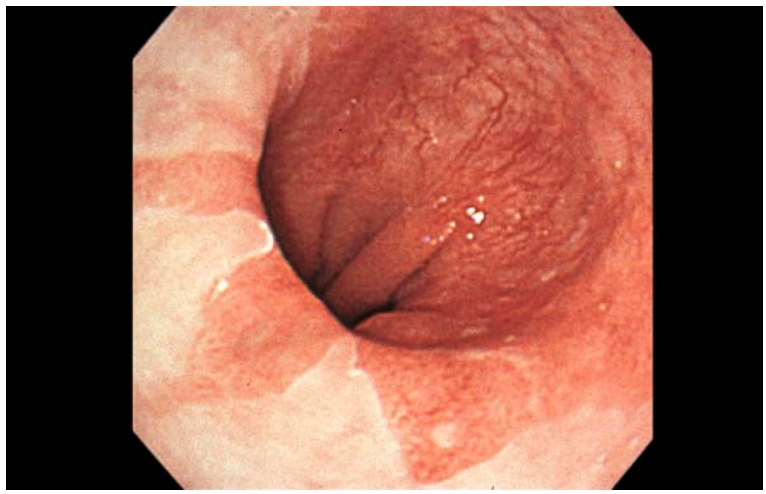


FIG. 12-4. Endoscopic appearance of longitudinal vessels in Barrett's mucosa. Many longitudinal vessels are evident through the columnar mucosa of the esophagus

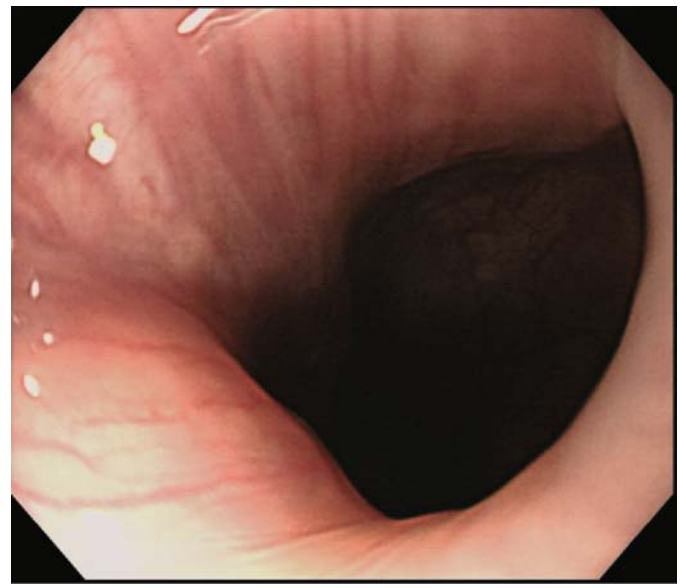


Fig. 12-5. Endoscopic appearance of longitudinal vessels at the level of the upper esophageal sphincter. Many longitudinal vessels are observed through the squamous mucosa of the esophagus, 19 cm from the incisors

Fig. 12-6. Macroscopic appearance of Barrett's esophagus. There is a clear border between the squamous and the columnar epithelium of the esophagus. Thickened squamous epithelium is evident above the Barrett's mucosa

junction; the figure averaged from 3 and 11 mm, and reliable assessment of this small distance during endoscopy is difficult (Lambert and Sharma 2005).

12.1.3. Macroscopic Appearance of Barrett's Esophagus

Barrett's mucosa has a rough brownish appearance, resembling gastric mucosa (Figs. 12-6, 12-7). Changes of reflux esophagitis are often evident in the squamous epithelium proximal to the Barrett's mucosa. Thickening of the squamous epithelium, with or without keratinization, may be seen. Lugol's iodine staining of Barrett's epithelium can demonstrate remaining islands of squamous epithelium in the metaplastic columnar mucosa at endoscopy (Figs. 12-8, 12-9) and in esophageal resection specimens (Takubo et al. 2003) (Fig. 12-10).

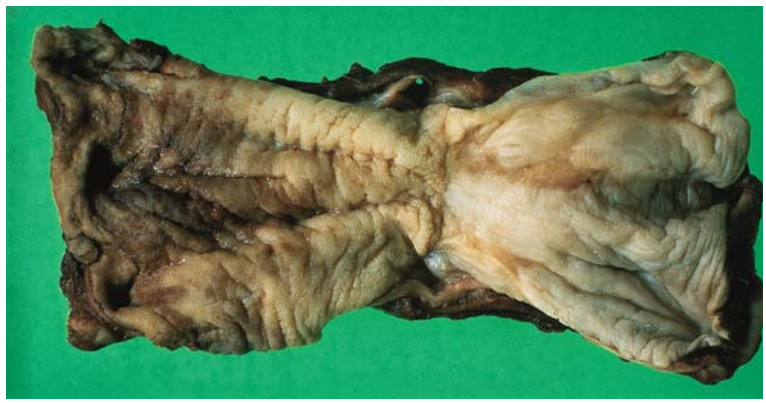


FIG. 12-7. Macroscopic appearance of Barrett's esophagus after total gastrectomy. There is a stenotic area toward the proximal end (on the *right*)

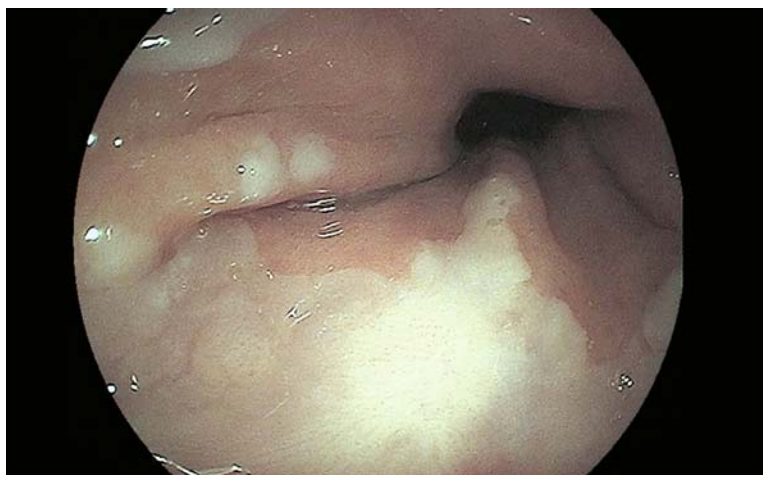


FIG. 12-8. Endoscopic appearance of Barrett's esophagus. Squamous islands are clearly visible in the salmon pink columnar-lined mucosa

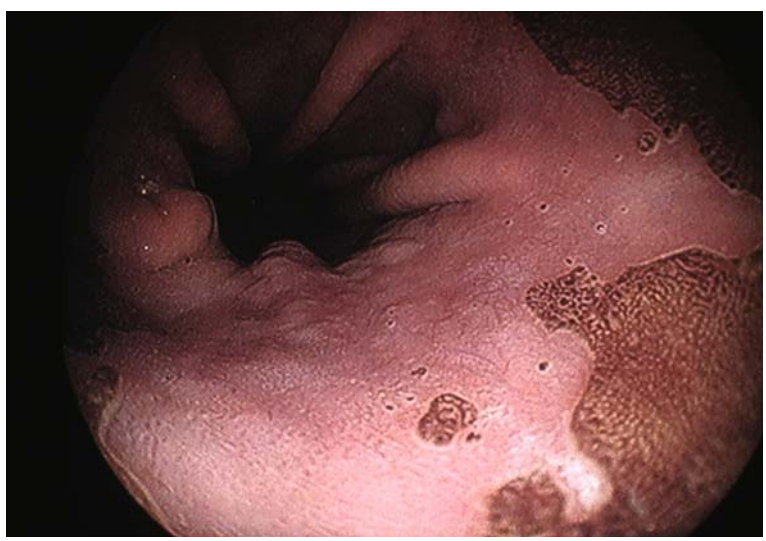


FIG. 12-9. Endoscopic appearance of Barrett's esophagus after Lugol's iodine staining. Squamous islands are clearly visible in the yellow columnar-lined mucosa

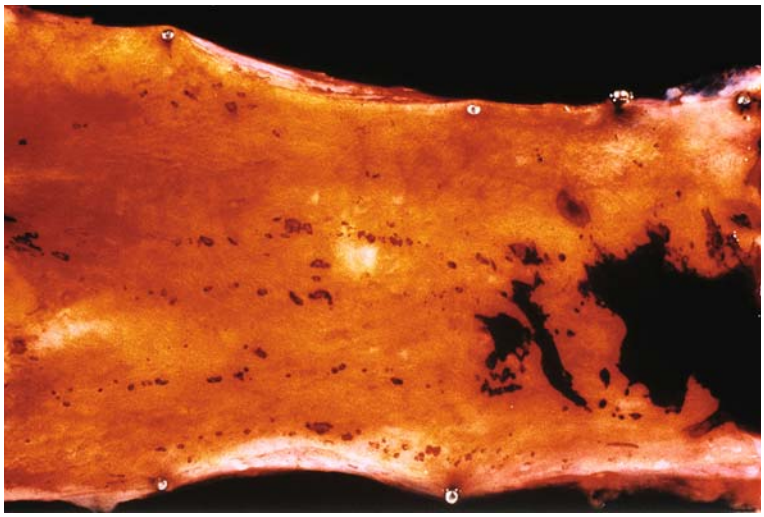


FIG. 12-10. Macroscopic appearance of Barrett's esophagus after Lugol's iodine staining. There are multiple small foci of squamous epithelium, positive with Lugol's stain, within the yellow Barrett's mucosa. These squamous islands represent the orifices of esophageal glands proper

12.1.4. Histological Appearance

There is not usually any severe fibrosis or heavy inflammatory cell infiltrate in Barrett's esophagus (Fig. 12-11). Barrett's mucosa has been classified, on the basis of data obtained mainly from endoscopic biopsy specimens, into fundic, junctional (cardiac) (Fig. 12-12), and specialized columnar (intestinal) types (Fig. 12-13), in what was thought to be the order of arrangement from the distal end (Paull et al.). Recent observations of resected specimens, however, have indicated that these types tend to be arranged in a complex mosaic pattern (Thompson et al.).

The specialized columnar-type epithelium has goblet cells, absorptive epithelial cells, and cells resembling gastric foveolar cells. This epithelium is considered to be difficult to distinguish morphologically from intestinal metaplastic epithelium of the stomach, particularly with regard to mucin histochemistry and the distribution of endocrine cells (Mangla 1981). Many Japanese researchers have agreed with this opinion of Mangla. It has been stated that Barrett's epithelium is very similar to the incomplete type of intestinal metaplasia of the stomach (Rosai). Although Barrett's epithelium was formerly believed to lack Paneth cells, similar to incomplete-type intestinal metaplasia of the stomach, it has now been shown that these cells may be present (see Fig. 12-13). This criterion serves as a basis for considering the specialized columnar epithelium to represent a type of intestinal metaplasia (Schreiber et al. 1978).

The presence of pancreatic acinar-like cells (pancreatic metaplasia) was reported in Barrett's mucosa in 11 of a series of 350 biopsy specimens from 120 patients (Krishnamurthy and Dayal 1995). Nokubi (1996) has reported many pancreatic acinar-like cells in gastric cardiac mucosa near the squamocolumnar junction (see Section 2.2.1.2.3. Pancreatic Metaplasia, p. 19).

Ciliated epithelial metaplasia has also been reported (refer to Chapter 2, p. 17). Histologically, therefore, Barrett's epithelium appears to be very complex, and findings differ from patient to patient (Nakamura et al.). When excretory ducts of the esophageal glands proper open into Barrett's epithelium, the duct epithelium may be hyperplastic (Fig. 12-14). Remaining islands of squamous epithelium are occasionally observed in resection and biopsy specimens from cases of Barrett's esophagus, and these are usually tangential sections of hyperplastic ducts or duct orifices (Takubo et al. 1995).

As already noted, the definition of Barrett's esophagus in Japan is the presence of a metaplastic columnar-lined mucosa (Aoki), whereas in the United States it is metaplastic replacement of any length of the esophageal epithelium that can be recognized at endoscopy and is confirmed by biopsy of the tubular esophagus to show specialized intestinal metaplasia, excluding intestinal metaplasia of the cardia (The Practice Parameters Committee of the American College of Gastroenterology; Sampliner 2002). Intestinal metaplasia cannot, however, always be demonstrated in

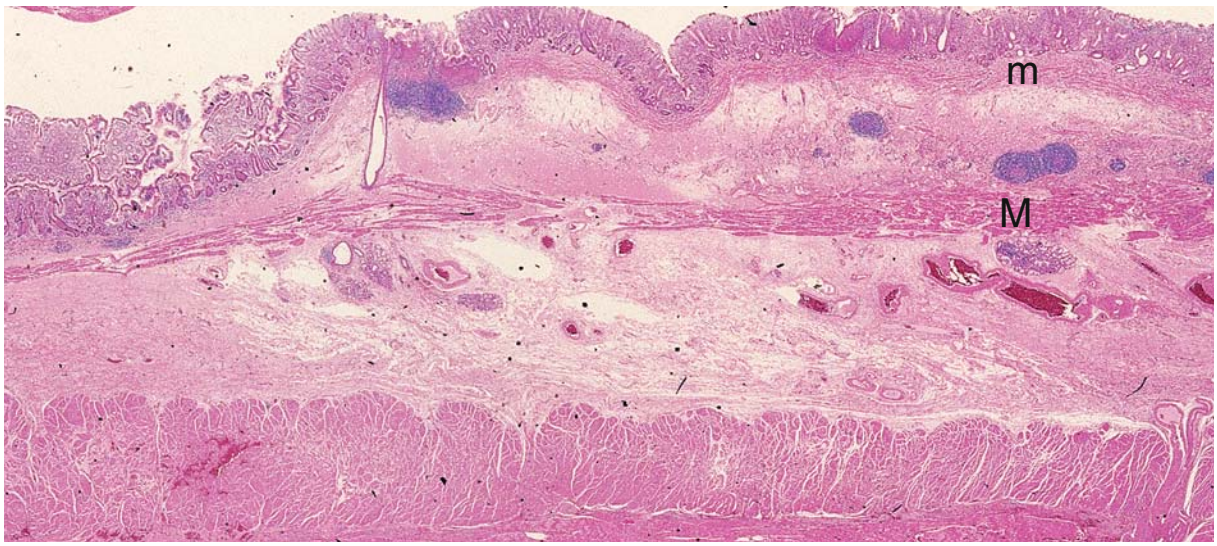


FIG. 12-11. Barrett's esophagus at low magnification. There is a thin muscularis mucosae (*m*) just beneath the columnar epithelial mucosa, and a thick muscularis mucosae (*M*) of the original esophagus

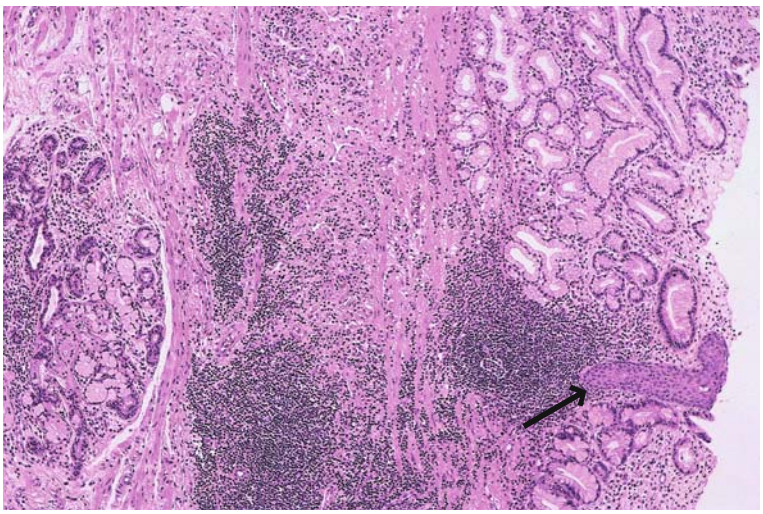


FIG. 12-12. Junctional type mucosa of Barrett's epithelium. *Arrow*, excretory duct of an esophageal gland proper

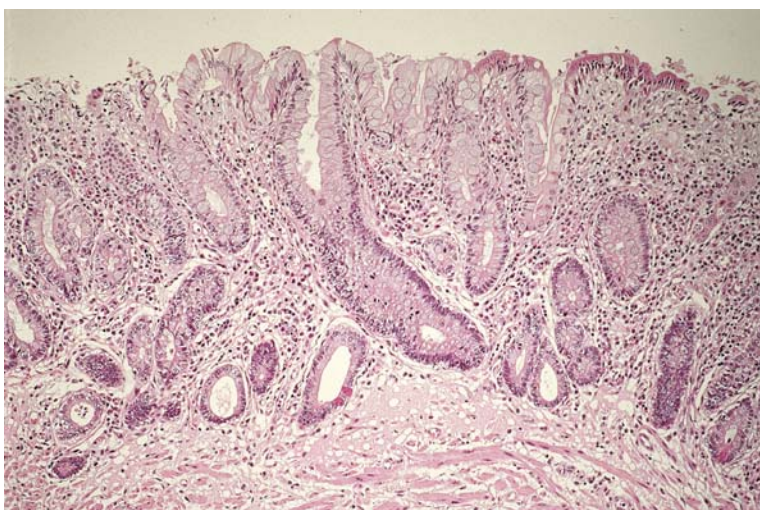


FIG. 12-13. Specialized columnar epithelium of Barrett's epithelium. Goblet cells and Paneth cells are evident in the mucosa

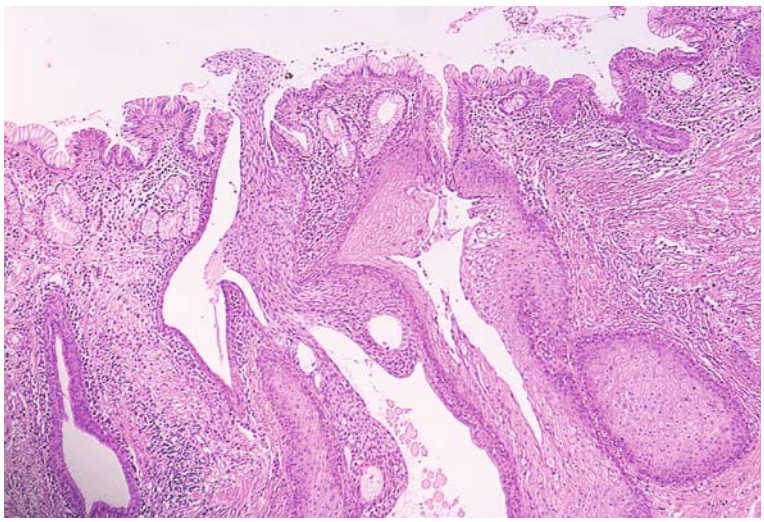


Fig. 12-14. Excretory ducts of the esophageal glands proper in Barrett's esophagus. Hyperplasia of ductal epithelium is evident

biopsies of esophageal mucosa in cases of endoscopically evident Barrett's esophagus (Stolete and Vieth 2005).

12.1.4.1. Double Muscularis Mucosae in Barrett's Esophagus

Barrett's esophagus often shows both a thick (deep) muscularis mucosae from the original esophagus and a thin (superficial) muscularis mucosae of the metaplastic columnar epithelial mucosa (Takubo and Kato 1987). This author has named this change double muscularis mucosae (1987, 1991) (see Fig. 12-11). There had not been any published reports of a systematic investigation of this change before the author's aforementioned two papers. This finding had, however, been previously described in a case report of double adenocarcinoma in Barrett's esophagus by Kato et al. (1981), who had concluded that it was corroborative evidence of a congenital origin for Barrett's esophagus. Following the author's 1987 report, Iwasaki et al. (1990) reported double muscularis mucosae in a case of multiple early adenocarcinomas of Barrett's esophagus. Tada et al. (1990) also reported double muscularis mucosae in a case of adenocarcinoma that arose in Barrett's esophagus after a total gastrectomy, but they did not conclude whether the Barrett's epithelium was congenital or acquired.

Histologically, edematous lamina propria of the original esophagus lies between the two layers of muscularis mucosae. The deep muscularis mucosae is continuous with that of the gastric mucosa, and lies beneath the esophageal squamous epithelium. Smooth muscle fibers of the superficial muscularis mucosae of the columnar epithelial mucosa show an irregular arrangement and spread in a complex manner into the lamina propria. Although it has been reported that this irregular arrangement of muscle fibers with spread into the lamina propria is specific for Barrett's esophagus, this appearance is also common in gastric intestinal metaplasia. The proximal end of the thin muscularis mucosae becomes indistinct and disappears in fibrous tissue deep to the transition zone between the Barrett's epithelium and the original squamous epithelium, or at the distal edge of an ulcer or erosion. The distal end of the superficial muscularis mucosae connects with the deep muscularis mucosae in the esophagogastric junction zone. Thus it is apparent that Barrett's esophagus is not a change that occurs within the epithelium alone but rather is a change which involves the epithelium, lamina propria, and muscularis mucosae. There have not been any studies, however, which have investigated the issue of whether the columnar epithelium induces the stroma (lamina propria, muscularis mucosae) or vice versa.

It should be noted that smooth muscle fibers with an irregular arrangement, unaccompanied by Barrett's epithelium, are also sometimes seen in the lamina propria in the region of the

esophagogastric junction in other situations, although rarely; these include invasion by carcinoma, esophagitis, radiotherapy, and sclerotherapy (Unakami). Unlike the muscularis mucosae associated with Barrett's epithelium, however, these muscle fibers are only seen in a very limited area.

12.1.4.2. Squamous Reepithelialization and Pseudoregression of Barrett's Esophagus

There have been occasional reports of squamous reepithelialization occurring in Barrett's esophagus after proton pump inhibitor (PPI) therapy, laser treatment, photodynamic therapy, and mucosal resection (Sampliner and Fass 1993; Overholt and Panjehpour 1996; Tanaka et al. 1996). Florid squamous metaplasia may be seen in Barrett's mucosa after photodynamic therapy (Biddlestone et al. 1998).

After antireflux surgery, regenerated squamous epithelium may be seen to overlie persisting Barrett's epithelium. Also, in cases of squamous reepithelialization after endoscopic resection or PPI therapy, Barrett's mucosa may remain in the lamina propria under the regenerated squamous epithelium (Fig. 12-15a); this phenomenon has been termed pseudoregression of Barrett's esophagus or buried glands. Following PPI therapy, the squamous islands are widened and squamous reepithelialization occurs from the duct–columnar

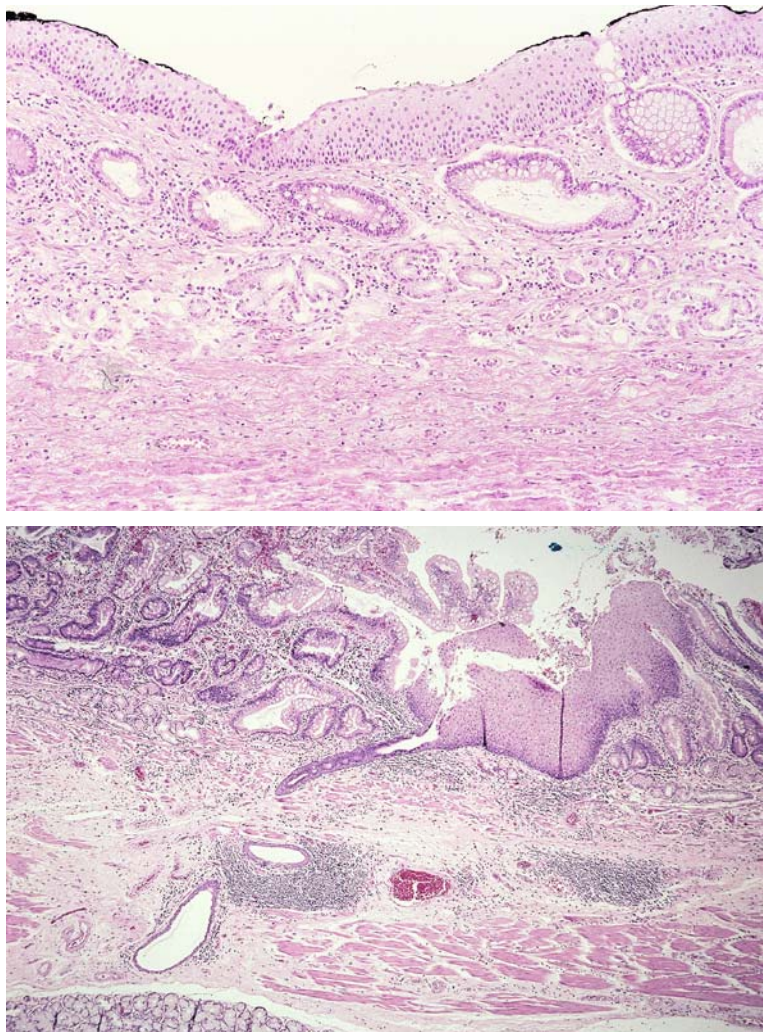


FIG. 12-15. **a** Pseudoregression of Barrett's esophagus. Barrett's mucosa remains in the lamina propria beneath regenerated squamous epithelium. **b** A squamous island in Barrett's esophagus. An esophageal gland proper opens into Barrett's mucosa. A small island is adjacent to the gland ductal orifice

junctions as well as from the squamocolumnar junction on the mucosal surface (Coad et al. 2005). A case of intramucosal adenocarcinoma arising in Barrett's esophagus under neosquamous epithelium after squamous reepithelialization has been reported (van Laethem et al. 2000).

12.1.4.3. Esophageal Glands Proper and Squamous Islands in Barrett's Esophagus

The esophageal glands proper lie in the submucosa of the esophagus, and their excretory ducts always open into the esophageal mucosa (Fig. 12-15b). Therefore, the identification of openings of the esophageal glands into columnar-lined mucosa is a pathognomonic feature of columnar-lined esophagus (Coad et al. 2005; Takubo et al. 2005). This, then, is one of the criteria that may be used for the histological diagnosis of Barrett's epithelium (Rosai; Takubo et al.). In a study of complete serial sections of squamous islands within columnar-lined mucosa, all squamous islands were found to be continuous with an underlying gland duct. Therefore, the squamous islands represent an extension of squamous epithelium from submucosal gland ducts (Coad et al. 2005). The present author, as a rule, judges Barrett's epithelium to be present if an esophageal gland proper opens into columnar epithelial mucosa in a biopsy or resection specimen. There is a very large individual variation, however, in the total number of esophageal glands proper. Although there are two or three esophageal glands proper, on average, per square centimeter of esophageal mucosa, it is sometimes not possible to find any at all in the region of the esophagogastric junction.

12.1.4.3.1. Targeted Biopsy of Squamous Islands in Barrett's Esophagus

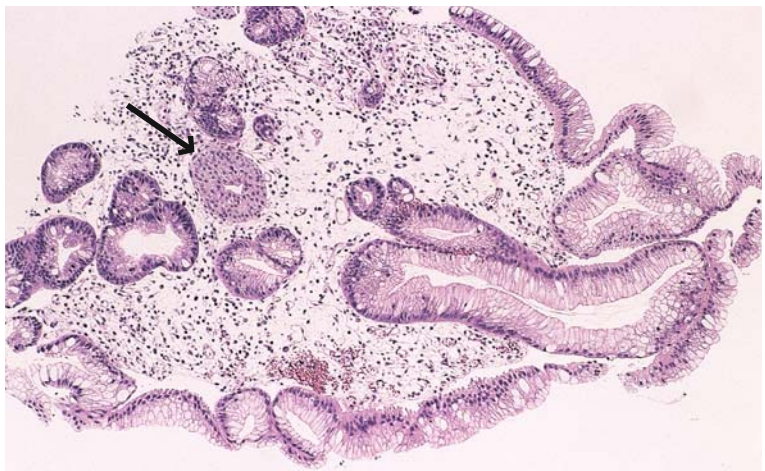
The present author has found ducts of the esophageal glands proper in 10% of random biopsy specimens from cases of Barrett's esophagus (Fig. 12-16a). Therefore, 10% of patients can have an unequivocal diagnosis of Barrett's esophagus made purely on the basis of the histology of biopsy specimens (Takubo et al. 1995). In another study, esophageal glands proper or their ducts were demonstrated in 78% of targeted biopsy specimens of squamous islands (Takubo et al. 2005). Also, Coad and Shepherd (2003) and Coad et al. (2005) confirmed that squamous islands are universally associated with esophageal gland ducts.

12.1.5. Barrett's Esophagus After Gastrectomy, Esophagectomy, and Surgery for Achalasia

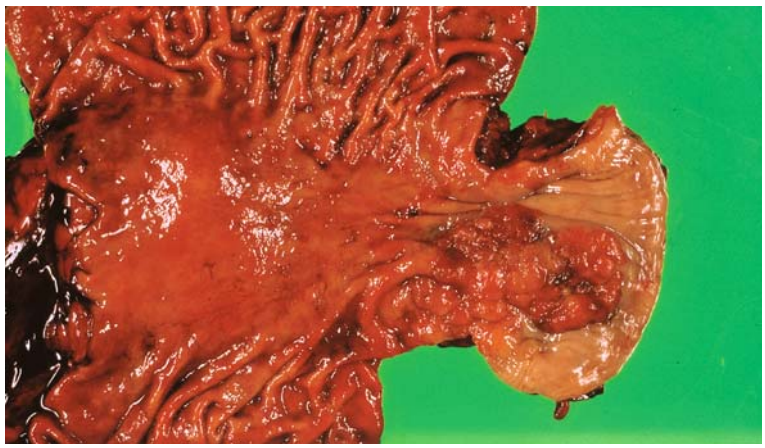
Reports of the development of Barrett's esophagus after total gastrectomy (see Fig. 12-7) and surgery for achalasia have been becoming more frequent. Barrett's esophagus after total gastrectomy was first reported in an autopsy case of Zollinger–Ellison syndrome, 6 years after the gastrectomy (Davidson, 1964). Taniguchi et al. (1982) reported 5 such cases of Barrett's esophagus, comprising 3 that occurred after gastrectomy for gastric cancer and 2 that followed surgery for achalasia. Also, Tada et al. (1990) noted a further 9 reported cases of Barrett's esophagus following total gastrectomy, and Westhoff et al. added a case of Barrett's esophagus that occurred 6 months after a total gastrectomy (2004). These reports strongly support the idea that Barrett's esophagus is an acquired condition. The development of Barrett's esophagus in these situations has been attributed to reflux esophagitis occurring secondary to the total gastrectomy or the surgery for achalasia. Based on this there is general agreement that reflux of not only acid gastric contents, but also alkaline intestinal contents, can induce Barrett's epithelium. Peitz et al. (2005) reported that 8 (32%) of 25 patients with a history of total gastrectomy had Barrett's mucosa in the remnant esophagus. Seven of the 8 were short segment and 1 was long segment. They found complete-type intestinal metaplasia with Paneth cells and absorptive cells.

12.1.6. Cervical Esophagitis and Barrett's Esophagus After Thoracic Esophagectomy

Barrett's esophagus and reflux esophagitis may also occur in the cervical esophagus after thoracic esophagectomy for esophageal carcinoma, with anastomosis of the cervical esophagus to the reconstructed thoracic stomach.



a



b

FIG. 12-16. **a** Biopsy specimen from Barrett's esophagus. A duct (*arrow*) is seen in the intestinal-type Barrett's mucosa. This is presumptive evidence that the material has come from the esophagus. **b** Macroscopic appearance of a primary adenocarcinoma of the esophagus associated with Barrett's epithelium (polypoid-type advanced carcinoma)

12.1.7. Barrett's Ulcer

When an esophageal ulcer is completely or partially surrounded by Barrett's mucosa, it is termed a Barrett's ulcer. Barrett's ulcers may perforate into adjacent organs, and 39 cases of perforated Barrett's ulcer have been reported (Guillem et al. 2000; Nagumo et al. 2005). Perforation has most commonly occurred into the pleural cavity, mediastinum, left atrium, trachea, bronchi, aorta, pericardium, and pulmonary veins.

12.2. Primary Adenocarcinoma of the Esophagus

It is thought that primary adenocarcinomas of the esophagus can arise from the esophageal glands proper, the esophageal cardiac glands, ectopic gastric mucosa, embryonal rests, and metaplastic columnar epithelium (Barrett's epithelium). In published reports, however, there has only been histopathological evidence of origin in Barrett's epithelium, ectopic gastric mucosa, esophageal cardiac glands, and esophageal gland proper. Primary adenocarcinoma of the esophagus represents less than 3.1% of all esophageal malignancies in Japan, and this figure has not increased in the past 13 years (http://esophagus.jp/Japan Esophageal Society, 2005). In contrast, the incidence of esophageal adenocarcinoma in Western countries has recently been rising rapidly and is now very high in white males. Adenocarcinoma now comprises more than 50% of all esophageal malignancies in some series (Devesa et al. 1998; Siewert et al. 2004). Although reflux esophagitis is still much less common in Japan than in Western countries,

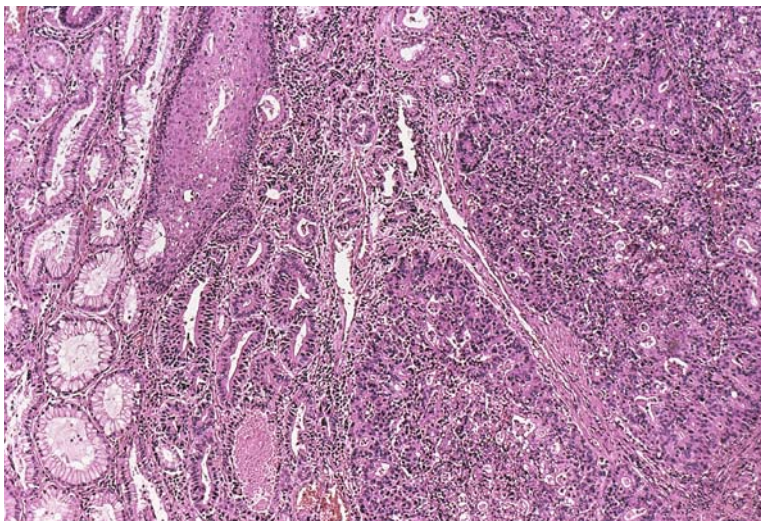


FIG. 12-17. Histological appearance of the lesion shown in Fig. 12-16b, showing the junctional area between the adenocarcinoma (on the proximal side) and Barrett's epithelium (on the distal side). The tumor is a moderately differentiated tubular adenocarcinoma. The duct of an esophageal gland proper is seen in the junctional zone

its incidence has increased over the past 20 years; however, severe gastroesophageal reflux disease (GERD) (grades C and D in the Los Angeles Classification System) remains rare in Japan.

12.2.1. Barrett's Adenocarcinoma

12.2.1.1. Definition of Barrett's Adenocarcinoma

When an adenocarcinoma is completely surrounded by Barrett's mucosa or squamous epithelium, the carcinoma is a definite case of Barrett's adenocarcinoma. If an adenocarcinoma is located adjacent to, but not completely surrounded by, Barrett's mucosa, it is an indefinite Barrett's adenocarcinoma (Figs. 12-16b, 12-17).

12.2.1.2. General Considerations

Morson and Belcher (1952) reported the first case of a primary adenocarcinoma arising in Barrett's esophagus. Adler and Rodriguez (1959) later emphasized the relationship between the two conditions. Barrett's esophagus has been reported to be associated with between 6.6% and 46% of cases of esophageal adenocarcinoma. It has been reported that there is a close relationship between adenocarcinoma and Barrett's epithelium that contains sulfomucin, but there are opposing views (Haggitt et al.).

The mean age of patients with adenocarcinoma complicating Barrett's esophagus, in Europe and America, is reported to be 58 years. There have, however, been seven cases reported in patients in their second decade (11–19 years of age) (Hassall et al. 1993).

This author found 2 cases (0.7%) of pure adenocarcinoma, with no squamous component, of 287 esophageal carcinomas that were studied in Japan. Both were cases of so-called Barrett's adenocarcinoma, associated with Barrett's epithelium.

12.2.1.2.1. Background Mucosa of Barrett's Adenocarcinoma

It is widely accepted that intestinal-type mucosa in the columnar-lined esophagus is the probable common precursor of adenocarcinoma. Many papers focusing on the background or original mucosa of Barrett's adenocarcinoma have maintained that adenocarcinoma arises in intestinal-type mucosa with goblet cells in the columnar-lined esophagus. However, although the incidence of primary adenocarcinoma of the esophagus in Japan is very low, accounting for about 4% of all esophageal malignancies, a cardiac-type background of esophageal adenocarcinoma is occasionally encountered. About 60%–70% of Japanese cases of primary adenocarcinoma of the esophagus we have encountered have a cardiac-type background mucosa without goblet cells. Therefore, it would appear that the presence of cardiac mucosa as well as intestinal-type mucosa in biopsy

specimens from columnar-lined esophagus indicates the need for follow-up. Further studies of histogenetic and molecular approaches to clarify the original mucosal type of Barrett's adenocarcinoma are needed.

12.2.1.3. Histological Appearances

Various histological variants of esophageal adenocarcinoma, including papillary adenocarcinoma, tubular adenocarcinoma, and signet ring cell carcinoma, with degrees of differentiation ranging from well to poor, have been reported. The tumors that this author has examined have all been well differentiated (Figs. 12-17 through 12-19). There has been one notable report of an adenocarcinoma, which was partly of signet ring cell type, that arose in mucosa covered by metaplastic columnar epithelium; this mucosa had atrophic gastric mucosa-like features (Berenson et al.). In a series reported by Nishimaki et al. (1991), only 2 of 13 cases of early adenocarcinoma arising in Barrett's esophagus were poorly differentiated and most of the 13 had arisen in the squamocolumnar junction zone. Tamai et al. (1993) reviewed 15 Japanese patients with superficial adenocarcinomas of Barrett's esophagus and reported that only one was poorly differentiated. Takemasa et al. (1997) reviewed 35 Japanese patients with superficial adenocarcinomas of Barrett's esopha-

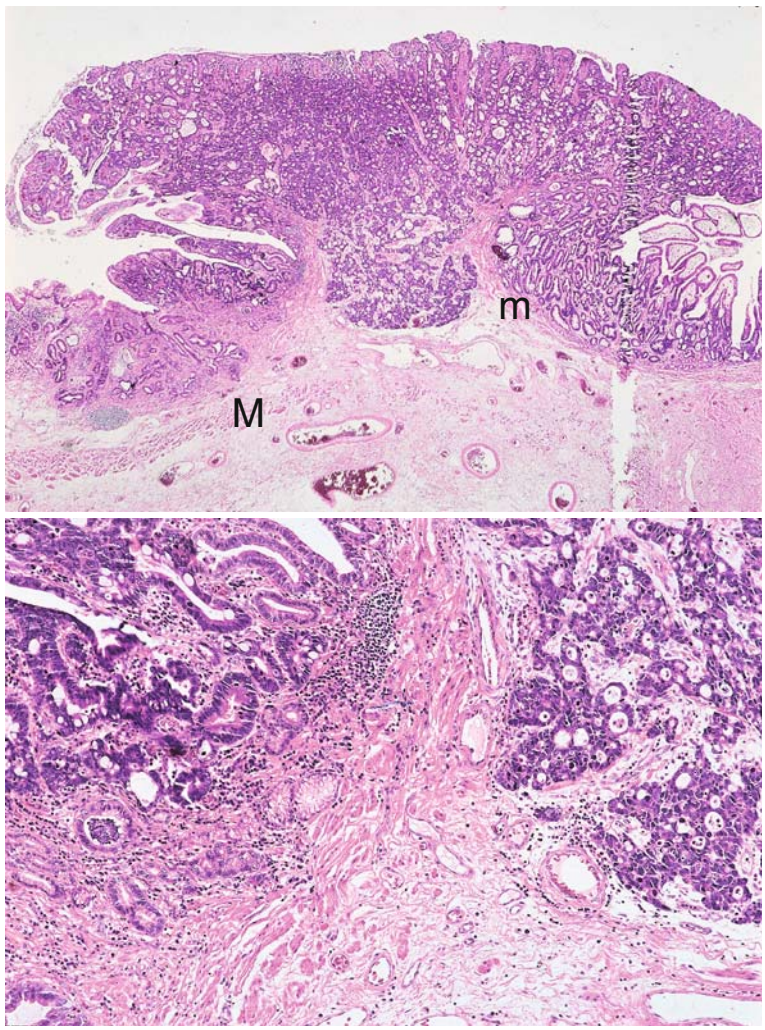


FIG. 12-18. **a** Barrett's adenocarcinoma. Moderately differentiated adenocarcinoma invading to the zone between the two layers of the muscularis mucosae. The invading tumor is surrounded by intramucosal well-differentiated tubular adenocarcinoma. *M*, original muscularis mucosae; *m*, newly developed muscularis mucosae. **b** Barrett's adenocarcinoma (close-up view of **a**). Moderately differentiated adenocarcinoma (*right*) invading to the zone between the two layers of the muscularis mucosae. Intramucosal well-differentiated tubular adenocarcinoma with no or minimal invasion (*left*) on the newly developed superficial muscularis mucosae

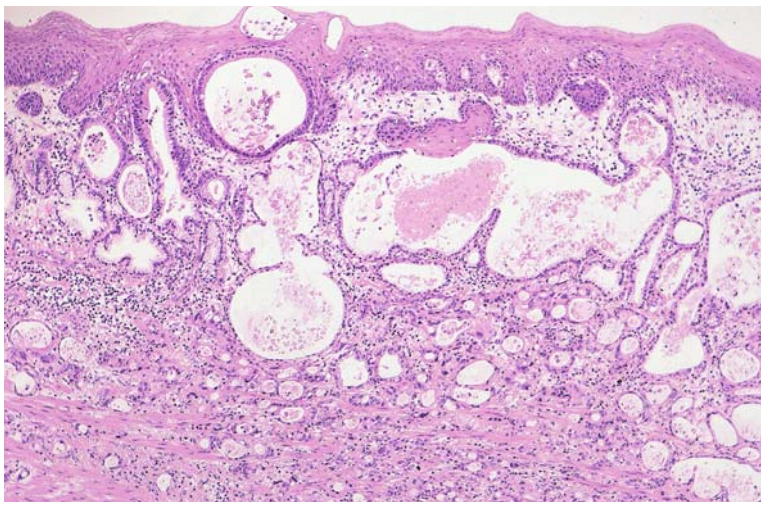


FIG. 12-19. Primary adenocarcinoma of the esophagus. This is a well-differentiated tubular adenocarcinoma that has infiltrated into the lamina propria without destroying the squamous epithelium

gus; most of these tumors had a protruding macroscopic appearance and were well differentiated. Fujisawa et al. (1999) reviewed 31 Japanese patients with early adenocarcinoma of Barrett's esophagus. The male:female ratio was 24:7, and patient age ranged from 32 to 84 years (mean age, 61 years). Thirty-three lesions were observed in the 31 patients, and 1 of them was poorly differentiated.

Most primary adenocarcinomas have a component of intramucosal spread, occasionally infiltrating into lamina propria beneath stratified squamous epithelium (see Fig. 12-19).

In the Japanese *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus* (8th and 9th editions) adenocarcinomas are classified into well, moderately, and poorly differentiated types, based on the histological classification of the *General Rules for Gastric Cancer Study*. The relationship, if any, between the histological grade of esophageal adenocarcinoma and prognosis remains to be elucidated.

12.2.1.3.1. High-Grade Dysplasia, Intramucosal Adenocarcinoma, and the Vienna Classification

Dysplasia, or adenomatous change, has been reported in noncancerous areas of Barrett's epithelium. High-grade dysplasia (WHO 2000) is reported to be associated with invasive adenocarcinoma arising in Barrett's esophagus. In Japan, high-grade dysplasia with no, or minimal, stromal invasion is considered to be intramucosal well-differentiated adenocarcinoma, but in Western countries the term high-grade dysplasia is generally used when there is no stromal invasion, as is the case for other sites in the gastrointestinal tract (Schlemper et al. 1997; Stolte 1999; Jass 2000). High-grade dysplasia is considered in Western countries to be a precursor of adenocarcinoma, but in Japan the same lesion is interpreted as an intramucosal adenocarcinoma of the esophagus (see Fig. 12-18a). This therefore suggests that adenocarcinoma of the esophagus arises de novo, rather than from a precursor lesion (see Fig. 12-18b).

Micrographs of high-grade dysplasia published in Western textbooks are considered in Japan to show adenocarcinoma, with or without invasion. Most Japanese pathologists do not see a need to diagnose high-grade dysplasia in the esophagus and stomach. Japanese pathologists, including the present author, consider that, for practical purposes, the concept of high-grade dysplasia is not necessary (Takubo et al. 2002, 2006). Vieth and Stolte (2005) also stated that, in routine practice, the diagnosis of high-grade dysplasia is very rare because most cases have already progressed to mucosal adenocarcinoma. Studies of p53 protein immunostaining have demonstrated positive staining in high-grade dysplasia (or well-differentiated mucosal adenocarcinoma, as defined in Japan) and multiple genetic abnormalities have also been reported. Also, "high grade dysplasia," "noninvasive carcinoma," and "suspicious of invasive

carcinoma" have all been included in category 4 of the Vienna Classification of Gastrointestinal Epithelial Neoplasia (see Table 11-1, p. 145), and local treatments such as endoscopic mucosal resection (see Section 11.2.17.1.1) or laser ablation would be indicated for each of these (Schlemper et al. 2000). Also, biopsy samples are limited, and there may be foci of invasion in the mucosa or in deeper layers elsewhere that have not been sampled.

TABLE 12-1. The histological classification of esophageal carcinoma, from the *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus* (8th and 9th editions), by the Japanese Society for Esophageal Diseases

I. Malignant epithelial tumors
  1. Squamous cell carcinoma
  2. Adenocarcinoma
  3. Adenosquamous carcinoma
    a. Coexistence of adenocarcinoma and squamous cell carcinoma
    b. Mucoepidermoid carcinoma
  4. Adenoid cystic carcinoma
  5. Basaloid (-squamous) carcinoma
  6. Undifferentiated carcinoma
    a. Small cell type
    b. Non-small cell type
  7. Others
II. Malignant nonepithelial tumors
III. Miscellaneous malignant tumors
  1. "Carcinosarcoma"
    a. So-called carcinosarcoma
    b. Pseudosarcoma
    c. True carcinosarcoma
  2. Malignant melanoma
  3. Others
IV. Tumor-like lesions
  1. Dysplasia

12.2.1.3.2. Low-Grade Dysplasia

Some micrographs of low-grade dysplasia occurring in Barrett's esophagus that have been published in Western textbooks have been judged by pathologists in Japan to show intramucosal adenocarcinoma.

12.2.1.4. Cytological Features of Adenocarcinoma

The cytological features of esophageal adenocarcinoma are similar to those of gastric adenocarcinoma. Cell clusters forming papillary and tubular structures are seen (Fig. 12-20). The nuclei are irregular in size and have fine granular chromatin. As with gastric adenocarcinoma, there may also be intracytoplasmic lumina (microcysts); these are highly suggestive of malignancy if seen in cytological samples from the esophagus (Ohno et al.) (Fig. 12-21).

12.2.1.5. Lymph Node Metastasis in Esophageal Adenocarcinoma

The relationship between the depth of tumor invasion and the incidence of lymph node metastasis has been reported in several papers, and this literature was reviewed by Vieth and Stolte (2005)

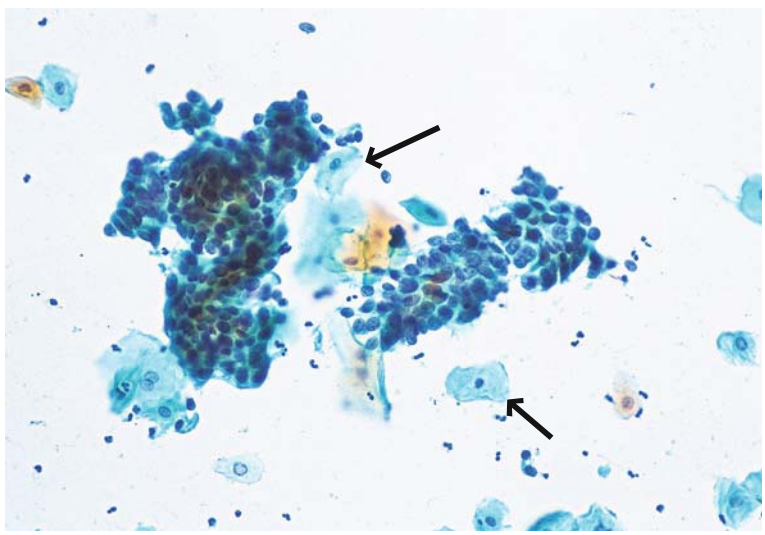


FIG. 12-20. Cytological appearance of an esophageal adenocarcinoma (Papanicolaou stain). Cell clusters from the adenocarcinoma, and surface cells from the stratified squamous epithelium (*arrows*) of the esophagus, are evident

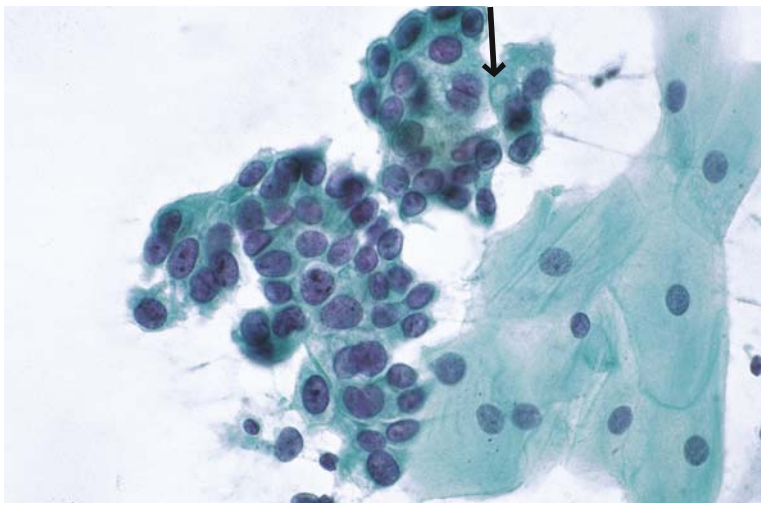


Fig. 12-21. Cytological appearance of an esophageal adenocarcinoma (Papanicolaou stain). The cell clusters have a papillary structure and the tumor cells have microcysts (*arrow*) in their cytoplasm

and Vieth and Rösch (2006). For mucosal adenocarcinomas, Hölscher et al. (1997, $n = 10$), Ruol et al. (1997, $n = 4$), van Sandick et al. (2000, $n = 12$), and Stein et al. (2000, $n = 38$) reported no lymph node metastasis, whereas Rice et al. (1998) found that 1 of 29 cases (3%) had a lymph node metastasis.

For submucosal adenocarcinomas, the same five papers found an incidence of lymph node metastasis between 8% and 36%. In a series by Westerterp et al. (2005), no lymph node metastases were seen in 31 intramucosal adenocarcinoma with or without stromal invasion limited within the lamina propria mucosae, but there was 1 lymph node metastasis of 23 mucosal adenocarcinomas that invaded the muscularis mucosae. Vieth and Stolte reported the incidence of lymph node metastasis in Barrett's intramucosal carcinoma to be 2 (1%) of 207 cases (2005). Liu et al. (2005) reported lymph node metastasis in 0 of 30 carcinomas limited to the lamina propria but in 2 (12%) of 17 carcinomas that invaded the muscularis mucosae.

12.2.1.5.1. Photodynamic Therapy, Endoscopic Mucosal Resection, and Endoscopic Submucosal Dissection of Mucosal Adenocarcinoma

Mucosal adenocarcinomas very rarely metastasize to lymph nodes, so photodynamic therapy, endoscopic mucosal resection, or endoscopic submucosal dissection, are the first-line treatments of choice. Excellent long-term results of photodynamic therapy have been reported (Pech et al. 2005), but endoscopic mucosal resection and endoscopic submucosal dissection are considered to be even better treatments for mucosal adenocarcinoma because the depth of invasion of the adenocarcinoma can then be assessed histologically.

The recommendation in Japan is that endoscopically resected specimens should be cut into 2-mm-thick slices and that all the tissue should be examined histologically so that the depth of tumor invasion can be accurately assessed.

12.2.1.5.2. Lymphovascular Invasion in Esophageal Adenocarcinoma

Vieth and Stolte (2005) reported a series of 237 mucosal adenocarcinomas and 47 submucosal adenocarcinomas that had been removed by endoscopic mucosal resection. They found lymphatic vessel invasion in 1 of the mucosal carcinomas (0.4%). For the submucosal carcinomas, 3 of 22 (14%) that invaded the inner third, 3 of 11 (27%) which invaded the middle third, and 3 of 14 (21%) that invaded the outer third, showed lymphatic vessel permeation. No venous invasion was seen in any of the mucosal or submucosal carcinomas.

12.2.1.6. Esophagogastric Junction Carcinoma

Adenocarcinomas of the esophagogastric junction zone are considered to arise from gastric cardiac

mucosa, Barrett's esophagus, or the esophageal cardiac glands. It is often difficult to determine whether these tumors arise in the esophagus or the stomach.

In cases of adenocarcinoma of the esophagogastric junction zone the cancerous and noncancerous areas of the resected specimen need to be serially sectioned for histology. The tumor is regarded as esophageal when Barrett's epithelium is found, but as gastric when there is no Barrett's epithelium. There is a view that a carcinoma of the esophagogastric junction region should be judged to be gastric if dysplasia is found in gastric mucosa in the vicinity, but this criterion has not been useful in practice. As it is thought that the clinical behavior of adenocarcinoma of the esophagogastric junction zone is similar whether it arises in the esophagus or the stomach, the distinction thus is not important. It has, however, been reported that concomitant Barrett's epithelium improves the prognosis for patients with adenocarcinoma of the distal esophagus (Johansson et al.).

Cameron et al. (2002) examined the relationship between intestinal metaplasia and small adenocarcinomas, less than 2 cm in diameter, within 2 cm of the esophagogastric junction zone, and concluded that most adenocarcinomas of the esophagogastric junction zone arise in a background of intestinal-type mucosa.

12.2.1.7. Adenocarcinoma in Barrett's Esophagus After Total Gastrectomy

Four cases of primary adenocarcinomas arising in Barrett's esophagus, which had developed after total gastrectomy, have been reported (Noguchi et al. 2003). The first was that of a 64-year-old man who developed a well to moderately differentiated tubular adenocarcinoma, which invaded the esophageal muscularis propria, 16 years after a total gastrectomy (Tada et al. 1990). The second was a 52-year-old man who developed a well-differentiated mucosal adenocarcinoma 16 years after a total gastrectomy (Konishi et al. 1991). In the four cases reviewed by Noguchi et al., all were men aged 52 to 69 years, and the interval from the gastrectomy to the detection of the esophageal adenocarcinoma ranged from 17 to 38 years (mean, 27 years). Three of the tumors were well to moderately differentiated adenocarcinomas, and one was a mixed well and poorly adenocarcinoma with coexisting small cell carcinoma surrounded by squamous epithelium.

12.2.1.8. Squamous Cell Carcinoma, Basaloid Squamous Carcinoma, Adenosquamous Carcinoma, Mucoepidermoid Carcinoma, Adenocarcinoma with Lymphoid Stroma, Carcinosarcoma, Choriocarcinoma, Alpha-Fetoprotein-Producing Carcinoma, and Carcinoid Tumor Complicating Barrett's Esophagus

It is known that esophageal squamous cell carcinoma may develop in patients with Barrett's esophagus, suggesting a relationship between the two conditions. The first case was reported by Shine and Allison (1966). A total of 16 such cases, comprising 13 men and 3 women, have been reported to date (Paraf et al. 1992). According to available data on the location of the squamous cell carcinoma in relation to the Barrett's epithelium, the tumor was located at the squamocolumnar junction in 3 cases, in the columnar epithelium (Barrett's epithelium) in 3, and in the squamous-lined mucosa devoid of Barrett's epithelium in 7. It is an apparent paradox that squamous cell carcinoma can arise in an esophagus lined by columnar epithelium but this has been attributed to either multipotential differentiation of Barrett's epithelium, or to the presence of islands of squamous epithelium in Barrett's epithelium. Squamous cell carcinoma, in this setting, may also arise in the ductal epithelium of the esophageal glands proper. None of the reports describing the coexistence of Barrett's epithelium and squamous cell carcinoma have given details of the histopathological features of the nonneoplastic squamous epithelium or of the Barrett's epithelium, however. A case of concomitant squamous cell carcinoma and adenocarcinoma, both arising in Barrett's esophagus, has also been reported (Allan et al. 1986). In the recent report, only 20 cases of esophageal squamous cell carcinoma associated with Barrett's mucosa (Dessureault et al. 2002).

A case of basaloid squamous carcinoma arising in Barrett's esophagus has been reported

(Kaushik et al. 2003); this tumor extended to the submucosa.

Adenosquamous carcinoma (Ishijima et al. 1988; van Rees et al. 2002) and mucoepidermoid carcinoma (Pascal and Clearfliield 1987) have also been reported to arise in Barrett's esophagus, and a case of adenocarcinoma with lymphoid stroma has been reported (Takubo and Lambie).

Two cases of adenocarcinosarcoma arising in Barrett's esophagus have also been reported (Dworak and Koerfgen 1993; Rosty et al. 1996); these tumors each consisted of an adenocarcinoma as the carcinomatous component and a spindle cell sarcoma as the sarcomatous component (Dworak and Koerfgen 1993). From the micrographs in these papers, the histological appearance of these tumors seems to have been very similar to that of most carcinosarcomas of the stomach.

A choriocarcinoma has been reported to have arisen in association with an adenocarcinoma in Barrett's esophagus (Aonuma et al. 1986). A case of choriocarcinoma and yolk sac tumor arising in Barrett's esophagus has also been reported (Wasan et al. 1994); this case had a coexisting adenocarcinoma. A case of carcinoma with components of choriocarcinoma, hepatoid carcinoma, small cell carcinoma, and adenocarcinoma of usual type, associated with Barrett's esophagus, has also been reported (Motoyama et al. 1995).

A few cases of neuroendocrine carcinoma arising in Barrett's esophagus have been reported (Slavin et al.; Saw et al.). A case of small cell carcinoma arising in Barrett's esophagus has been reported (Saint Martin and Chejfec 1999).

Seven cases of alpha-fetoprotein-producing adenocarcinoma arising in Barrett's esophagus (Kobayashi et al. 2001), and a few cases of carcinoid tumor arising in Barrett's esophagus (Cary et al. 1993; Hoang et al. 2002), have been reported.

12.2.1.9. Experimental Barrett's Esophagus and Carcinogenesis

In an experimental study by Bremner et al. (1970), Barrett's esophagus was induced in dogs by forming hiatal herniae and performing cardioplasties and mucosal resections, in an attempt to provide evidence that Barrett's esophagus is an acquired condition. Their report has been cited in many subsequent papers on Barrett's epithelium. Gillen et al. (1988) and Fink et al. (1991) also reported the results of their experiments on Barrett's esophagus in dogs.

Carcinogenesis in Barrett's esophagus has been studied experimentally in rats and dogs (Segawa 1993; Kawaura 1994), with a relationship between esophagitis and the occurrence of squamous cell carcinoma being suggested. Adenocarcinoma arising in experimental Barrett's esophagus has also been reported; this report suggested that there was a close relationship between dysplasia in the columnar epithelium and the development of adenocarcinoma (Kawaura).

12.2.2. Adenocarcinoma of the Cervical Esophagus

Besides Barrett's adenocarcinoma, adenocarcinomas have also been reported to arise in ectopic gastric mucosa in the upper esophagus (Carrie 1950). According to Danoff et al., the first case report of an adenocarcinoma of the upper esophagus was published in 1928, although the precise origin of this tumor was unclear. Ishii et al. (1991) reviewed 38 cases of adenocarcinoma of the cervical esophagus; in 8 of these an origin in ectopic gastric mucosa could be demonstrated histologically. Hirayama et al. (2003) reviewed 30 cases of adenocarcinoma that had arisen in ectopic gastric mucosa; these included 14 cases from Western countries and 16 from Japan. Intestinal metaplasia was seen in the ectopic gastric mucosa in 1 of these cases, which was an advanced adenocarcinoma.

Sakamoto et al. (1970) reported a case of adenocarcinoma of the cervical esophagus in a 64-year-old man. The tumor was tubular and papillary and had invaded to the muscularis propria; there was an adjacent island of ectopic gastric mucosa that had cardiac and pyloric gland-like areas. Figures 12-22 through 12-24 show the gross and histological features of this tumor; macroscopically it was advanced and had accompanying sclerosis, and there was ectopic gastric mucosa in the vicinity. Christensen and Sternberg reported two cases of cervical esophageal adenocarcinoma in which there was adjacent ectopic columnar mucosa

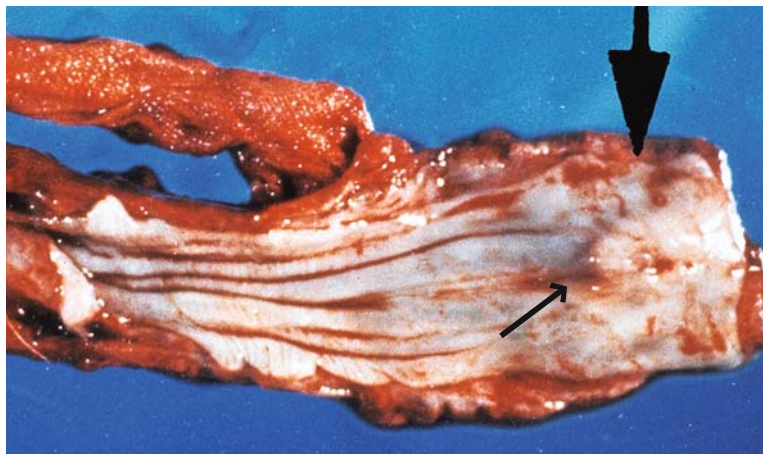


Fig. 12-22. Macroscopic appearance of an adenocarcinoma of the cervical esophagus. A sclerotic carcinoma (*arrows*) is seen in the esophageal wall (diffusely infiltrative, sclerotic type of advanced carcinoma)

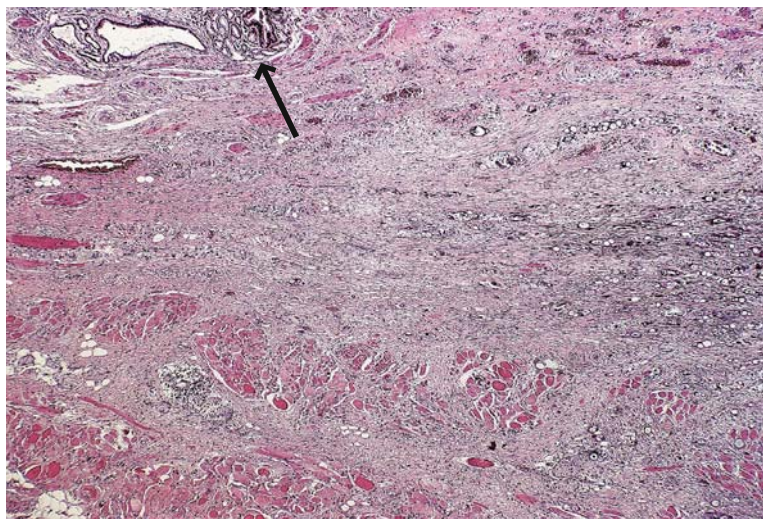


Fig. 12-23. Adenocarcinoma of the cervical esophagus (histological appearance of the lesion shown in Fig. 12-22). The adenocarcinoma is located adjacent to an island of ectopic gastric mucosa. *Arrow*, a cardiac gland-like structure in the island of ectopic gastric mucosa

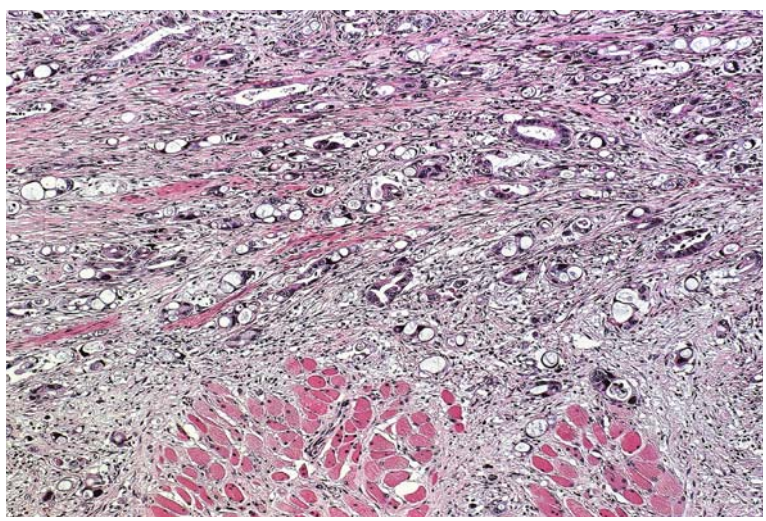


Fig. 12-24. Adenocarcinoma of the cervical esophagus. This is a moderately differentiated tubular adenocarcinoma that infiltrates into the striated muscle of the muscularis propria, with associated fibrosis

with intestinal metaplasia. There were chief cells and parietal cells in the ectopic mucosa in both these cases. A case of intramucosal adenocarcinoma arising in ectopic gastric mucosa of the cervical esophagus was reported by Kammori et al. (1996); the tumor was treated by surgical mucosal resection. Several cases of early adenocarcinoma arising in ectopic gastric mucosa and treated by endoscopic mucosal resection have been reported from both Japan and Western countries (Pech et al. 2001, Hirayama et al. 2003). A case of adenocarcinoma with submucosal invasion was reported (Alrawi et al. 2005).

In contrast to adenocarcinoma arising in Barrett's epithelium, the incidence of adenocarcinoma arising in ectopic gastric mucosa appears to be extremely low in comparison to the high incidence of ectopic gastric mucosa itself (7.8%–20% of the general population).

Three cases of hyperplastic polyp of cervical ectopic gastric mucosa have been reported (see Chapter 9, p. 114).

12.2.3. Adenocarcinoma Arising from Esophageal Cardiac Glands

Seven cases of adenocarcinoma arising from esophageal cardiac glands beneath squamous epithelium have been reported (2004). The adenocarcinomas reported by Seki et al. were mostly covered by normal squamous epithelium.

The overlapping of columnar epithelium and flat stratified squamous epithelium is common in the esophagogastric junction zone (see Chapter 2, p. 12), but the length of the overlapping zone is no more than 12 mm. Minute carcinomas in this area may be reported as adenocarcinomas arising from esophageal cardiac glands.

12.2.4. Adenocarcinoma Arising from Esophageal Glands Proper

Fabre et al. (2003) reported a case of a 64-year-old woman with an adenocarcinoma in situ that occurred in an esophageal gland proper.

Chapter 13
Carcinomas Other Than Squamous Cell Carcinoma and Adenocarcinoma

13.1. Adenosquamous Carcinoma (Coexistence of Adenocarcinoma and Squamous Cell Carcinoma)

It was previously thought that adenosquamous carcinoma of the esophagus was analogous to adenosquamous carcinoma of the large bowel or stomach, and that mucoepidermoid carcinoma of the esophagus was analogous to mucoepidermoid carcinoma of the salivary glands. That is, it was thought that adenosquamous carcinoma and mucoepidermoid carcinoma of the esophagus were distinct entities and easily distinguishable. It has been found, however, that in practice the distinction is difficult, and that many cases show mixed features of adenosquamous carcinoma and mucoepidermoid carcinoma. The *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*, 8th and 9th editions, published in Japan, deal with these mixed tumors collectively as adenosquamous carcinomas, and specifies their subclassification into adenosquamous carcinoma (coexisting adenocarcinoma and squamous cell carcinoma) and mucoepidermoid carcinoma only when typical histological features allow their distinction (see Table 12-1, p. 206). The World Health Organization (WHO) classification of esophageal tumors (2000), however, classifies adenosquamous and mucoepidermoid carcinomas as distinct entities (see Table 11-2, p. 149). This chapter, too, classifies them as distinct entities; adenosquamous carcinoma in this chapter corresponds to coexisting adenocarcinoma and squamous cell carcinoma in the *Guidelines*.

Adenosquamous carcinoma has components of squamous cell carcinoma and tubular or papillary adenocarcinoma, and these components are relatively independent of each other within the same cancer cell nest or as discrete cell nests (Figs. 13-1 through 13-3). Collision tumors of adenocarcinoma and squamous cell carcinoma are thus included in this category.

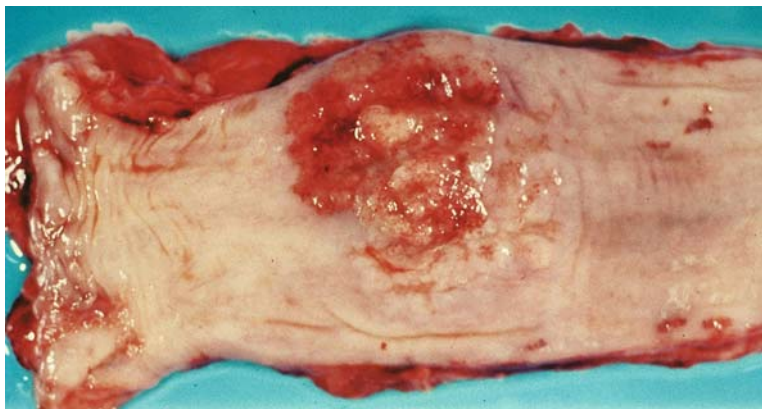


FIG. 13-1. Macroscopic appearance of an adenosquamous carcinoma (slightly depressed type with slightly elevated portions of superficial carcinoma)

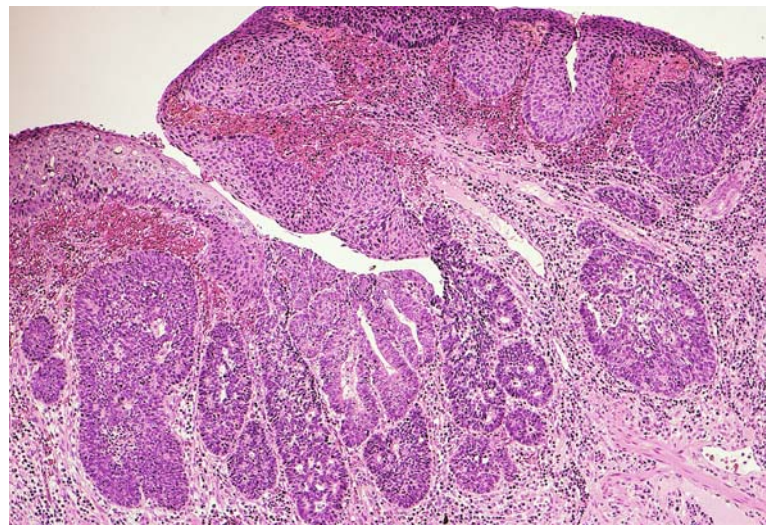


FIG. 13-2. Mucosal lesion of an adenosquamous carcinoma. This tumor has associated intraepithelial spread

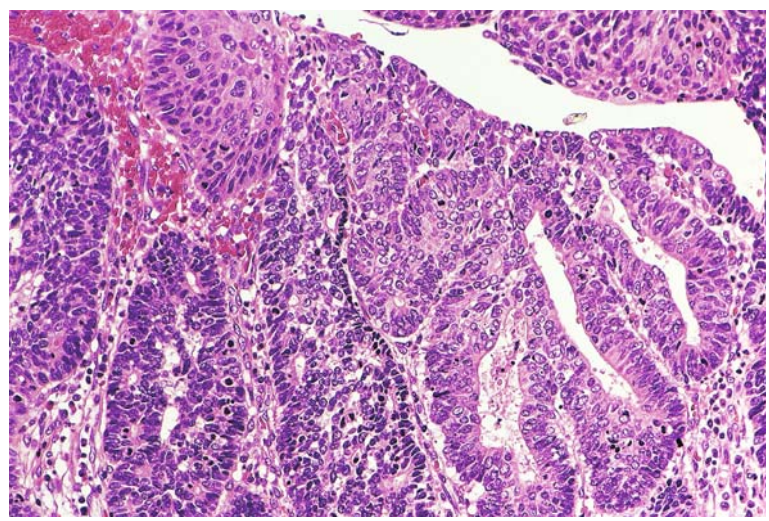


FIG. 13-3. Close-up view of Fig. 13-2. Tubular structures and a component of squamous cell carcinoma can be distinguished

It has been found, however, that 20% to 30% of esophageal squamous cell carcinomas have mucous cells and/or some glands, although these components of adenocarcinoma are often very minor (Kuwano et al.; Takubo et al.). The *Guidelines* define adenosquamous carcinoma as having components of both squamous carcinoma and adenocarcinoma, each of which must account for at least 20% of the total tumor. Nezu et al. (1991), however, proposed that a carcinoma should be classified as adenosquamous if each component formed at least 10% of the tumor. Based on this definition, 11 (1.0%) of 1128 esophageal carcinomas resected at the National Cancer Center Hospital, Tokyo, Japan, were classified as adenosquamous. In this author's study of 178 esophageal carcinomas, there were 5 examples (2.8%) of adenosquamous carcinoma and mucoepidermoid carcinoma (adenosquamous carcinoma as defined in the *Guidelines*) in total.

Areas of adenosquamous carcinoma showing tubule formation are often positive with mucin stains and are also usually positive for markers of glandular differentiation such as carcinoembryonic antigen (CEA) (Fig. 13-4), secretory component (SC) (Fig. 13-5), and lactoferrin.

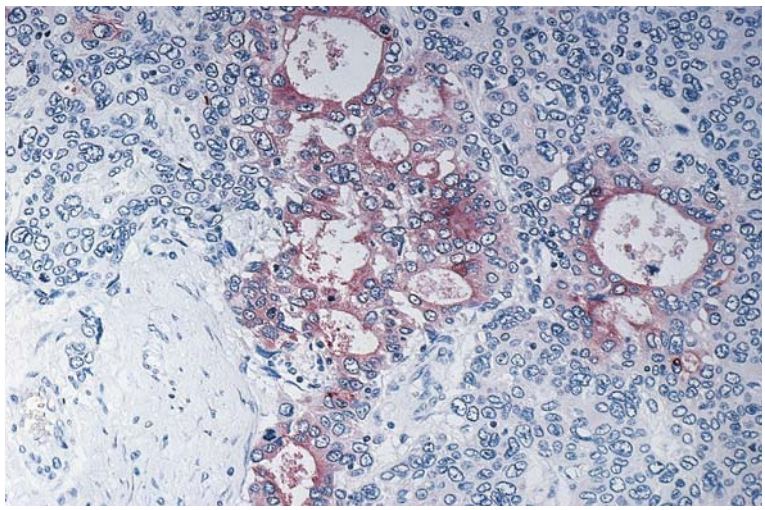


FIG. 13-4. Adenosquamous carcinoma (carcinoembryonic antigen immunostain). Areas of tubule formation stain positively

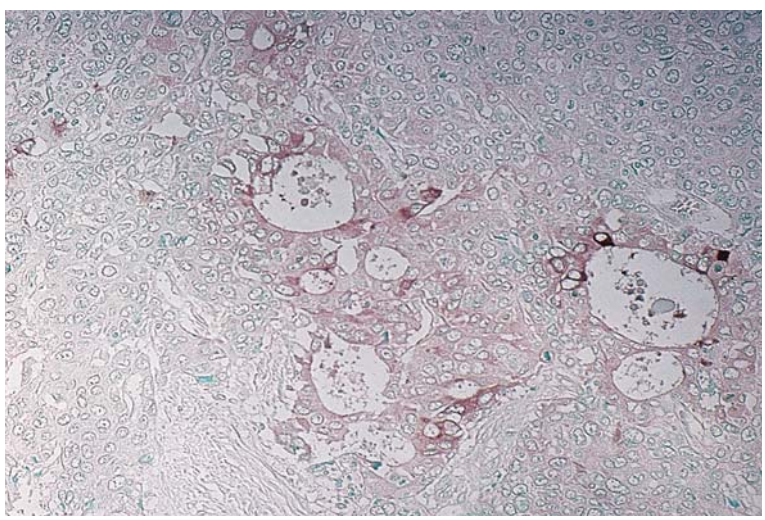


FIG. 13-5. Adenosquamous carcinoma (secretory component immunostain). Areas of tubule formation stain positively

Metastatic deposits of adenosquamous carcinoma have similar histology to that of the primary carcinoma.

A case of adenosquamous carcinoma in which an adenocarcinoma, presumed to have arisen in Barrett's esophagus, was accompanied by squamous metaplasia, has been reported (Pascal and Clearfield 1987). A case of adenosquamous carcinoma that produced alpha-fetoprotein has also been reported (Kawai et al. 2003).

13.2. Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma of the esophagus resembles that of the salivary glands, but although the prognosis of mucoepidermoid carcinoma of the salivary glands is relatively favorable, that of mucoepidermoid carcinoma of the esophagus is very poor. Peritoneal or pleural carcinomatosis has occurred in some cases.

Mucoepidermoid carcinoma of the esophagus often has an unusual macroscopic appearance, with marked sclerosis of the esophageal wall (Mafune et al.). This appearance is classified as type 3 or 4 (Fig. 13-6) in the Macroscopic Classification of Esophageal Carcinoma published in the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*, 8th and 9th editions (see Table 11-5, p. 159).

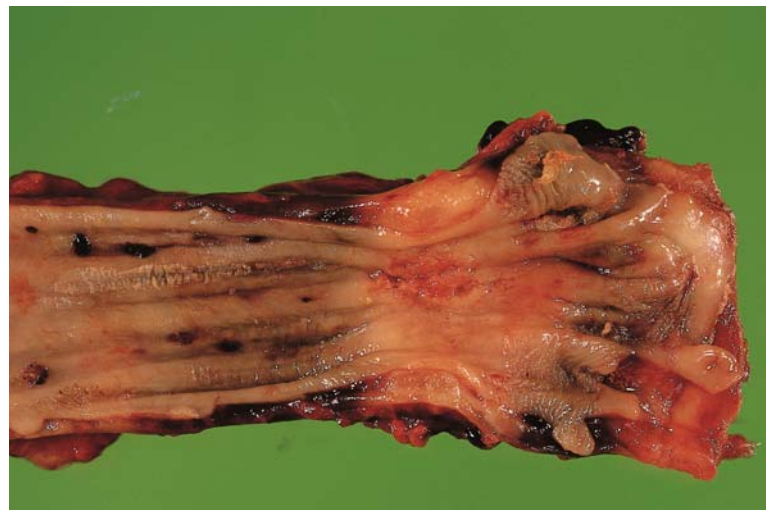


Fig. 13-6. Macroscopic appearance of a mucoepidermoid carcinoma (diffusely infiltrative type of advanced carcinoma)

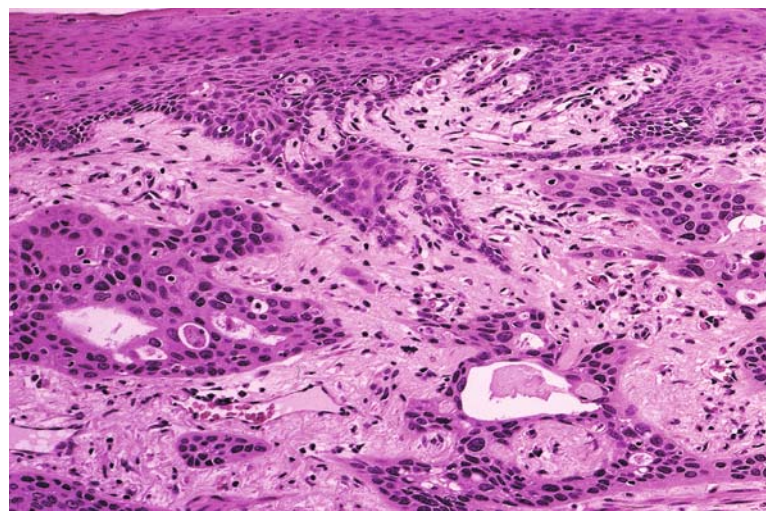


Fig. 13-7. Mucosal lesion of a mucoepidermoid carcinoma. Ductlike structures are evident

Histologically, these tumors consist of squamous cell carcinoma with mucin-positive cells and occasional ductlike structures (Figs. 13-7 through 13-9). There is usually no clear distinction between the squamous and adenocarcinoma components in the tumor nests but, as already noted, it is often difficult to distinguish mucoepidermoid carcinoma from adenosquamous carcinoma (see Section 13.1. Adenosquamous Carcinoma).

Some mucoepidermoid carcinomas with marked sclerosis of the esophageal wall (Fig. 13-10) show a mixture of three histological components, i.e., signet ring cells having intracellular microcysts (Figs. 13-11, 13-12), signet ring cells containing abundant mucus (Figs. 13-13, 13-14), and squamous cells. The intracellular microcysts often fail to stain for mucin. These tumors often have only a small intraepithelial component (see Fig. 13-11) or lack such a component. Some tumor cells in mucoepidermoid carcinomas may be positive with immunohistochemical stains for CEA, SC, or lactoferrin.

Cytologically, mucoepidermoid carcinomas show atypical keratinizing cells which resemble malignant squamous cells (Fig. 13-15), and other cells with the characteristics of glandular cells.

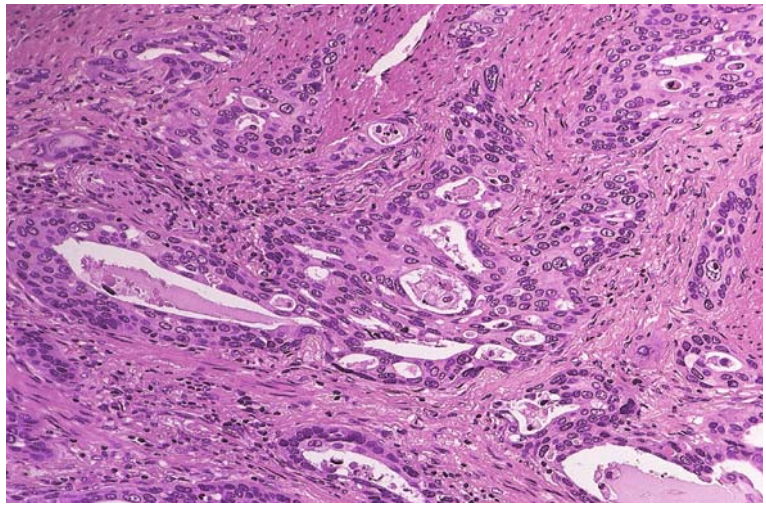


Fig. 13-8. Mucoepidermoid carcinoma. Cells lining the ductlike structures are relatively flat

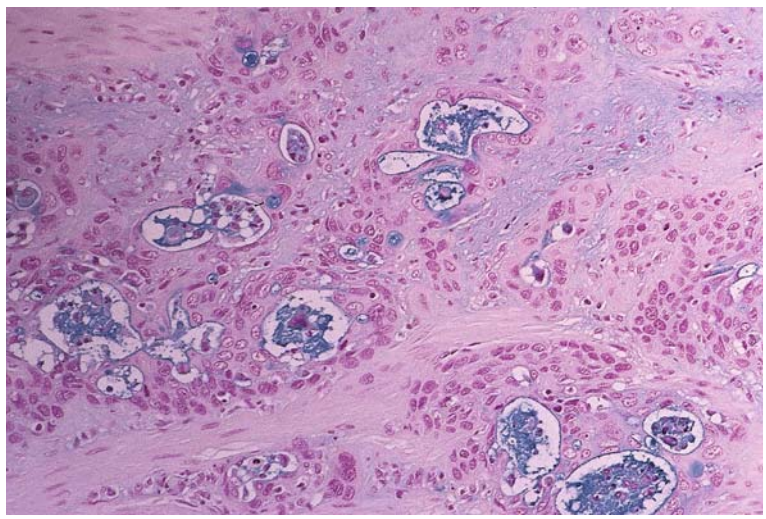


Fig. 13-9. Mucoepidermoid carcinoma (Alcian blue stain). The lumina of the ductlike structures and scattered tumor cells stain positively

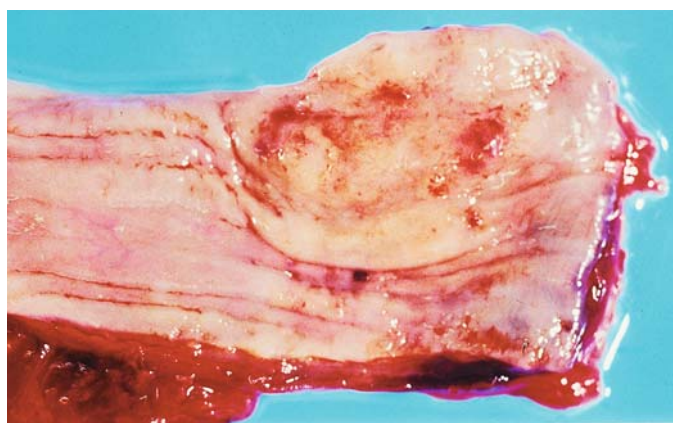


Fig. 13-10. Macroscopic appearance of a mucoepidermoid carcinoma (diffusely infiltrative type of advanced carcinoma)

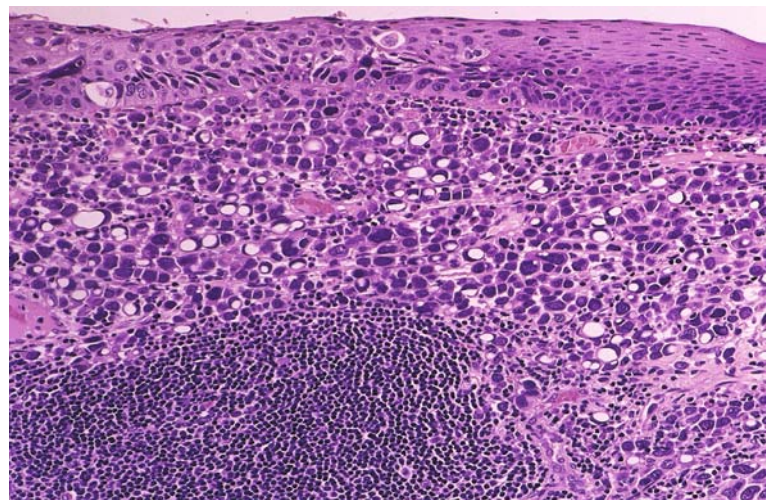


FIG. 13-11. Mucosal lesion of a mucoepidermoid carcinoma. Clear cells are seen in the intraepithelial component and signet ring cells are seen in the invasive component

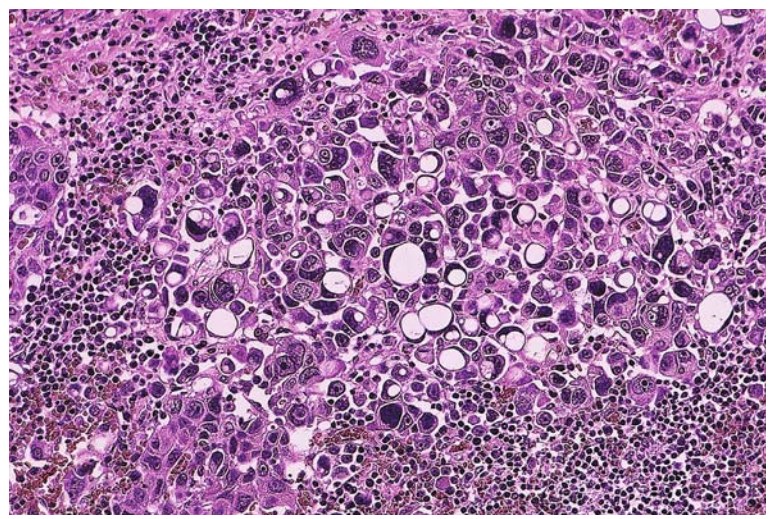


FIG. 13-12. Mucoepidermoid carcinoma. Wide intracellular microcysts are evident in the signet ring cells

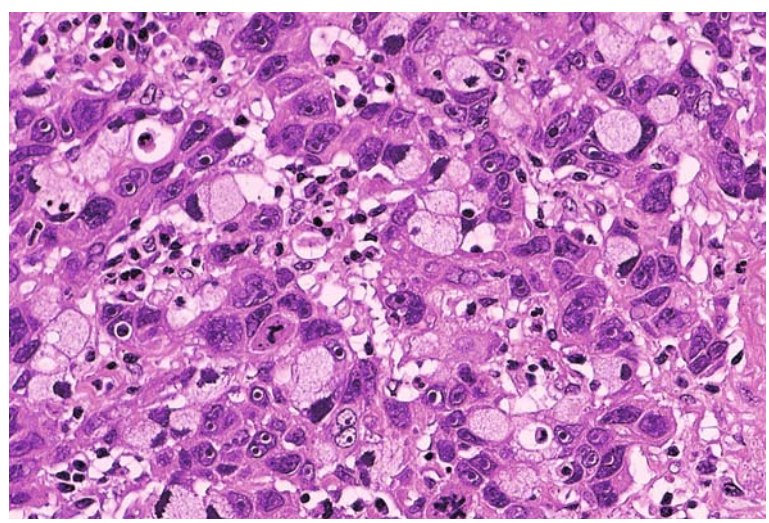


FIG. 13-13. Mucoepidermoid carcinoma. Mucous-type signet ring cells are seen

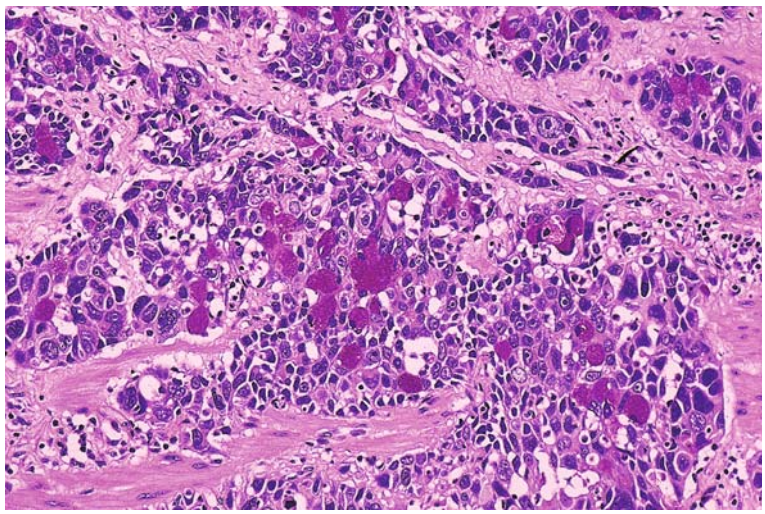


Fig. 13-14. Mucoepidermoid carcinoma (periodic acid–Schiff stain). Mucous-type signet ring cells show positive cytoplasmic staining

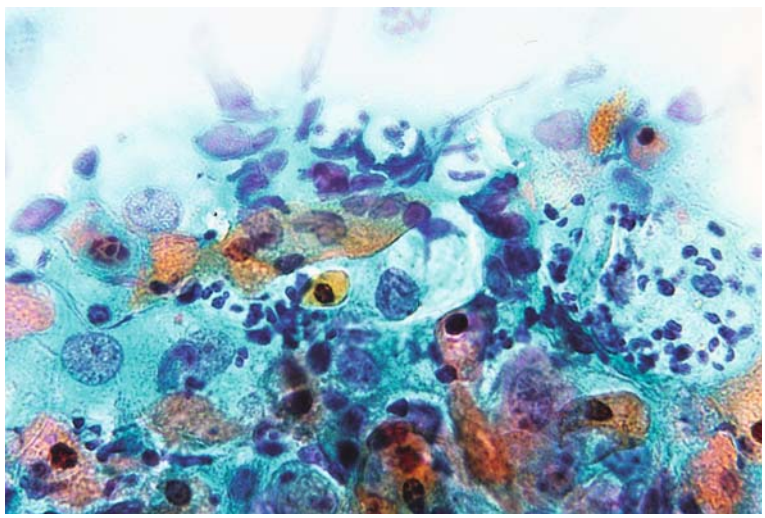


Fig. 13-15. Cytological appearance of a mucoepidermoid carcinoma (Papanicolaou stain). The tumor cells have an appearance similar to that of a high-grade squamous carcinoma

These latter cells have pale or foamy cytoplasm and eccentric nuclei, appearing mildly atypical (Fig. 13-16). Most of the nuclei have a nucleolus, and mucin stains are sometimes positive (Fig. 13-17). In addition, there are cells intermediate between these two types, with nuclei that resemble those of malignant squamous cells but cytoplasm that is similar to that of glandular cells (Fig. 13-18). Occasional tumor cells may have intracellular microcysts, or pairs of cells may form glands. These features allow a cytological diagnosis of mucoepidermoid carcinoma to be made (Ohno and Takubo 1989).

Electron microscopy shows an abundance of intracellular keratin filaments that are not so dense as those seen in squamous cell carcinomas. The tumor cells have relatively small desmosomes and many microvilli (Fig. 13-19); intracellular microcysts (intracellular lumina) containing microvilli, and intercellular lumina, are also seen (Fig. 13-20). Keratin filaments are occasionally found enclosing the intracellular microcysts. The intracellular microcysts are considered to be an ultrastructural marker of adenocarcinoma, and bundles of keratin filaments are characteristic of squamous cell carcinoma. In other words,

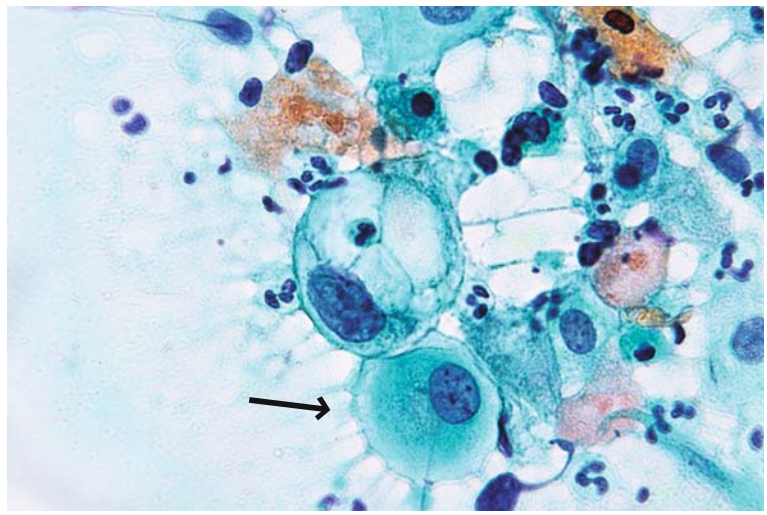


Fig. 13-16. Cytological appearance of a mucoepidermoid carcinoma (Papanicolaou stain). Occasional tumor cells have an appearance similar to the cells seen in adenocarcinoma (*arrow*) without prominent nuclear atypia

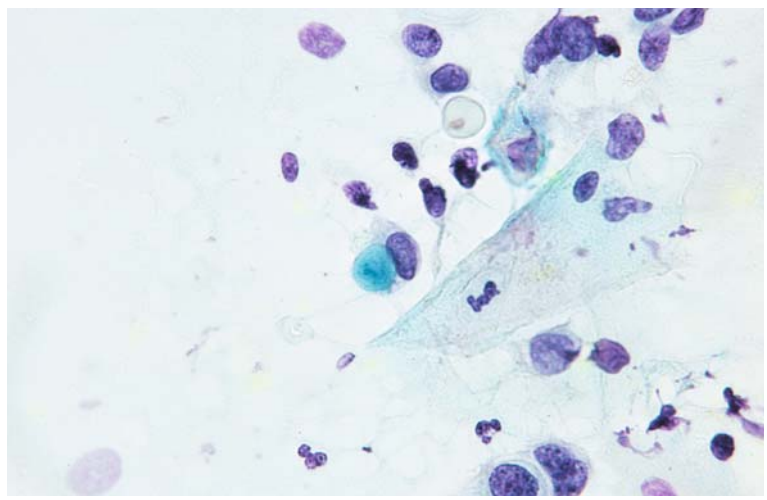


Fig. 13-17. Cytological appearance of a mucoepidermoid carcinoma (Alcian blue stain). The smear shows a mucous-type signet ring cell that stains positively with Alcian blue

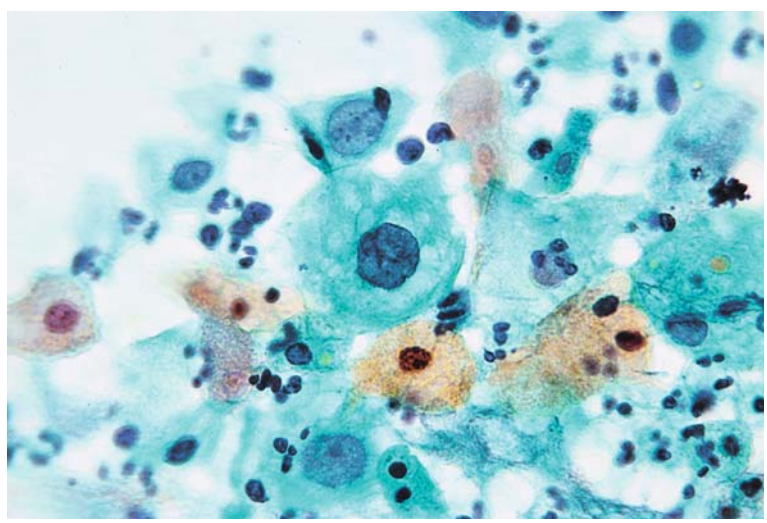


Fig. 13-18. An intermediate-type cell of a mucoepidermoid carcinoma (Papanicolaou stain). The nucleus of the intermediate cell resembles that of a malignant squamous cell and the cytoplasm resembles that of a malignant glandular cell

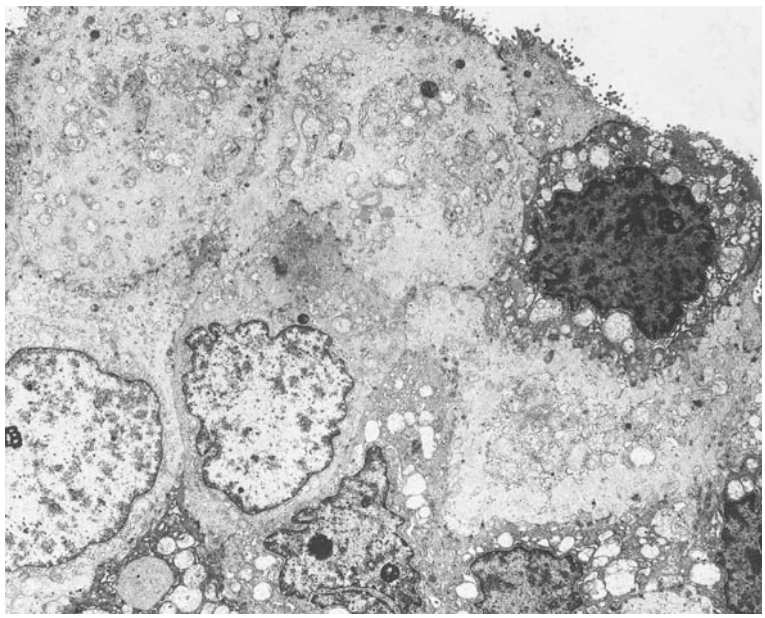


FIG. 13-19. Electron micrograph of a mucoepidermoid carcinoma. This image shows a portion resembling squamous cell carcinoma

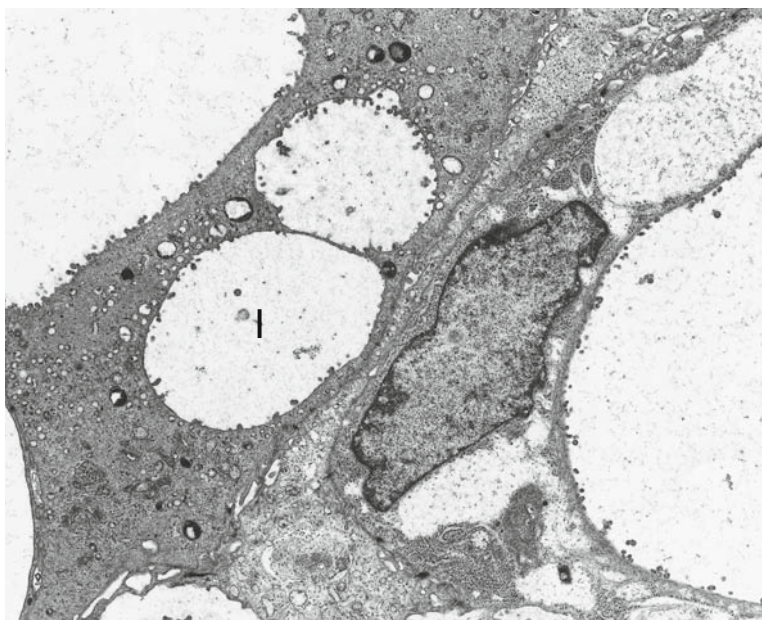


FIG. 13-20. Electron micrograph of a mucoepidermoid carcinoma. There are a number of intracellular lumina (*I*) with many microvilli

these cells have the ultrastructural features of both adenocarcinoma and squamous cell carcinoma.

13.3. Adenoid Cystic Carcinoma

The first report of a primary adenoid cystic carcinoma of the esophagus, in the form of an original article, was published by Bergmann and Charnas (1958); they reported their case as a cylindroma. According to Marcial Rojas and Vallecillo (1959), the *Color Atlas of Pathology* (Lippincott) by the U.S. Naval Medical School, published in 1958, showed a micrograph of an adenoid cystic carcinoma that had occurred in the lower esophagus of a 55-year-old man. Marcial Rojas and Vallecillo described this as the second reported case of a pure adenoid cystic carcinoma of the esophagus.

These three articles have frequently been cited in subsequent papers.

Adenoid cystic carcinoma of the esophagus is rare. According to Suzuki and Nagayo, this tumor accounts for 0.06%–0.07% of all esophageal carcinomas. With regard to prognosis, a review of 45 cases by Mafune et al. revealed an extremely poor outcome, with death in all cases within 5 years of diagnosis, and with frequent distant organ metastasis, in clear contrast to adenoid cystic carcinoma of the salivary glands.

Macroscopically, these tumors often protrude above the surrounding mucosa, more than do the usual esophageal squamous cell carcinomas, and if superficial they tend to show the plateau-type pattern or the predominantly subepithelial type pattern, as described in the Macroscopic Classification given in the Japanese *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (see Table 11-5). Most reported cases have been advanced, however. Ulceration has only been described in about half the cases (Fig. 13-21).

Adenoid cystic carcinomas of the esophagus are histologically similar to those that occur in the salivary glands, consisting of cells with the characteristics of myoepithelial and ductal cells. Esophageal adenoid cystic carcinomas, however, tend to show a more predominant solid pattern, much greater atypia of tumor cells, and frequent mitotic figures and necrotic foci. Intraepithelial spread may also be seen (see Figs. 13-21, 13-22). The tumor cells have scanty cytoplasm and proliferate in a cribriform or solid pattern (Fig. 13-23).

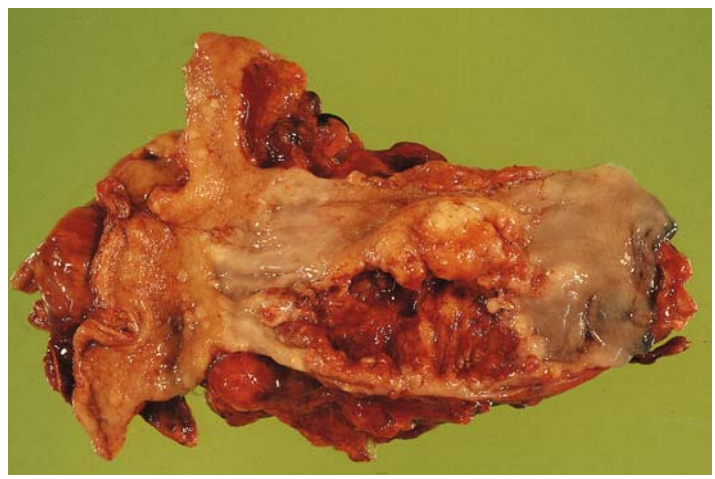


Fig. 13-21. Macroscopic appearance of an adenoid cystic carcinoma (ulcerative and localized type with protruding portions of advanced carcinoma). Intraepithelial spread of carcinoma is evident

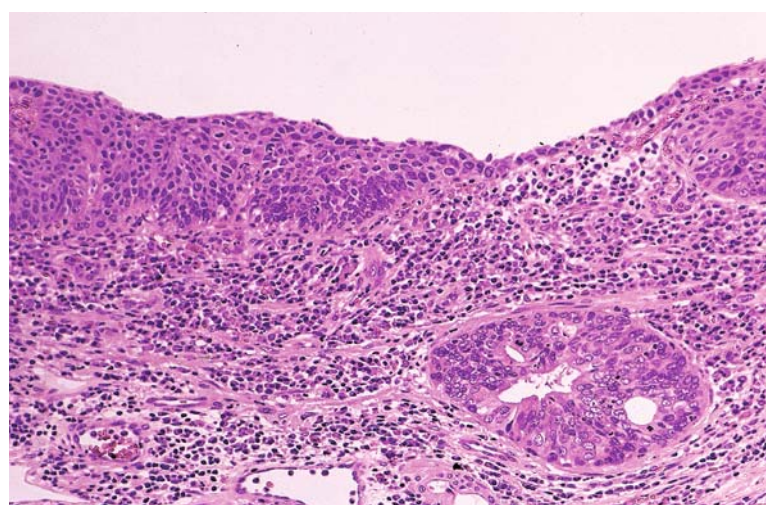


Fig. 13-22. Mucosal lesion of an adenoid cystic carcinoma. There is accompanying intraepithelial spread of tumor

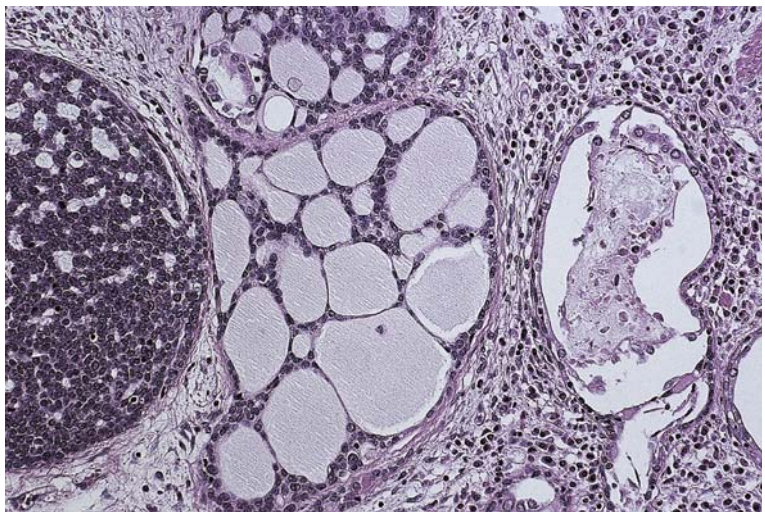


FIG. 13-23. Adenoid cystic carcinoma. There are foci of solid proliferation and cribriform pattern, and there are also some ductlike structures

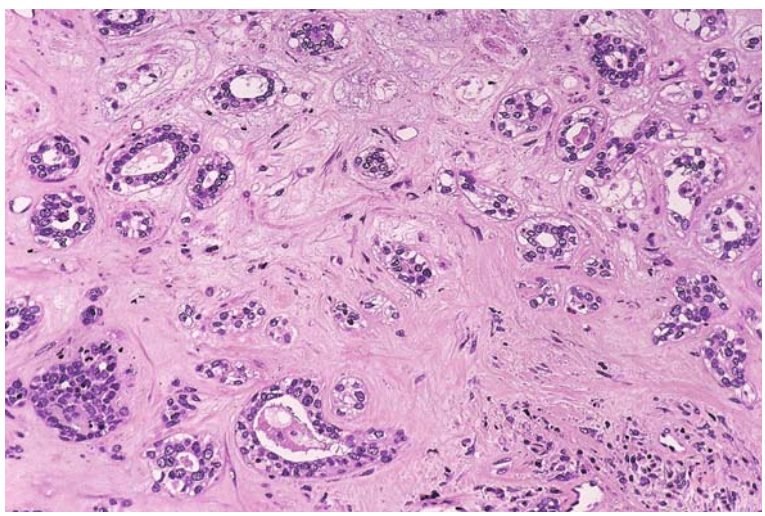


FIG. 13-24. Adenoid cystic carcinoma. This section shows a portion composed of ductlike structures. There are clear cells resembling myoepithelial cells on the basement membrane, with ductal cells lining the ductal lumina

Myoepithelial-like cells in the duct-like structures are situated on the basement membrane, under the ductal epithelial cells that line the lumina, and have relatively clear cytoplasm (Fig. 13-24), but ductlike structures are said to be infrequent in adenoid cystic carcinomas of the esophagus. Gland-like spaces in the areas with a cribriform pattern contain basement membrane material that stains positively with Alcian blue and periodic acid–Schiff (PAS), and also with immunohistochemical stains for laminin and type IV collagen. Epithelial mucin (positive with mucicarmine) is present in the lumina of the ductlike structures. Myoepithelial-like tumor cells show positive staining for actin (Fig. 13-25) and S-100 protein.

Nowadays, in Japan, assignment to this category tends to be restricted exclusively to tumors showing typical histological features indistinguishable from those of adenoid cystic carcinomas arising in the salivary glands.

On electron microscopy, adenoid cystic carcinomas are characterized by stratified annular basement membranes within a cribriform cell pattern (Fig. 13-26). There are also several layers of basement membrane between the tumor cells and the stroma (Fig. 13-27), and there are intercellular lumina (Fig. 13-28).

Although there has been controversy about the origin of primary adenoid cystic carcinoma of the esophagus, the opinion that it arises in the

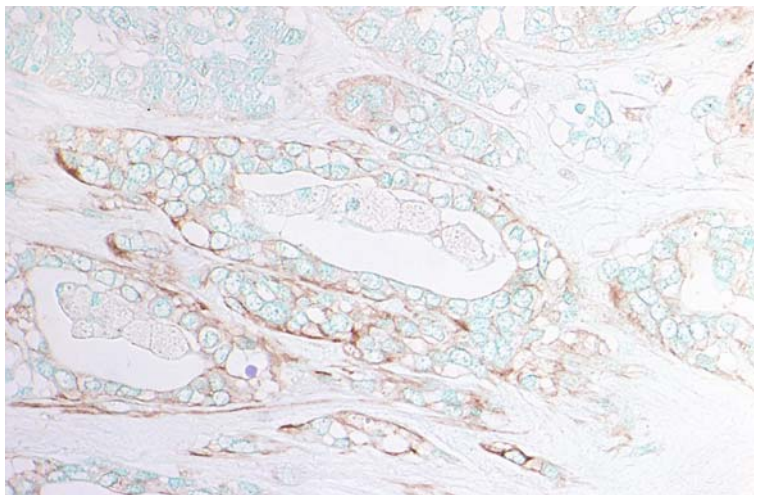


FIG. 13-25. Adenoid cystic carcinoma (actin immunostain). There are actin-positive cells in the ductal structures

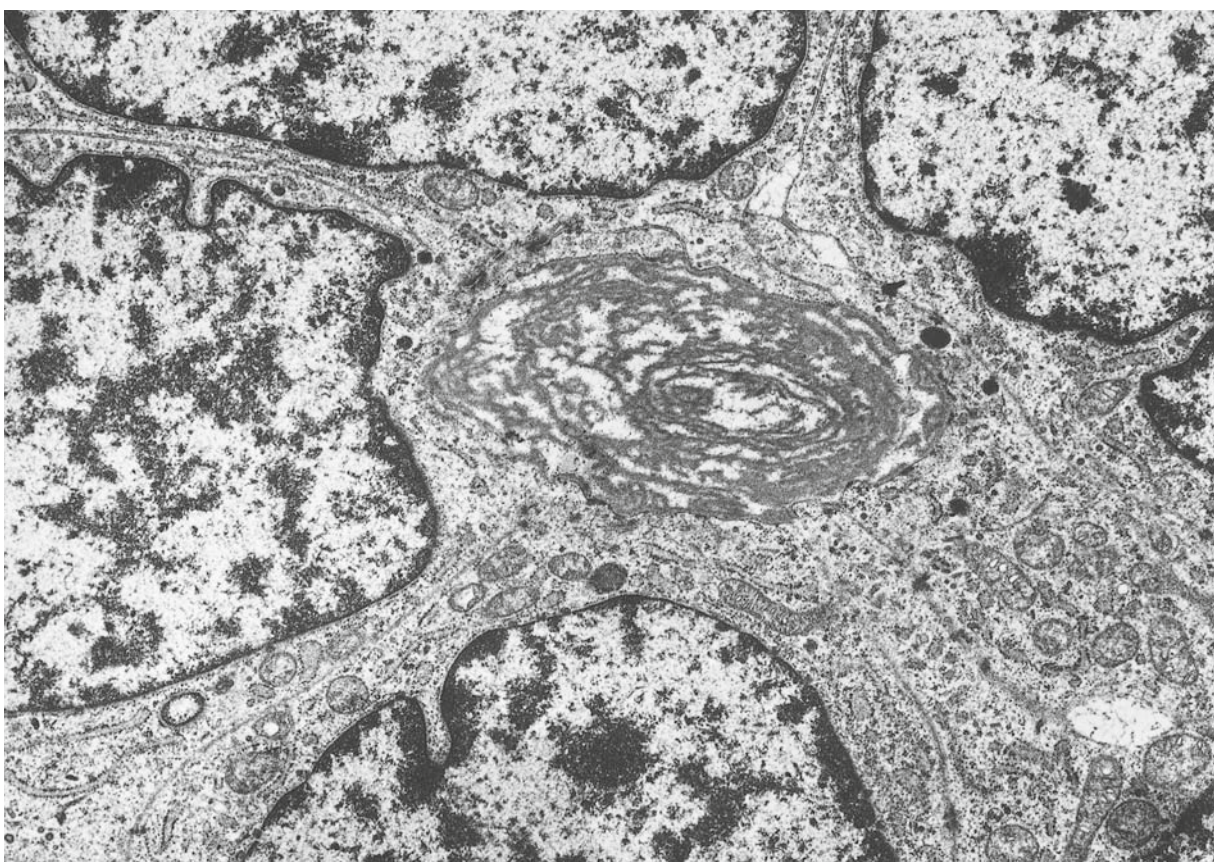


FIG. 13-26. Electron micrograph of an adenoid cystic carcinoma. Concentric, stratified annular basement membranes are seen

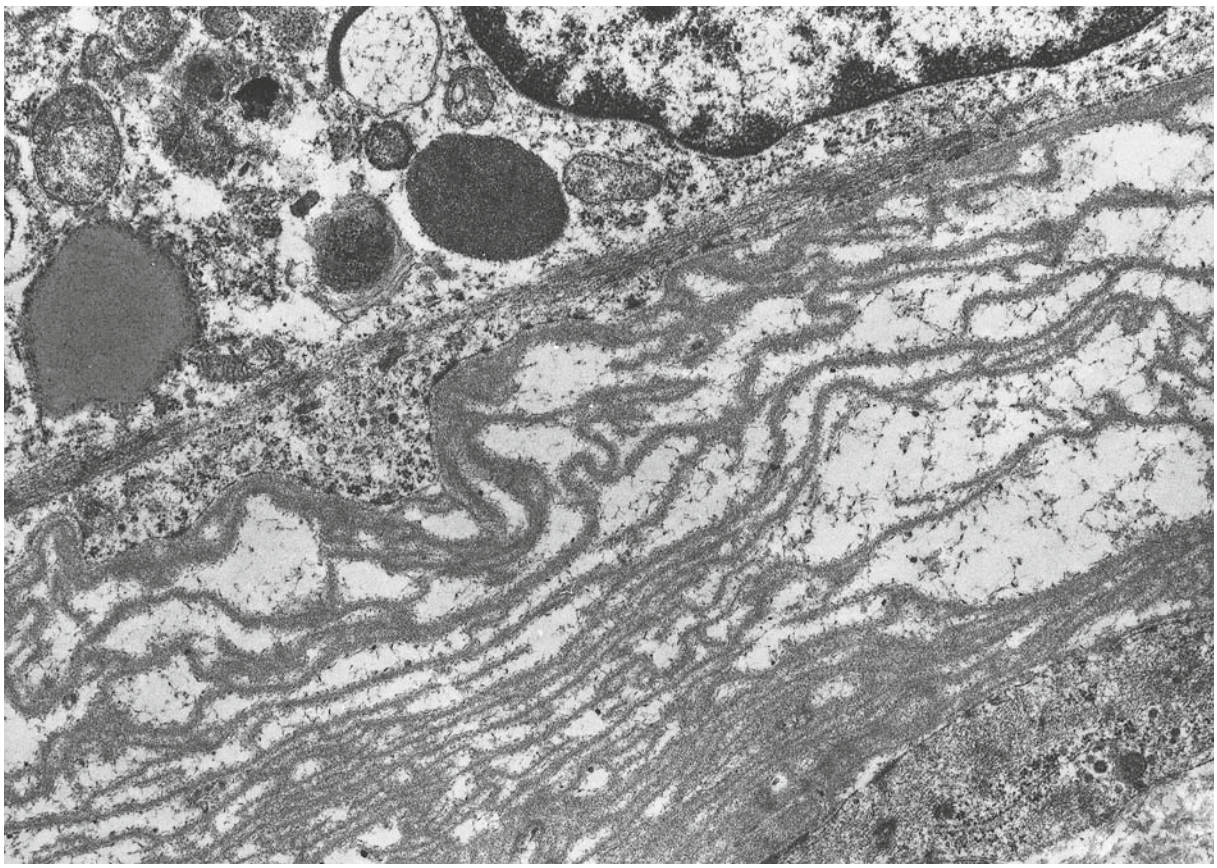


FIG. 13-27. Electron micrograph of an adenoid cystic carcinoma. Stratified basement membranes are seen around the tumor cells

esophageal glands proper is now the most convincing. In the case reported by Kabuto et al., cancer nests were mainly located beneath the mucosal epithelium, strongly suggesting that they had originated in the esophageal glands proper in the submucosa. Because adenoid cystic carcinomas arise in tissues that have glandular apparatus and excretory ducts, such as the salivary glands, mammary glands, and bronchi, this author does not totally reject the view that these tumors arise in the esophageal glands proper, as these also have excretory ducts. Intraepithelial spread has been found in a considerable number of reported cases, however, and keratinizing foci have also sometimes been evident; these observations, together with other differences when compared to adenoid cystic carcinomas arising at the other sites already mentioned, have led this author to believe that esophageal adenoid cystic carcinomas do not always arise in the esophageal glands proper.

Moreover, as the distinction between adenoid cystic carcinoma and basaloid squamous carcinoma has not been well defined, this author does not classify any tumor that does not show a pattern of differentiation into two-cell types as an adenoid cystic carcinoma, even if it otherwise resembles this entity. This author considers that most tumors previously reported as adenoid cystic carcinomas of the esophagus should now be reclassified as basaloid squamous carcinomas.

13.4. Undifferentiated Carcinoma

The histological classification of esophageal carcinoma in the Japanese *Guidelines for Clinical and Pathologic Studies on Carcinoma of the*

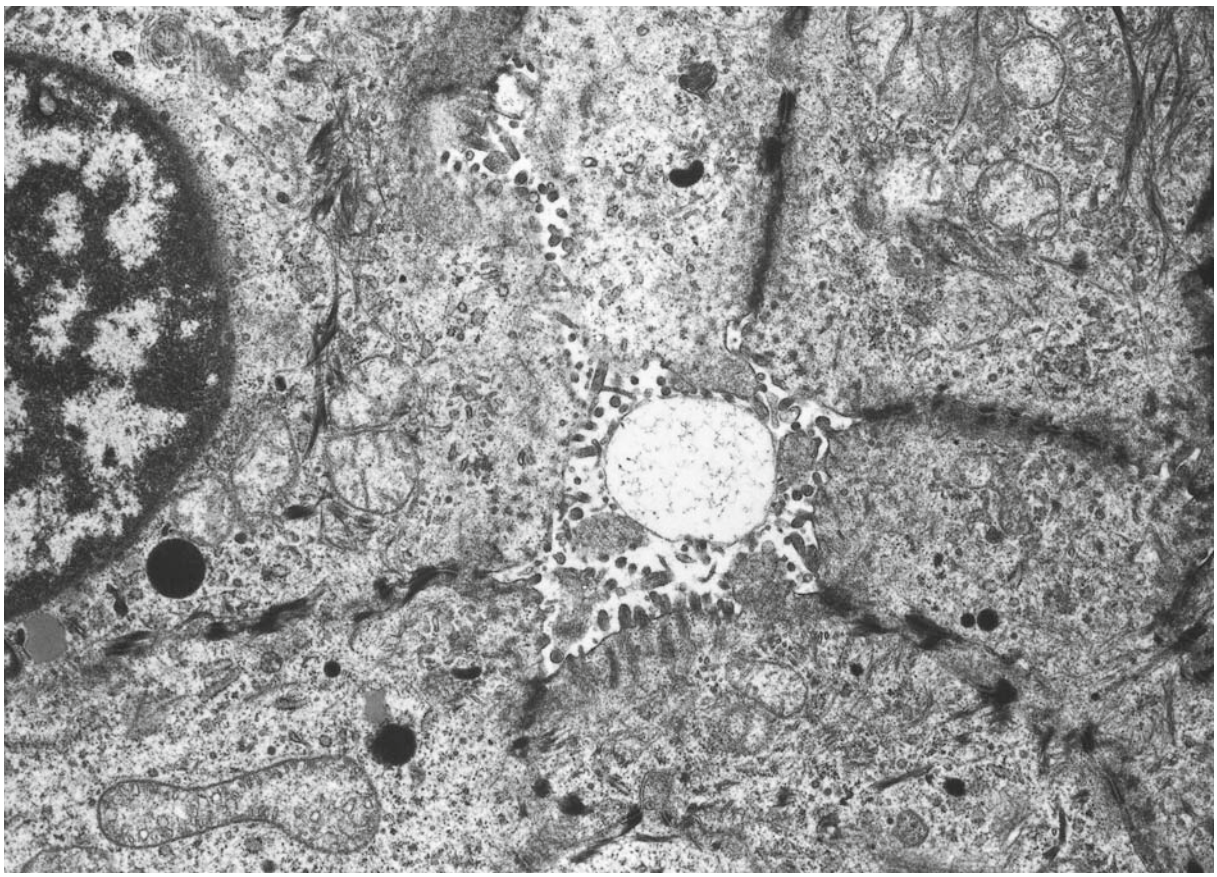


FIG. 13-28. Electron micrograph of an adenoid cystic carcinoma. There is an intercellular lumen between tumor cells

Esophagus (see Table 12-1, p. 206) includes a category of undifferentiated carcinoma, which is subclassified into small cell and non-small cell types. This author has never encountered an undifferentiated carcinoma of the esophagus that was not of small cell type, however. The WHO classification (see Table 11-2, p. 149) lists small cell carcinoma and undifferentiated carcinoma as two distinct entities. In the WHO classification, undifferentiated carcinoma is defined as a tumor that has no ductal or squamous epithelial structures and does not include small cell carcinoma. No micrographs showing the histological features of undifferentiated carcinoma (WHO) are given.

Small cell carcinomas have been reported to occasionally arise at numerous sites other than the lung, including the paranasal sinuses, salivary glands, hypopharynx, larynx, trachea, esophagus, stomach, large intestine, thymus, skin, prostate, and uterine cervix. Extrapulmonary small cell carcinomas account for about 5% of all small cell carcinomas in humans. In particular, extrapulmonary small cell carcinomas occur most frequently in the esophagus.

Primary undifferentiated small cell carcinoma of the esophagus was first reported by McKeown in 1952; this first report described two cases. The first case report from Japan was by Taniguchi et al. (1973); this tumor was adrenocorticotropic hormone (ACTH) producing. These two reports have been cited frequently in subsequent papers on primary esophageal small cell carcinoma.

In an extensive survey conducted by the Japanese Society for Esophageal Diseases, undifferentiated carcinoma and small cell carcinoma

comprised 0.4% of all surgically resected esophageal carcinomas and 2.7% of all autopsy cases of esophageal carcinoma. In another report, small cell carcinomas were said to account for as many as 7.6% of all resected esophageal carcinomas (Tateishi et al. 1976). In this author's series of 421 patients who underwent resections for esophageal cancer there were 6 (1.4%) in whom all or part of the tumor was of small cell type. Case reports of a further 11 primary small cell carcinomas of the esophagus have been published in recent years (Beyer et al. 1991; Caldwell et al. 1991; Law et al. 1994), and the total number of cases reported to date exceeds 150, including 79 Japanese cases (Mafune et al.). More recently 199 cases of small cell carcinoma of the esophagus were reviewed (Casas et al. 1997).

Esophageal small cell carcinomas grow rapidly, one reported tumor having a doubling time of less than 1 month (Sasajima). The prognosis is extremely poor. In Japan, the mean survival period after diagnosis is 8 months, and only 13% of patients survive for longer than 1 year; the reported survival period is even shorter for Western patients (Deplaix et al. 1993). Only a few cases of longer survival, exceeding 2 years, have been reported; almost all these patients underwent chemotherapy in addition to surgical resection or radiotherapy. Thus, the role of chemotherapy in the treatment of primary small cell carcinoma of the esophagus has gradually become recognized (Uchida et al.). The importance of chemotherapy has been further underlined by the fact that small cell carcinoma, even if found early, tends to quickly recur after initial surgical or radiation treatment (Kuwano et al.). A patient with intramucosal small cell carcinoma of the esophagus was reported to have lived for more than 28 months after endoscopic mucosal resection and chemotherapy (Takeshita et al. 2000). The case of a 77-year-old man who had small cell carcinoma with extensive lymph node metastases, and who was treated by a subtotal esophagectomy and extended node dissection and survived for more than 7 years, has also been reported (Yachida et al. 2001).

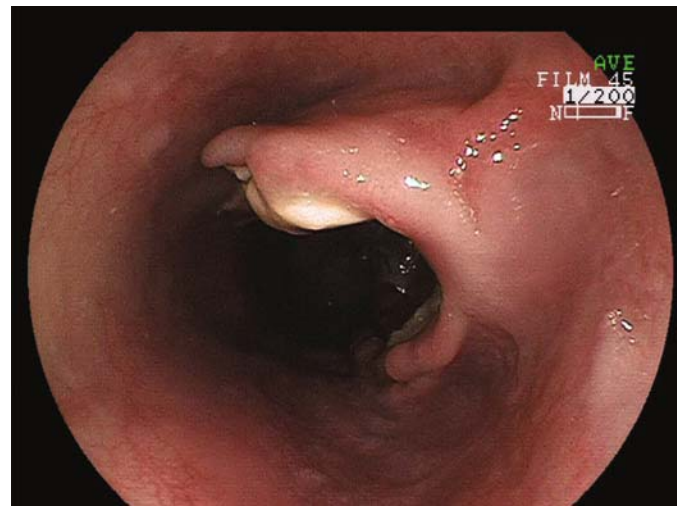
An increase in the serum level of neuron-specific enolase (NSE) has been found in patients with esophageal small cell carcinoma, so this may become a useful test for patient monitoring during therapy (Sasajima et al.). Elevation of the serum level of parathyroid hormone-related protein has also been reported in a patient with an esophageal undifferentiated carcinoma (Nozu et al. 1995). An increase in the serum level of bombesin has been seen in some patients with pulmonary small cell carcinoma, and a similar increase has been speculated to occur in esophageal small cell carcinoma; however, there are no accurate data on this at the present time. Two cases of granulocyte colony-stimulating factor (G-CSF)-producing small cell carcinoma of the esophagus have also been reported (Sato et al. 2005).

Macroscopically, esophageal small cell carcinomas are often protruding lesions, appearing to proliferate beneath the mucosal epithelium (Fig. 13-29a). If superficial, they are usually classified macroscopically as the predominantly subepithelial type (Figs. 13-29b, 13-30) in the Macroscopic Classification of Esophageal Carcinoma in the Japanese *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (see Table 11-5).

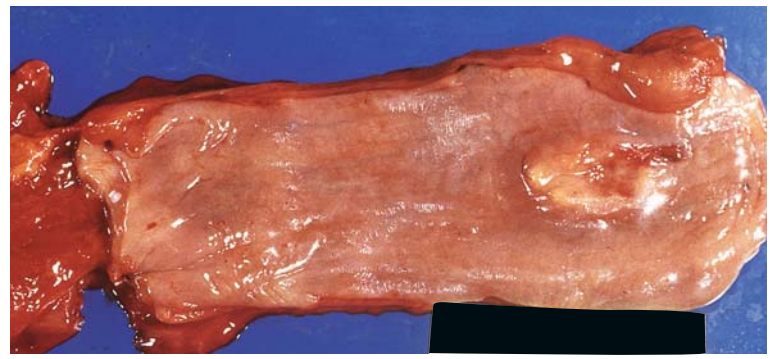
The histological appearance of small cell carcinoma of the esophagus is similar to that of small cell carcinoma of the lung. The tumor cells have sparse cytoplasm and small round nuclei with fine granular chromatin. Nucleoli are occasionally seen. The nuclei in biopsy specimens may be very elongated as a result of artifactual distortion. This elongation of nuclei seems to occur more frequently in small cell carcinoma than in malignant lymphoma.

Histological examination of surgical specimens reveals a proliferation of tumor cells that elevate the normal epithelium (Fig. 13-31). The cells proliferate in solid sheets (Fig. 13-32, pure type) and occasionally there is a cell-in-cell appearance. Many coexisting large tumor cells may also sometimes be found; this variant is called the mixed type of small cell carcinoma (Fig. 13-33). Squamoid (Fig. 13-34) or tubular differentiation (Fig. 13-35) may also be evident focally; if squamous or other non-small cell carcinoma components form a significant proportion of a tumor, it is classified as a combined small cell carcinoma (Figs. 13-36, 13-37).

As it is not unusual for small cell carcinomas to have components of other tumor types, it is impor-



a



b

FIG. 13-29. **a** Endoscopic appearance of an advanced undifferentiated small cell carcinoma. The tumor margin is covered by smooth nonneoplastic epithelium. **b** Macroscopic appearance of an undifferentiated small cell carcinoma (predominantly subepithelial type of superficial carcinoma). The tumor tissue is mainly covered by nonneoplastic epithelium

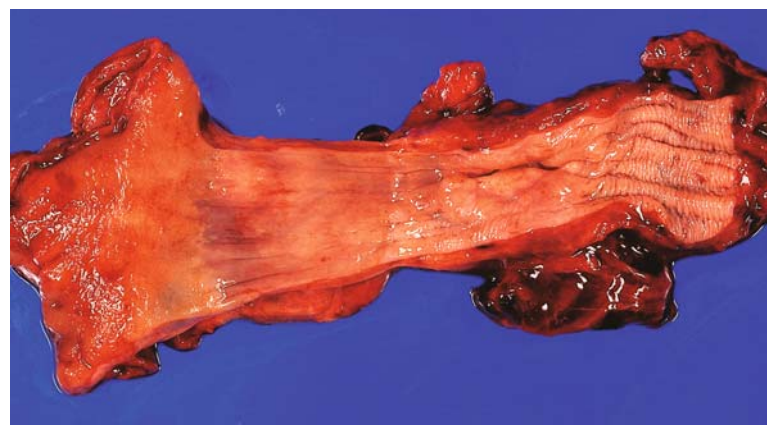


FIG. 13-30. Macroscopic appearance of an undifferentiated small cell carcinoma (ulcerative and infiltrative type of advanced carcinoma). The tumor tissue is mainly covered by nonneoplastic epithelium

tant to carefully examine many histological sections. Of 14 cases of surgically resected small cell carcinoma observed by this author (1998), 7 had areas of squamous cell carcinoma in situ that surrounded the main tumor (see Fig. 13-37). These tumors, with coexisting squamous cell carcinoma in situ, are also classified as the combined type of small cell carcinoma. Matsusaka et al. (1976) also

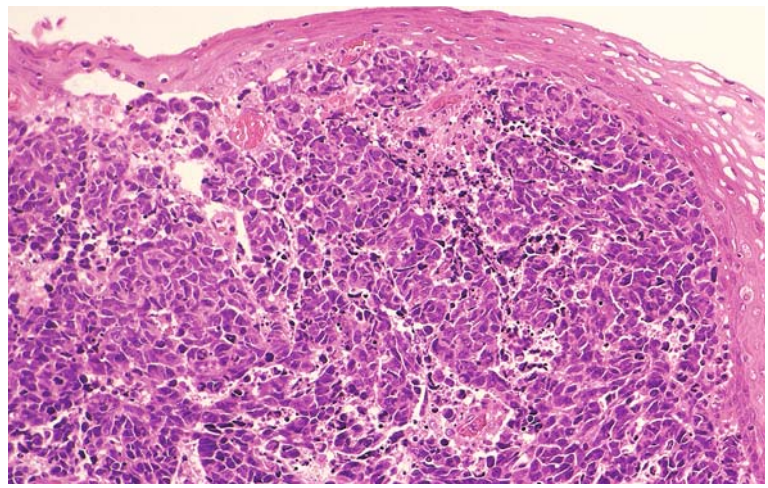


FIG. 13-31. Mucosal lesion of an undifferentiated small cell carcinoma. Undifferentiated tumor cells proliferate in the muscularis propria and elevate the normal epithelium

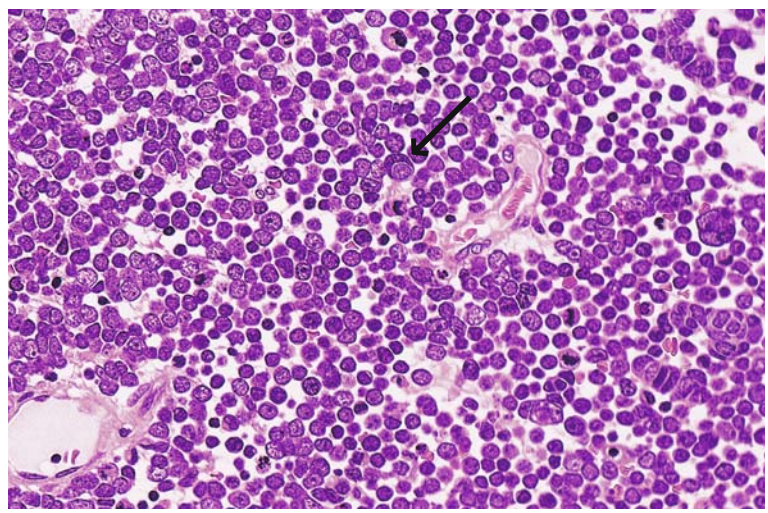


FIG. 13-32. Undifferentiated small cell carcinoma. There is a cell-in-cell appearance involving two tumor cells (*arrow*). This is a pure-type lesion, composed only of small cell carcinoma

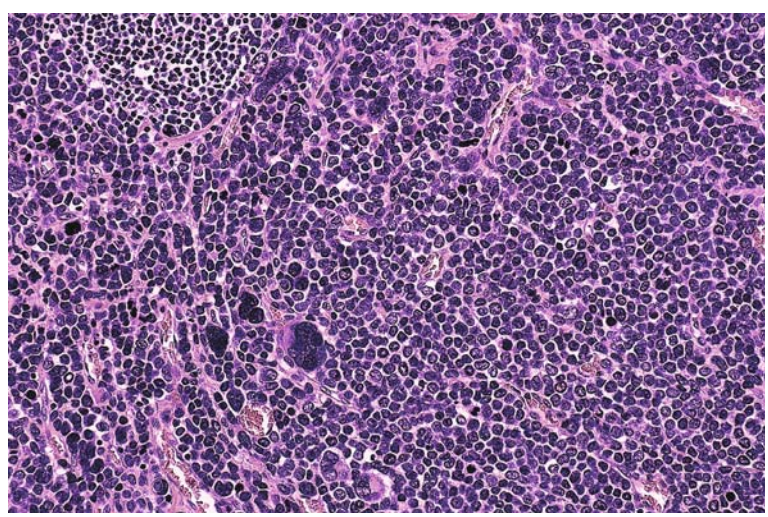


FIG. 13-33. Undifferentiated small cell carcinoma. This is a mixed-type lesion consisting of coexisting large cell and small cell carcinoma. There are lymphocytes in the *upper left* part of the figure

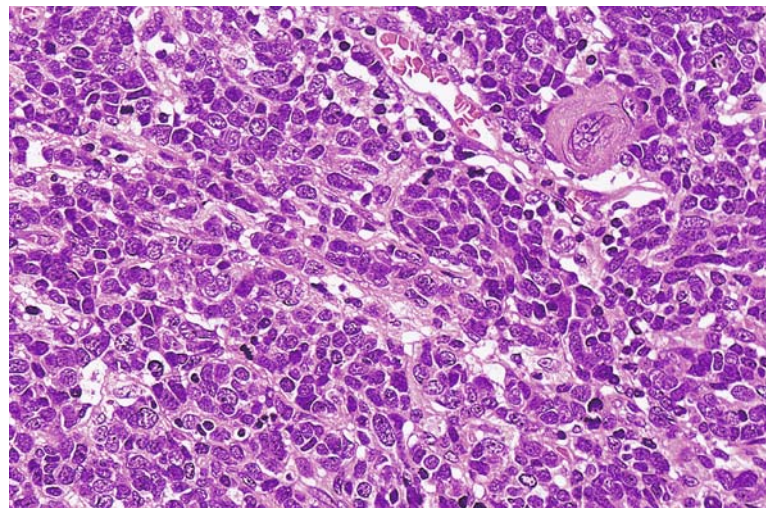


Fig. 13-34. Undifferentiated small cell carcinoma. There is a large squamoid cell within an undifferentiated small cell carcinoma

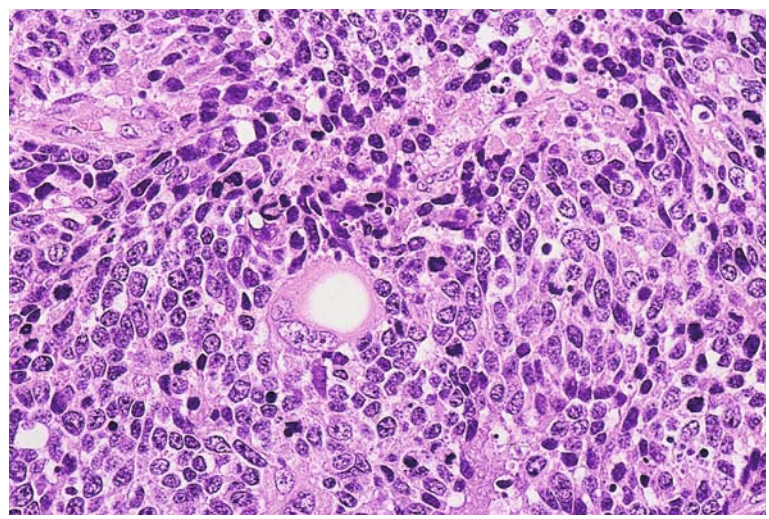


Fig. 13-35. Undifferentiated small cell carcinoma. Tubule formation is evident in the undifferentiated small cell carcinoma component

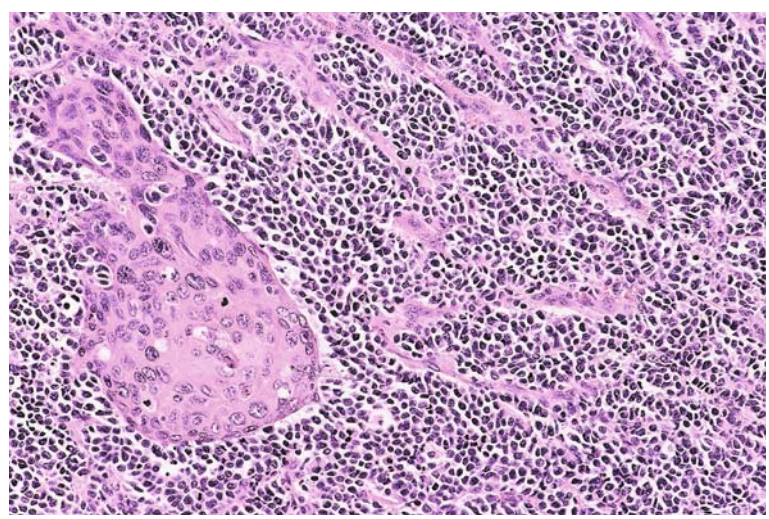


Fig. 13-36. Undifferentiated small cell carcinoma. This is a combined type small cell carcinoma showing a focus of squamous cell carcinoma

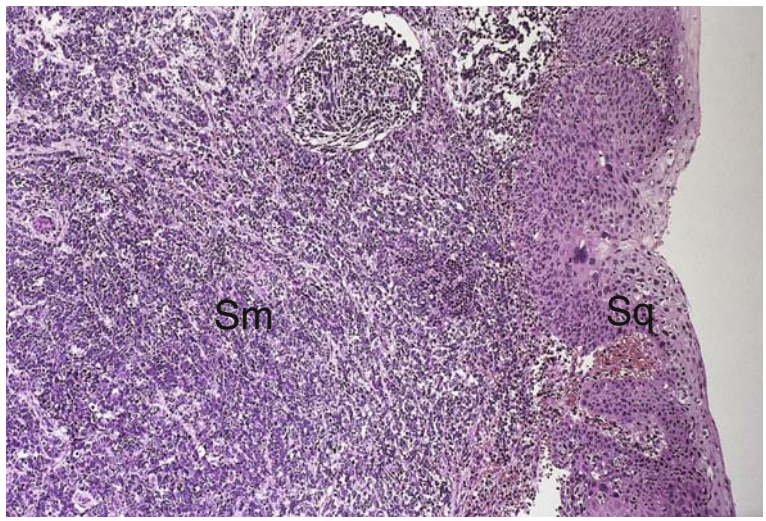


FIG. 13-37. Undifferentiated small cell carcinoma. A combined type small cell carcinoma showing squamous cell carcinoma in situ (*Sq*) and invasive small cell carcinoma (*Sm*)

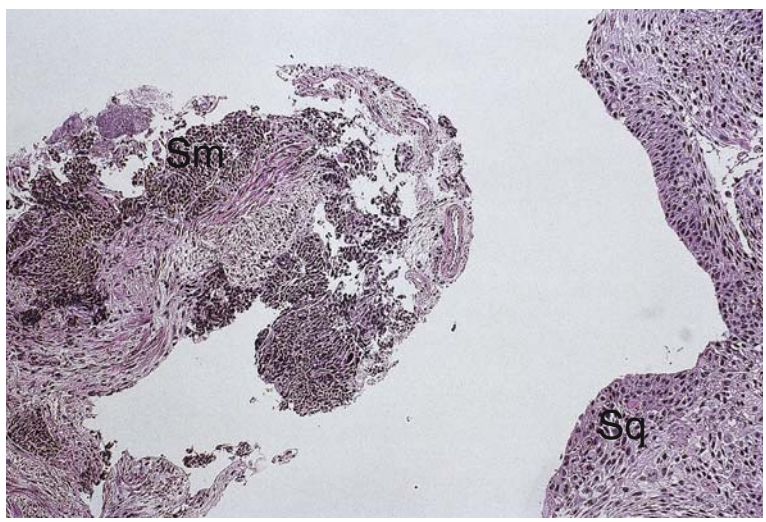


FIG. 13-38. Biopsy specimen from an undifferentiated small cell carcinoma. Components of small cell carcinoma (*Sm*) and squamous cell carcinoma (*Sq*) are seen

reported a case of primary esophageal small cell carcinoma that was associated with squamous cell carcinoma in situ. A further review of previous reports has revealed that the second case in the aforementioned report of McKeown was a combined type of small cell carcinoma (with squamous cell carcinoma), that differentiation into columnar or squamous epithelium was present in 2 of the 11 cases reported by Beyer et al., and that of 4 cases of small cell carcinoma reported by Ho et al. (1984), 2 were of the combined type. Thus, it is now considered that a substantial proportion of all small cell carcinomas of the esophagus are of the combined type.

Biopsy specimens may occasionally show coexisting small cell and non-small carcinoma (i.e., a combined small cell carcinoma) (Fig. 13-38). Particular caution is needed when encountering such tumors because they may require different treatment from a pure small cell carcinoma. Crush artifact is often seen in biopsy specimens.

Histological examination of esophageal small cell carcinomas that are resected after chemotherapy usually shows that most cancer cells have dis-

appeared, although some may remain and enlarge; edema and an inflammatory cell infiltrate are also often seen (Fig. 13-39).

The Grimelius method and chromogranin A staining may detect a small number of positive tumor cells (Fig. 13-40). Small cell carcinomas are often cytokeratin negative, but are often positive for epithelial membrane antigen (EMA) (Fig. 13-41), NSE (Fig. 13-42), bombesin, and CD57 (Noguchi et al. 2003).

Cytologically, most tumor cells have no or only very scanty cytoplasm, without evidence of keratinization (Fig. 13-43). They sometimes appear in clusters, but are generally loosely cohesive, showing no consistent arrangement and no gland formation. The tumor cells sometimes line up, however, forming a single-file pattern with nuclear molding (Fig. 13-44). The cell cytoplasm, if evident, stains light green with the Papanicolaou method. Some tumor cells exhibit an irregular nuclear shape, but there are no deep nuclear clefts. The chromatin is finely granular and hyperchromatic, and there is no thickening of nuclear membranes. Some tumor cells may have small nucleoli, but these are not strongly eosinophilic. The cells of esophageal small cell carcinomas appear to be larger and more diverse in shape than those of pulmonary small cell carcinomas, and occasionally

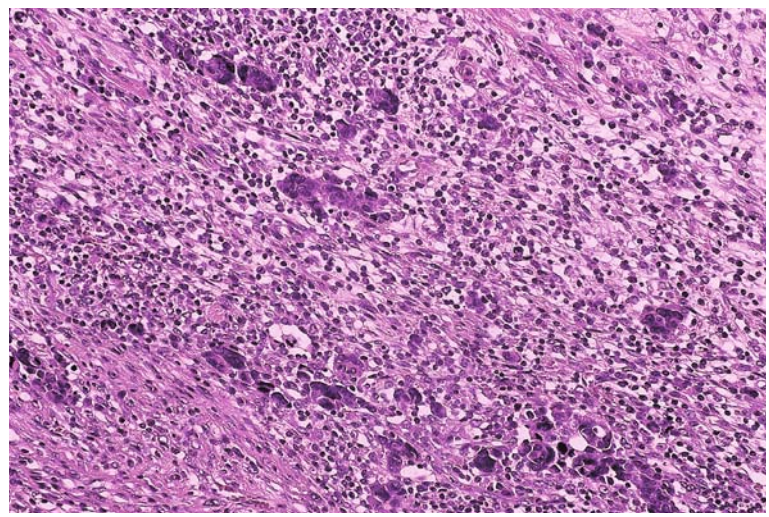


Fig. 13-39. Undifferentiated small cell carcinoma, postchemotherapy. Remaining tumor cells have enlarged, and there are surrounding lymphocytes, plasma cells, and histiocytes

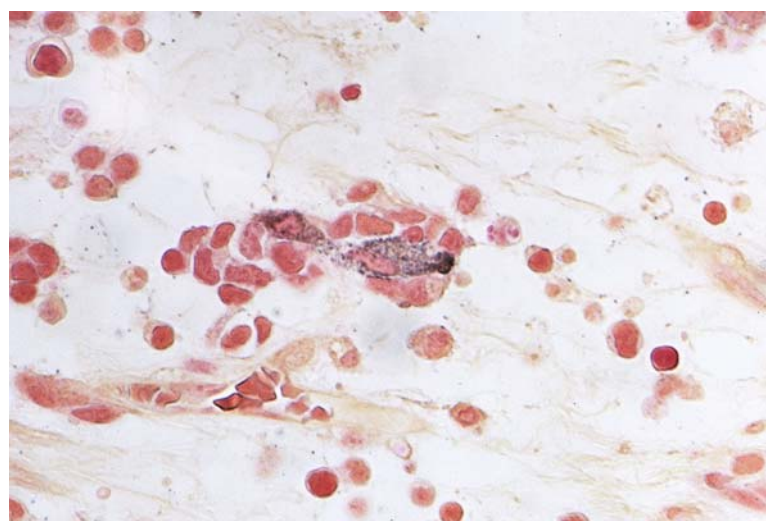


Fig. 13-40. Undifferentiated small cell carcinoma (Grimelius method). Two of the cells are Grimelius positive

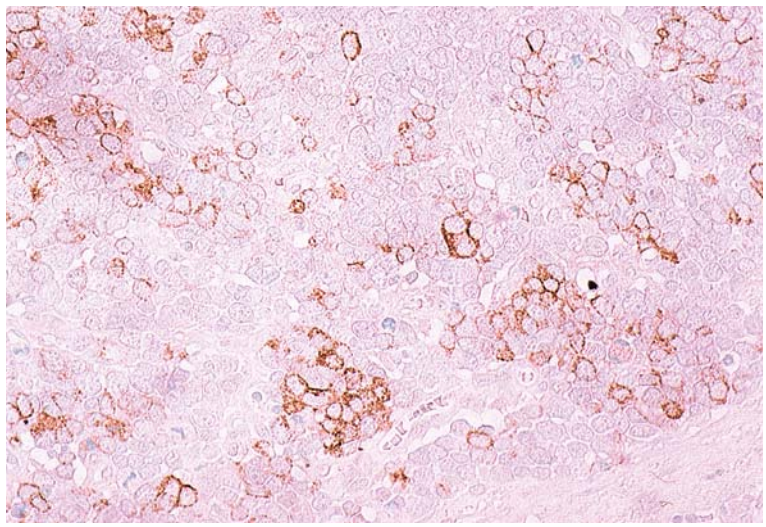


FIG. 13-41. Undifferentiated small cell carcinoma (epithelial membrane antigen immunostain). The cell membranes show diffuse positive staining

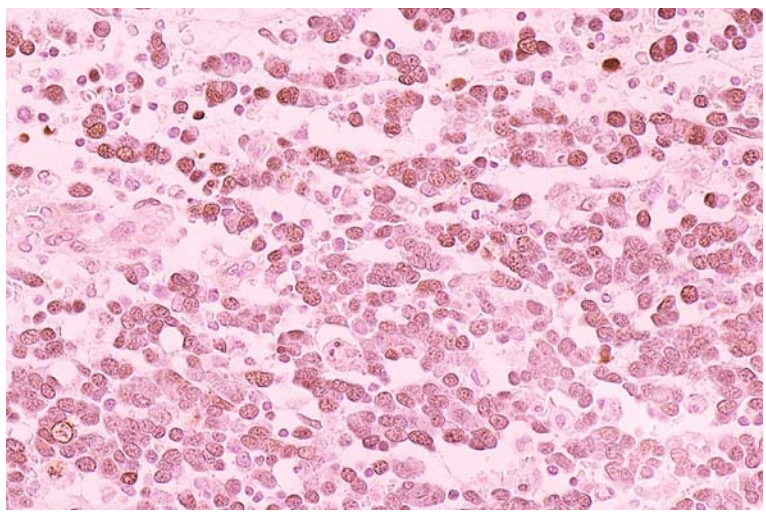


FIG. 13-42. Undifferentiated small cell carcinoma (neuron-specific enolase immunostain). The tumor cells show diffuse positive staining

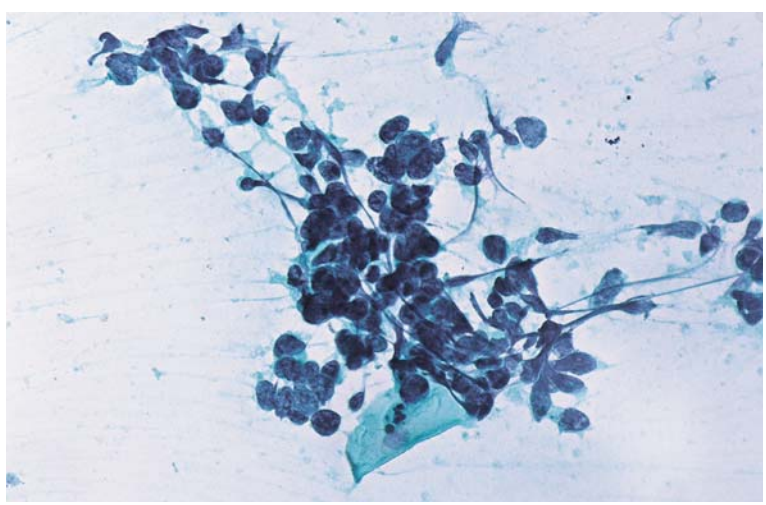


FIG. 13-43. Cytological appearance of an undifferentiated small cell carcinoma (Papanicolaou stain). The small tumor cells are loosely cohesive

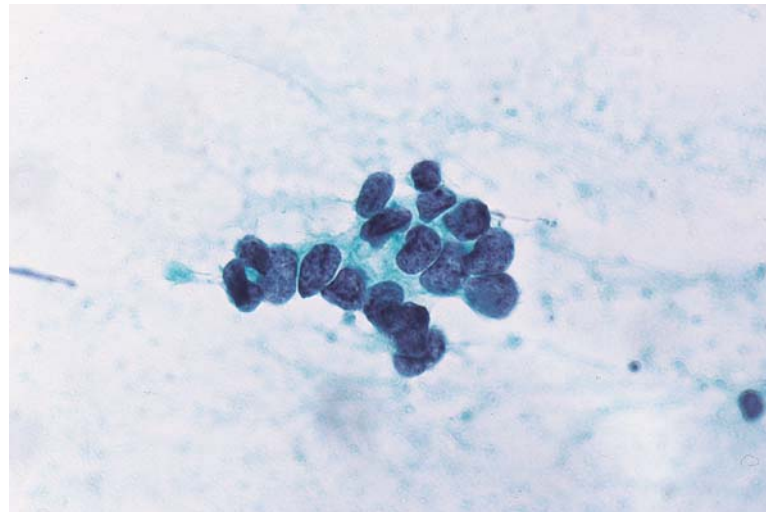


FIG. 13-44. Cytological appearance of an undifferentiated small cell carcinoma (Papanicolaou stain). A single-file arrangement of tumor cells is seen, with nuclear molding. Scant cytoplasm, finely granular nuclear chromatin, and faint nucleoli are evident

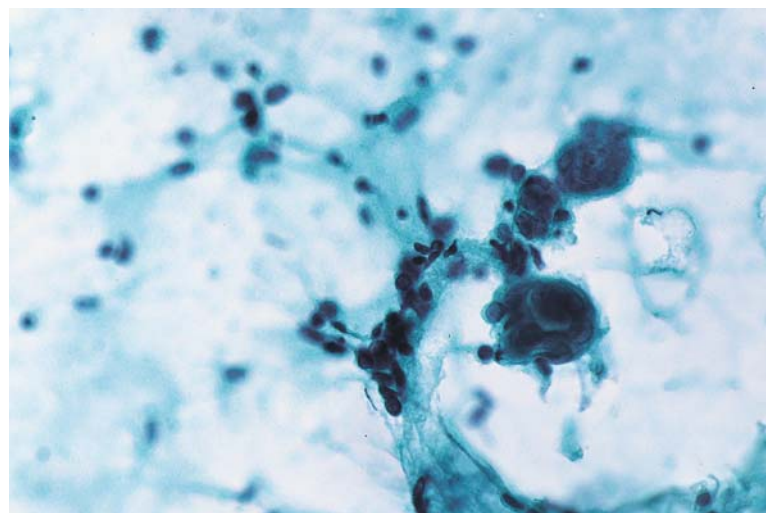


FIG. 13-45. Cytological appearance of an undifferentiated small cell carcinoma (Papanicolaou stain). There are aggregates of tumor cells, cytologically resembling malignant squamous cells

they have more conspicuous nucleoli. They sometimes aggregate to form cohesive masses, which might suggest squamous differentiation (Fig. 13-45).

Electron microscopy reveals sparse organelles in the tumor cells; neurosecretory-type granules may be found in peripheral areas of the cytoplasm (Fig. 13-46), and keratin filaments may also be seen.

As the tumor cells are sometimes argyrophilic and exhibit neurosecretory-type granules in their cytoplasm on electron microscopy, it is speculated that esophageal small cell carcinomas may arise from argyrophil cells in the mucosal epithelium, resembling carcinoid tumors. Mucosal epithelial cells are also suspected to be the origin, however, because esophageal small cell carcinomas are known to often have a coexisting component of squamous cell carcinoma in situ or invasive squamous cell carcinoma, and there has also been a case report of a small cell carcinoma with a coexisting mucus-producing mucoepidermoid carcinoma (Takubo et al. 1993). In addition, electron microscopic examination of esophageal small cell carcinomas often shows evidence of coexisting squamous or other differentiation (Reyes et al.). These observations make it more difficult to attribute the origin only to argyrophil cells in the

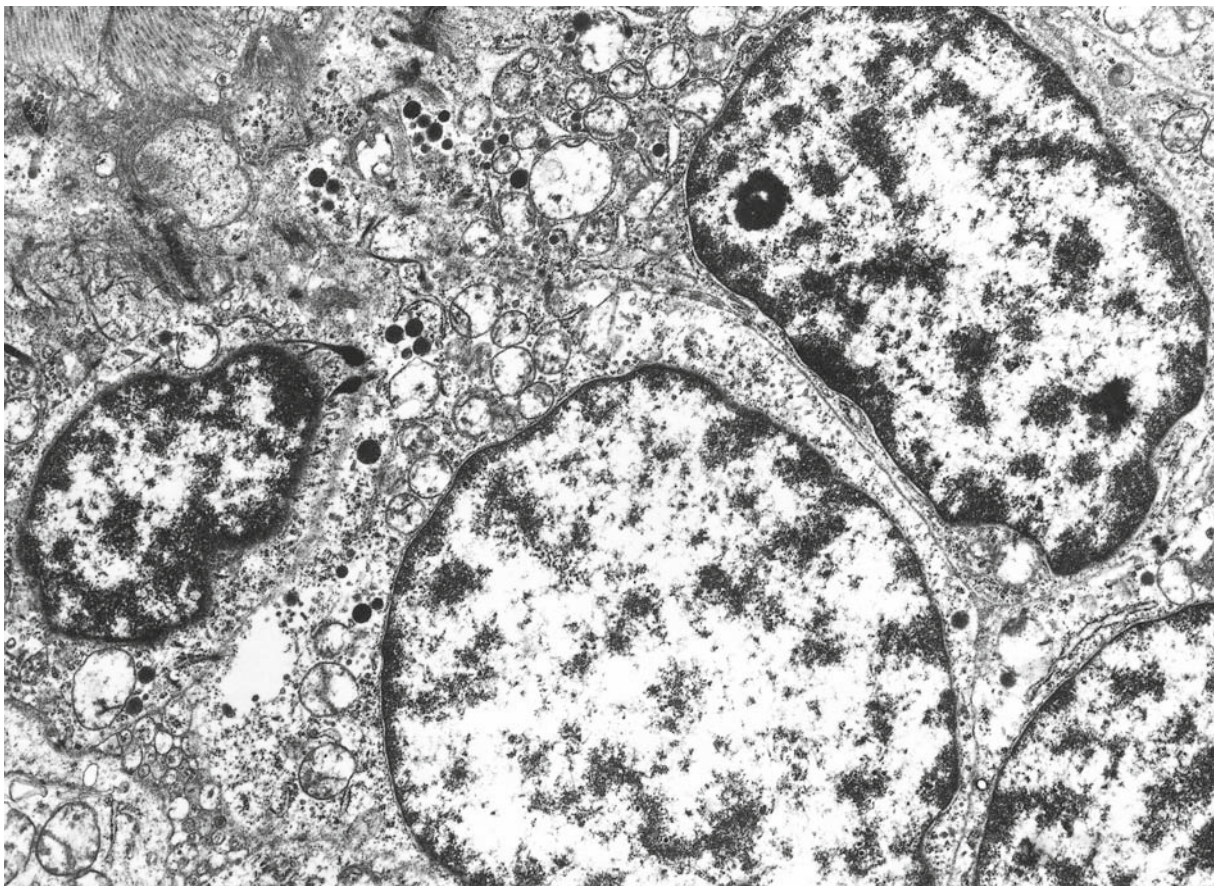


FIG. 13-46. Electron micrograph of an undifferentiated small cell carcinoma. There are dense-core neurosecretory-type granules in the peripheral cytoplasm of tumor cells

mucosal epithelium. It is considered that primary small cell carcinoma of the esophagus may arise de novo but may also sometimes initially develop as a squamous cell carcinoma in situ because, in cases of combined small cell carcinoma and squamous carcinoma in situ, the in situ squamous carcinoma often surrounds the small cell carcinoma (Takubo et al. 1999).

13.5. Basaloid Squamous Carcinoma, Basaloid Carcinoma

It has become apparent that basaloid squamous carcinoma may arise in the oral cavity, the upper respiratory tract, and the lung, in addition to the esophagus. Because the prognosis of basaloid squamous carcinoma of the head and neck is poorer than that of basaloid squamous carcinoma occurring elsewhere, it was proposed in 1986 that, in the head and neck, this entity should be categorized separately from usual squamous cell carcinoma (Wain et al.; McKay and Bilous). The second edition of the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (1972), published by the Japanese Society for Esophageal Diseases, had earlier classified this tumor as basal cell carcinoma, under the category of other carcinomas. The WHO classification (1990) of esophageal tumors had not yet addressed this entity. The new WHO classification (2000) of esophageal tumors has covered this entity (see Table 11-2).

It is considered that the prognosis of this entity in the esophagus is poorer than that of usual squamous cell carcinoma and is similar to that of basaloid squamous carcinoma of the oral cavity and upper respiratory tract. A study that reviewed 17 cases of basaloid squamous carcinoma of the esophagus documented only 1 patient who had survived for more than 5 years (Okushima et al.). Other reports, however, have stated that the prognosis of this tumor, if detected at an early stage, is similar to that of usual esophageal squamous cell carcinoma (Shimizu et al.). Yoshioka et al. (2004) reviewed 60 cases of basaloid squamous carcinoma of the esophagus; the outcome of the stages I, IIa, and IIb (International Union Against Cancer, UICC) cases was similar to that of usual squamous cell carcinoma, but stages III and IV cases had a poorer outcome than usual squamous cell carcinoma (Fig. 13-47).

Basaloid squamous carcinoma was observed as a minor component in 7.3% of usual squamous cell carcinomas in our Japanese series. In a review of 502 cases of esophageal malignancy in Korea, Cho et al. (2000) found 18 cases of basaloid squamous carcinoma, an incidence of 3.6%. Basaloid squamous carcinoma may also be found as the carcinomatous component in carcinosarcoma of the esophagus. This author classifies an esophageal tumor as a basaloid squamous carcinoma only when the tumor is composed predominantly of basaloid cells. The author's study of subserial sections from 178 consecutive surgically resected esophageal carcinomas found 3 basaloid squamous carcinomas (1.7%).

Until the 7th edition (1989), the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* did not give any clear explanation or micrographs of this entity. Therefore, tumors formerly reported in Japan as basal cell carcinoma or basaloid squamous carcinoma of the esophagus have included some poorly differentiated squamous cell carcinomas and undifferentiated small cell carcinomas.

Macroscopically, if superficial, basaloid squamous carcinomas often have a plateau-type or predominantly subepithelial-type appearance, according to the macroscopic classification of esophageal carcinoma described in the *Guidelines* (Fig. 13-48). When advanced, they tend to have a complex ulcerated appearance (Figs. 13-49, 13-50).

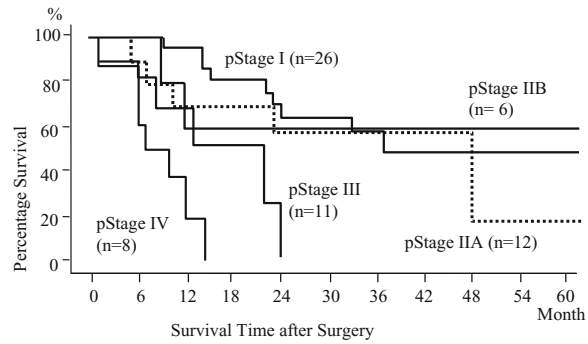


FIG. 13-47. Analysis of the crude survival following esophagectomy of 60 patients with esophageal basaloid squamous carcinoma. (Cited from Yoshioka et al. Jpn J Gastroenterol Surg 37, p 294)

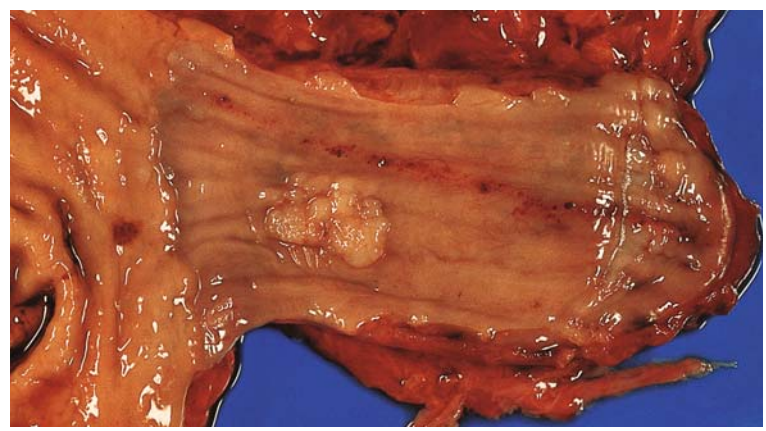


FIG. 13-48. Macroscopic appearance of a superficial basaloid squamous carcinoma (predominantly subepithelial type of superficial carcinoma)

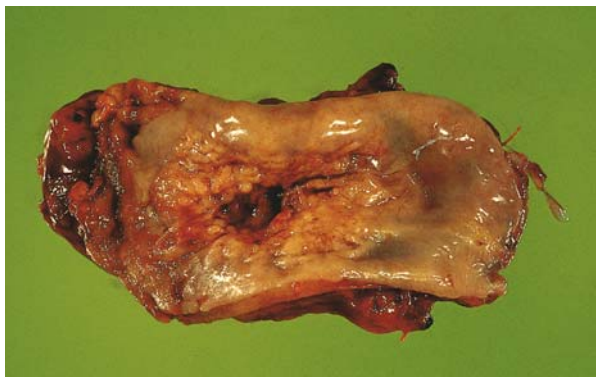


FIG. 13-49. Macroscopic appearance of an advanced basaloid squamous carcinoma (ulcerative and infiltrative type of advanced carcinoma)

Basaloid squamous carcinomas are characterized histologically by large cancer nests in which basaloid malignant epithelial cells are arranged in solid or trabecular patterns. Adenoid structures may be seen in some cases. There is not usually any intraepithelial component, but the tumor nests do make contact with the surface epithelium (Fig. 13-51). In contrast to basal cell carcinoma of the skin, a palisading pattern of tumor cells along basement membranes is relatively rare. The tumor cell nests may be centrally necrotic (Fig. 13-52). Small keratinizing foci may be found on rare occasions (Fig. 13-53), and a clear trabecular arrangement of cancer cells may sometimes be seen (see Figs. 13-53, 13-54). Basaloid squamous carcinomas with a trabecular pattern may in fact resemble carcinoid tumors, and basaloid squamous carcinomas

FIG. 13-50. Macroscopic appearance of the cut surface of a basaloid squamous carcinoma. There is extensive invasion into extraesophageal tissue

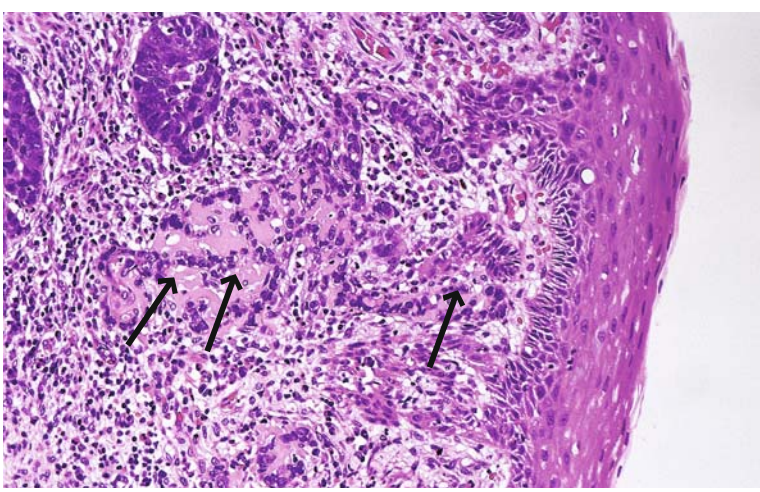


FIG. 13-51. Mucosal lesion of a basaloid squamous carcinoma. The tumor nests, with associated basement membrane material (*arrows*), are in contact with atypical squamous epithelium

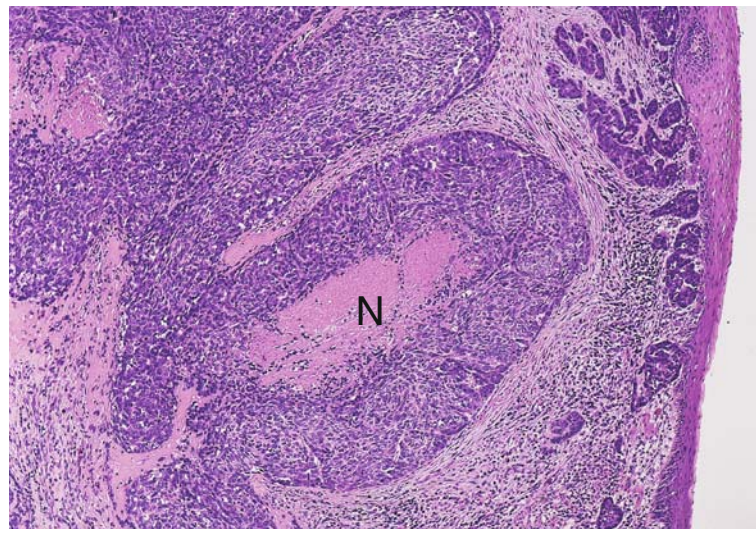


FIG. 13-52. Basaloid squamous carcinoma. A focus of coagulative necrosis (*N*) is seen in the center of a large tumor nest

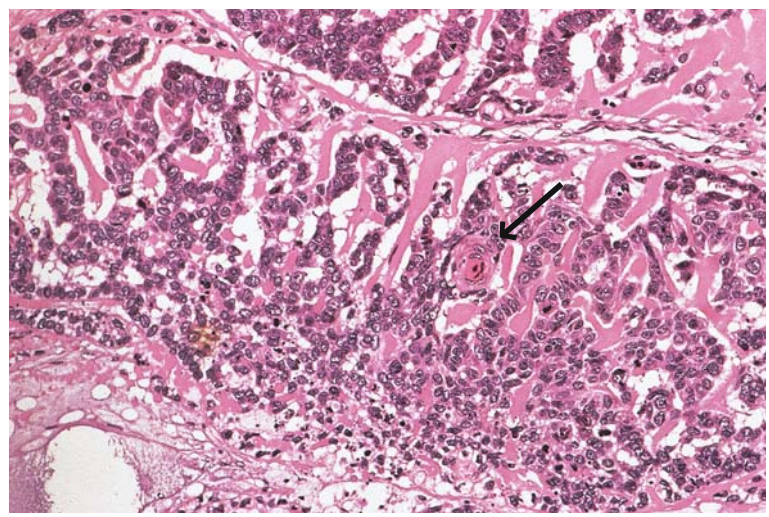


FIG. 13-53. Basaloid squamous carcinoma. Eosinophilic basement membrane material is evident between the tumor cells, which have a trabecular pattern. A small keratinized focus (*arrow*) is also seen

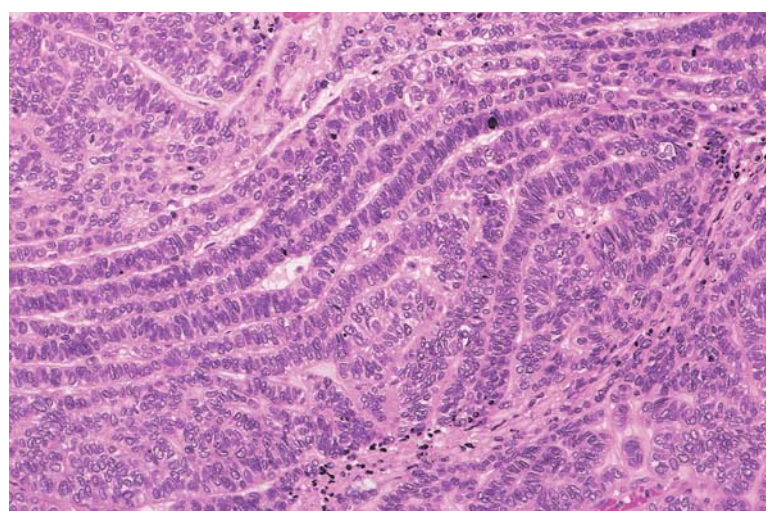


FIG. 13-54. Basaloid squamous carcinoma. The tumor cells are clearly arranged in a trabecular pattern

have actually been confused with primary carcinoid tumors of the esophagus in some case reports.

It is common for hyaline basement membrane material, which stains PAS positive, to be distributed within and around the tumor cell nests (Fig. 13-55). With immunohistochemical stains, this material is positive for laminin (Figs. 13-56, 13-57) and type IV collagen (Fig. 13-58). Stains for epithelial mucin are negative. Differing from adenoid cystic carcinoma, basaloid squamous carcinoma does not show a two-cell type pattern of myoepithelial and ductal epithelial cells, but the distinction between these entities remains unclear. Venous invasion is often seen in advanced cases; this invasion may occur into relatively large vessels, indicating that this entity has a propensity for vascular invasion.

In cytological preparations, the tumor cells are usually cohesive and resemble the basal cells of squamous epithelium (Fig. 13-59). In general, they have scanty cytoplasm, which stains light green with the Papanicolaou method; some naked nuclei may also be seen. The nuclei are round or oval and irregular in size. There is slight to moderate thickening of nuclear membranes, and nuclear

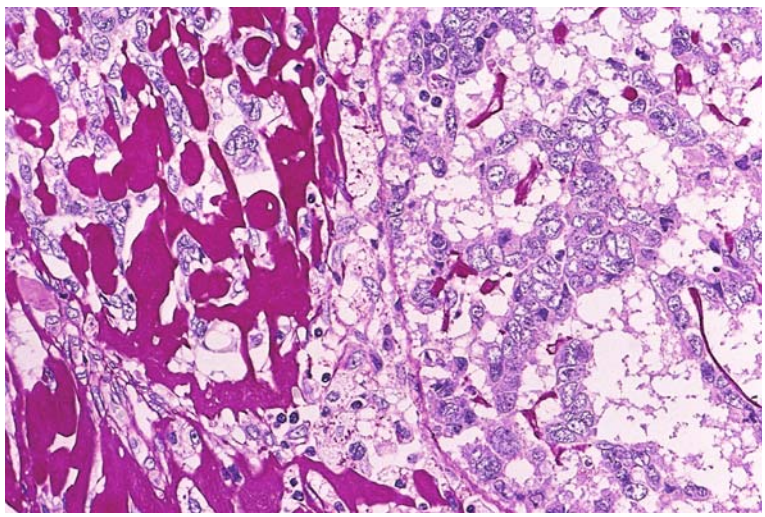


Fig. 13-55. Basaloid squamous carcinoma (periodic acid-Schiff stain). There is prominent accumulation of positive basement membrane material between the tumor cells

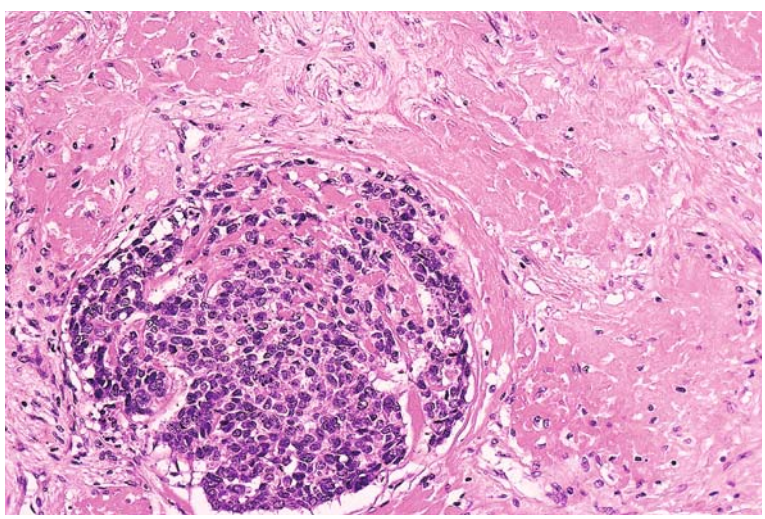


Fig. 13-56. Basaloid squamous carcinoma. A cancer nest is surrounded by a massive amount of basement membrane material

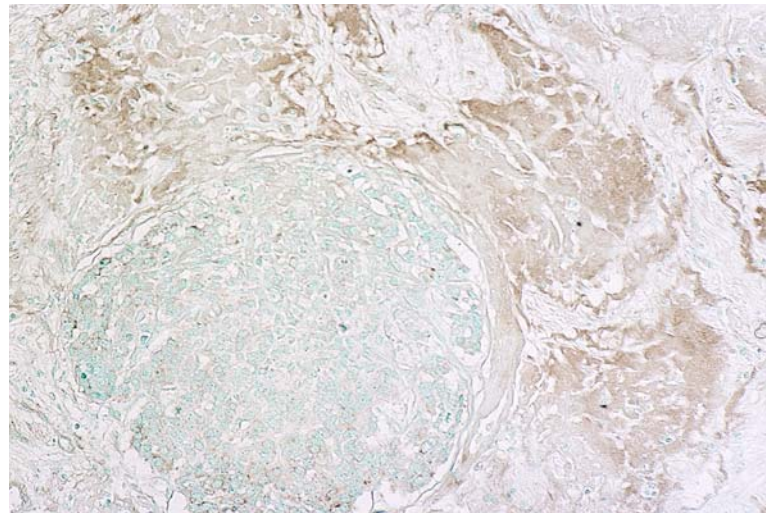


Fig. 13-57. Basaloid squamous carcinoma (laminin immunostain). The basement membrane material stains positive

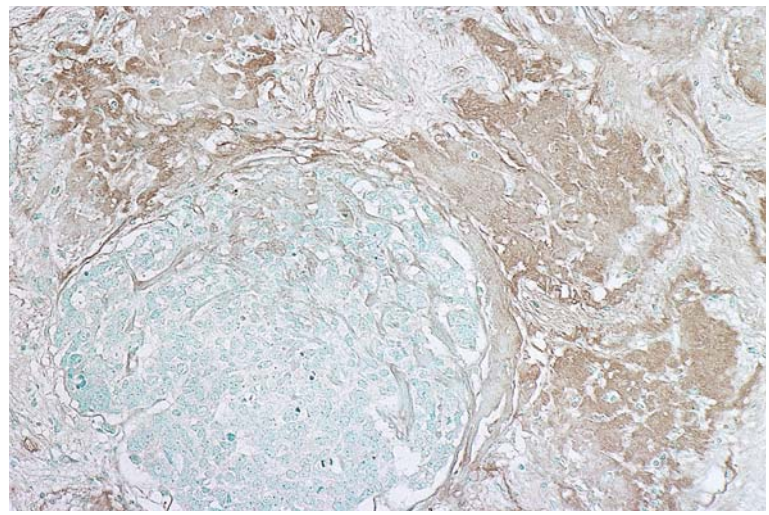


Fig. 13-58. Basaloid squamous carcinoma (type IV collagen immunostain). The basement membrane material stains positive

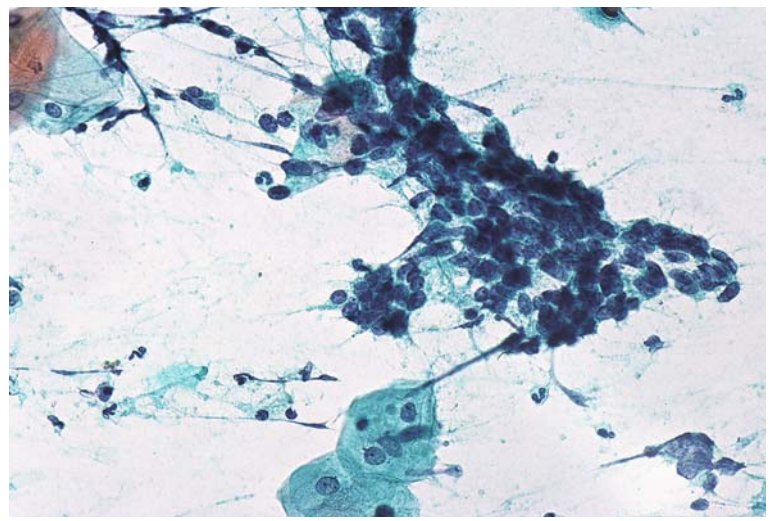


Fig. 13-59. Cytological appearance of a basaloid squamous carcinoma (Papanicolaou stain). Cohesive basaloid cells are seen. There are no keratinized cells present

chromatin is granular. Irregular and occasionally prominent nucleoli are often found (Fig. 13-60). Basement membrane material may also be seen in cytological smears (Fig. 13-61), and this stains positively with Alcian blue (Fig. 13-62). There are no keratinizing cells or glands. Basaloid squamous carcinomas are somewhat similar to small cell carcinomas cytologically but can be distinguished from them by the lack of file arrangements with nuclear molding and by the presence of thickened nuclear membranes.

Electron microscopy shows that the hyaline material consists of prominent multilayered basement membranes that surround the tumor cells (Fig. 13-63). A wavy pattern of prominent stratified basement membranes, surrounded by degenerate tumor cells, is occasionally seen (Fig. 13-64). These basement membranes, characteristic of basaloid squamous carcinoma, are thought to be produced by the tumor cells. There are no intercellular lumina in basaloid squamous carcinoma.

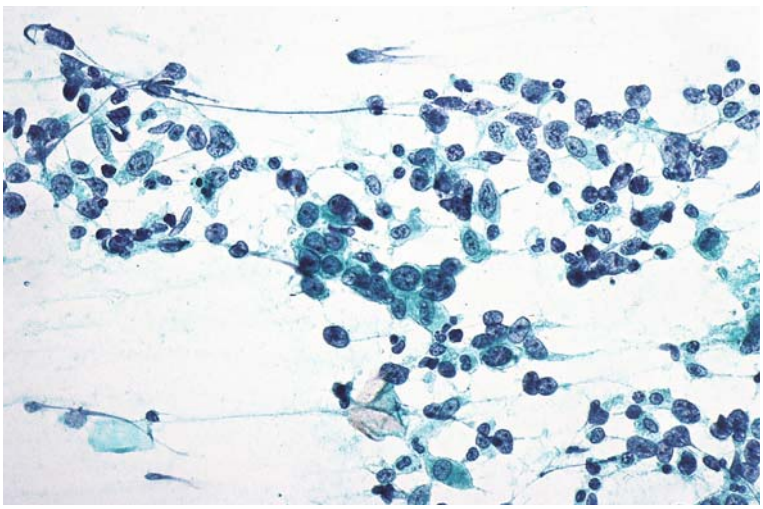


Fig. 13-60. Cytological appearance of a basaloid squamous carcinoma (Papanicolaou stain). The tumor cells have scanty cytoplasm and there is nuclear membrane thickening. The nuclei have one or two nucleoli

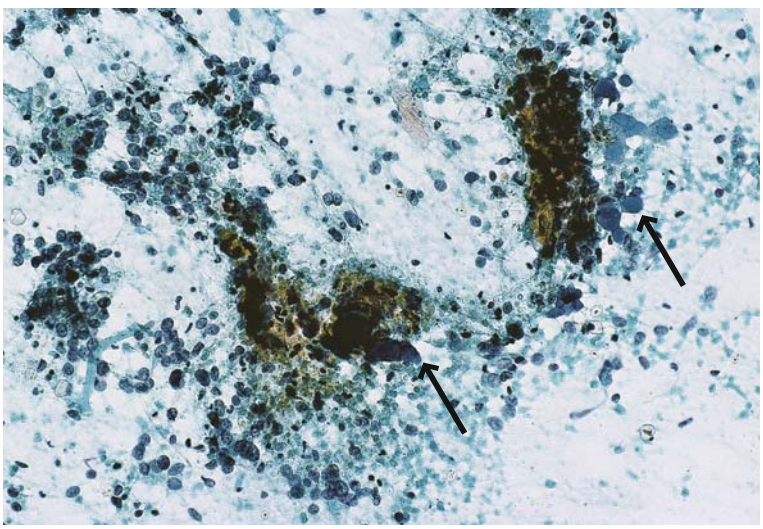


Fig. 13-61. Cytological appearance of a basaloid squamous carcinoma (Papanicolaou stain). Basement membrane material (*arrows*) is occasionally found between tumor cells

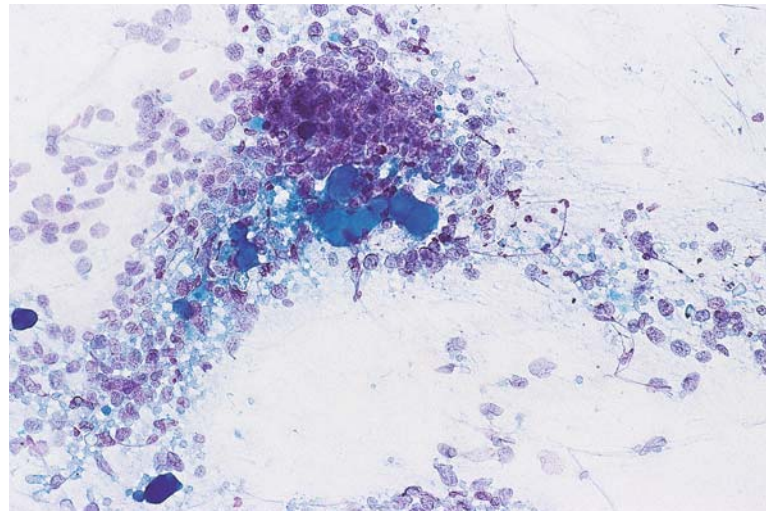


Fig. 13-62. Cytological appearance of a basaloid squamous carcinoma (Alcian blue stain). Basement membrane material is lightly stained with Alcian blue

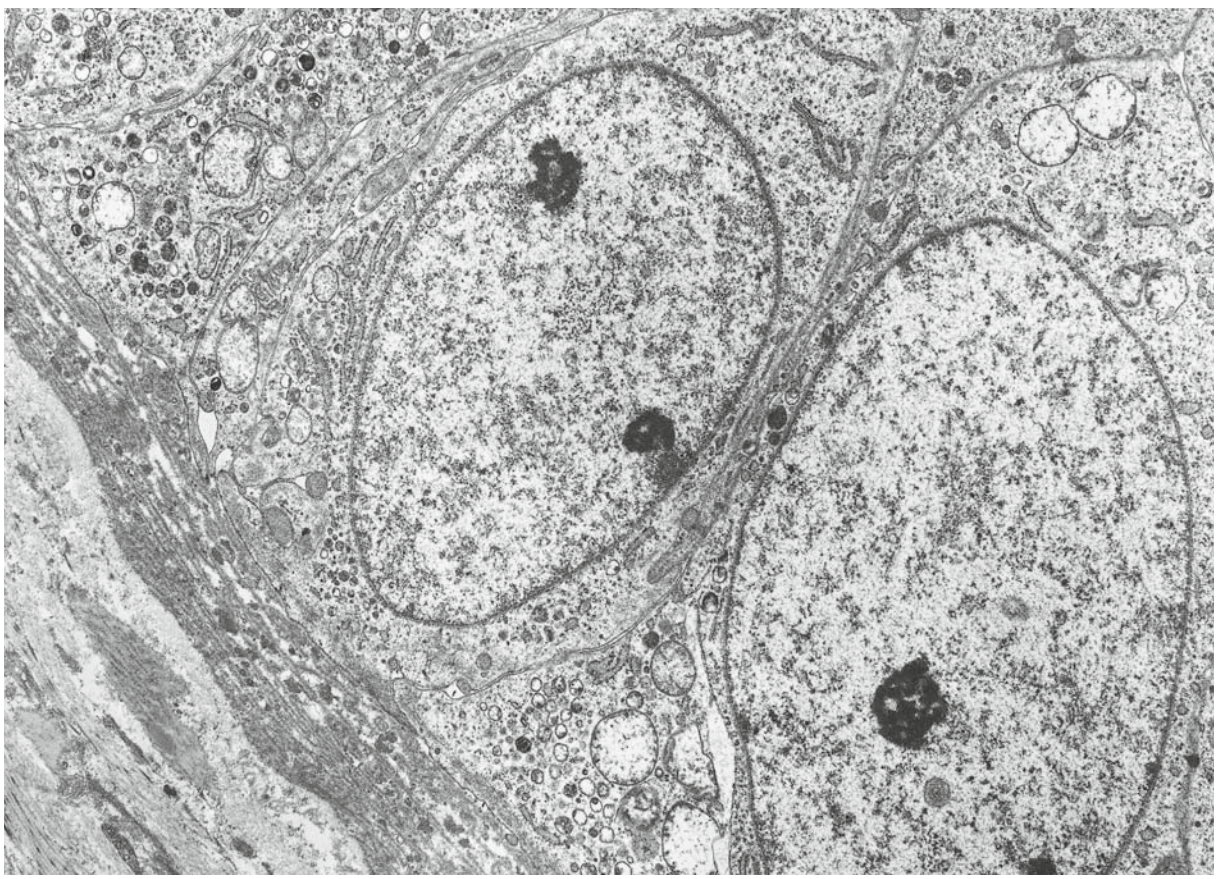


Fig. 13-63. Electron micrograph of a basaloid squamous carcinoma. Stratified basement membrane material surrounds the tumor cells

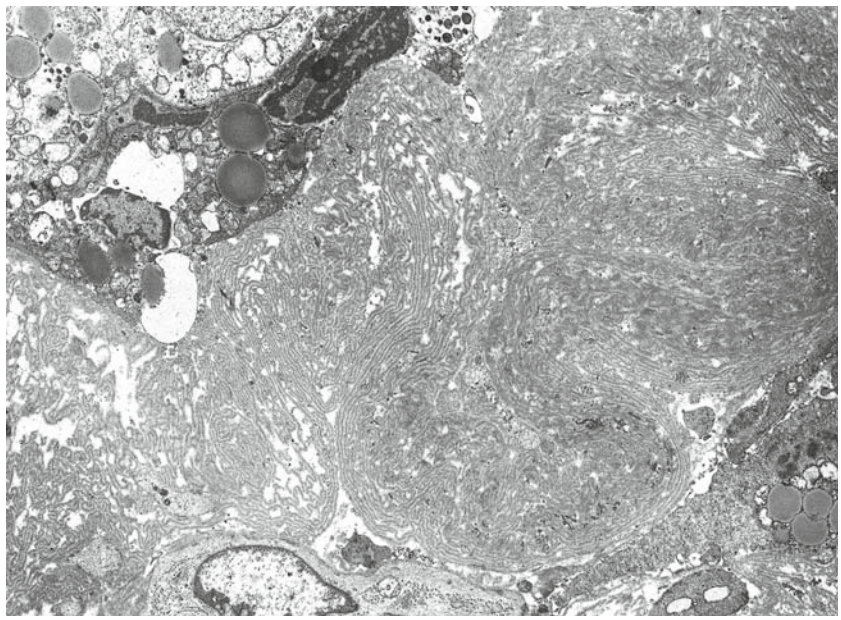


FIG. 13-64. Electron micrograph of a basaloid squamous carcinoma. A wavy pattern of prominent stratified basement membrane material is seen between degenerate tumor cells

13.6. Other Tumor Types

13.6.1. Carcinoid Tumor

According to a report by Brenner et al. (1969), the term carcinoid tumor was introduced in 1907, although the existence of the entity had been known earlier. Esophageal carcinoid tumors have been reported to arise in both squamous mucosa and Barrett's mucosa, but older case reports did not describe the adjacent mucosa in cases of carcinoid tumor. Cary et al. (1993) and Hoang et al. (2002) have reported carcinoid tumors arising in Barrett's esophagus.

Carcinoid tumors are rare in the esophagus, the incidence being the lowest of any site in the alimentary tract. Brenner et al. consider their report of a carcinoid tumor of the esophagus, published in 1969, to be the first. This tumor invaded the muscularis propria and had a lymph node metastasis; it was negative for the argentaffin reaction. A case of carcinoid tumor of the esophagogastric junction zone, which presumably arose in the stomach, had been reported before this case (Brodman and Pai 1968). Lindberg et al. (1997) reviewed 14 cases of esophageal carcinoid tumor reported in the English literature, and Yonekawa et al. (1991) reviewed 10 Japanese cases. Wakahama et al. (2000) reviewed 22 further cases of esophageal carcinoid; in this series the male-to-female ratio was 17:5.

Carcinoid tumors of the esophagus often metastasize to lymph nodes and are generally thought to have an unfavorable outcome. According to Lindberg et al. and Yonekawa et al., none of 24 patients survived for more than 3 years after surgery. Before 1993, only 1 reported patient, who had not been included in these two reports, had survived for longer than 5 years (Partensky et al. 1993), but Hoang et al. (2002) reported 4 cases of carcinoid tumor and suggested a favorable prognosis.

In most cases, macroscopic examination reveals a subepithelial mass with shallow surface ulcers.

The tumor cells are arranged in a trabecular or insular pattern and occasionally show rosette formations. They stain positively with the Grimelius and/or the Fontana–Masson method. Previously published micrographs of esophageal carcinoid tumors have shown features of atypical carcinoid tumor rather than the typical type, and they have also often had small cell carcinoma-like areas. Therefore, it appears acceptable to regard this entity as either an undifferentiated small cell car-

cinoma, an undifferentiated non-small cell carcinoma (as defined in the Japanese *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*, 9th edition), or as an undifferentiated carcinoma (as defined in the WHO histological classification of esophageal tumors). The WHO classification, however, places carcinoid tumors in the category of endocrine tumors, probably restricting the term to those tumors arising in Barrett's esophagus and exhibiting typical and classic histological features. Although the concept of the carcinoid family, which includes small cell carcinoma at one end of the spectrum, has been proposed, this author is of the opinion that, for the esophagus, only tumors with cells that stain diffusely positive by the Grimelius method and which contain multiple neurosecretory-type granules on electron microscopy should be categorized as carcinoid tumors.

One esophageal carcinoid tumor that occurred in a 55-year-old man (Chong et al.) was reported to have had cells that stained positively for mucin. This tumor occurred in the upper esophagus and also stained positively with the Grimelius and Fontana–Masson methods.

Figures 13-65 and 13-66 show the histological features of an ulcerative and localized type of tumor, as defined in the *Guidelines*, which occurred in the midesophagus of a 64-year-old man and was reported by Yonekawa et al. The tumor cells were diffusely positive with the Grimelius method and were found to contain many neurosecretory-type granules ultrastructurally. The tumor nests elevated the overlying noncancerous epithelium. There was no evidence of intraepithelial tumor or of Barrett's epithelium (see Fig. 13-65). The deeply invasive areas of the tumor showed a proliferation of polygonal cells, without keratinization, and the cytoplasm of the tumor cells was finely granular (see Fig. 13-66).

The doubling time of esophageal carcinoid tumors may be extremely short, reportedly 1.1 months (Hirata et al.), which is similar to that of small cell carcinoma (Sasajima). Considering this, together with the poor prognosis, this author considers that esophageal carcinoid tumors can be classified as undifferentiated carcinomas, as already noted, except when they have the classic, typical pattern. To detect carcinoid tumors, however, esophageal tumors showing a proliferation of polygonal cells, without keratinization, should be stained with the Grimelius method or with a chromogranin A immunohistochemical stain.

Basaloid squamous carcinomas sometimes show a trabecular growth pattern and have occasionally been mistakenly reported as primary esophageal carcinoid tumors. This problem should be borne in mind when diagnosing esophageal carcinoid tumors.

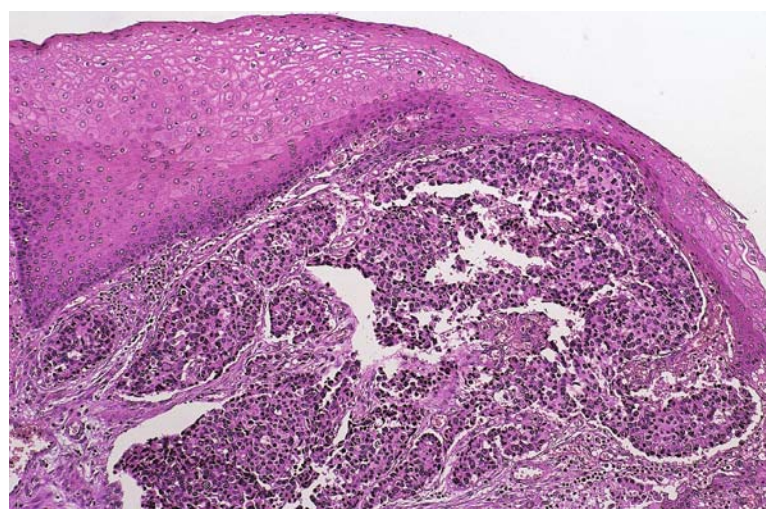


FIG. 13-65. Mucosal lesion of an esophageal carcinoid tumor. The tumor cells are proliferating and elevate the squamous epithelium

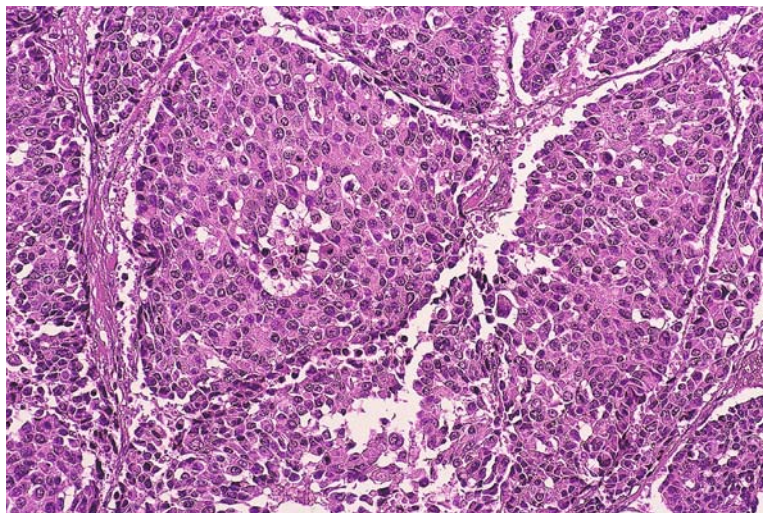


FIG. 13-66. Carcinoid tumor of the esophagus. A deeply infiltrative area shows that the tumor cells have granular cytoplasm. The nuclei are regular in size

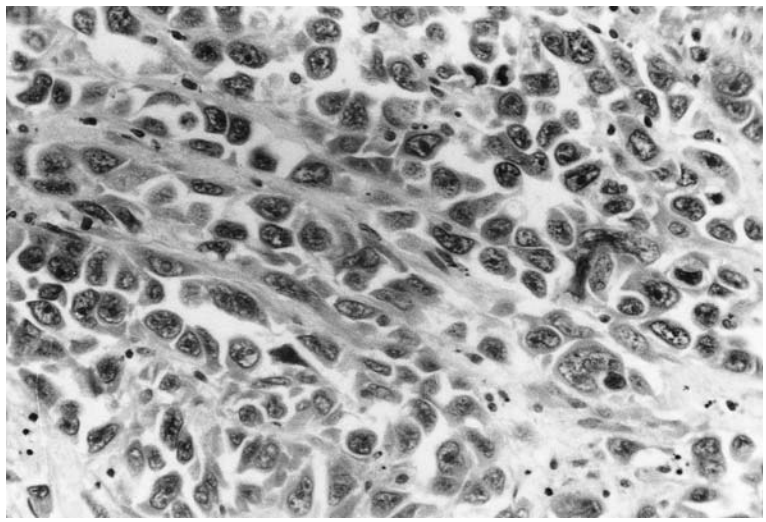


FIG. 13-67. Choriocarcinoma of the esophagus. Part of this tumor was an undifferentiated large cell carcinoma

13.6.2. Choriocarcinoma

Seven cases of primary esophageal choriocarcinoma have been reported to date, the first having been by Sasano et al. (1970). In some of these there has been an accompanying adenocarcinoma of usual type (McKechnie and Fechner, Aonuma et al.), and Barrett's esophagus was also present in three of the six reported cases (Aonuma et al.). There was, however, no component of adenocarcinoma in an autopsy case reported by Trillo et al.

The tumor reported by Sasano et al. occurred in a 74-year-old woman. It was basically a large cell carcinoma (Fig. 13-67), but part of the main lesion, and metastatic foci in the lung and liver, had an appearance extremely similar to that of choriocarcinoma (Fig. 13-68). There was a transition zone between an intramucosal area of choriocarcinoma and the undifferentiated large cell carcinoma component. Figures 13-67 and 13-68 show the histological appearance of this case. The tumor was composed of large syncytial cells with hyperchromatic nuclei (syncytiotropho-

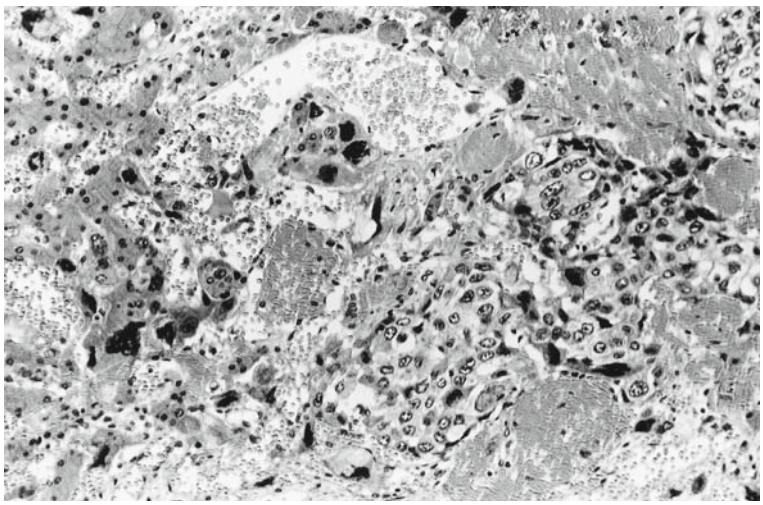


FIG. 13-68. Choriocarcinoma of the esophagus. The tumor is composed of syncytiotrophoblast, consisting of cells with hyperchromatic nuclei, and cytotrophoblast, consisting of cells with clear cytoplasm and pale nuclei

blast) and cells with clear cytoplasm and pale nuclei (cytotrophoblast); intermediate-type cells were also present. Necrosis and hemorrhage were conspicuous.

In one reported case, gynecomastia occurred because of a high blood level of human chorionic gonadotropin (HCG) (Wasan et al.).

With regard to the histogenesis of choriocarcinoma arising in the gastrointestinal tract, including the esophagus, differentiation from an adenocarcinoma of usual type is a possibility, but a choriocarcinoma arising within a squamous cell carcinoma of the esophagus has also been reported, in a 53-year-old man (Merimsky et al. 2000).

13.6.3. Paget's Disease

Lesions similar to the nipple lesions originally described by Paget (1874) may occur in the axillae, external genitalia, and anal region, and have been called extramammary Paget's disease. Lesions histologically resembling mammary or extramammary Paget's disease in the esophageal mucosa are termed Paget's disease of the esophageal epithelium. The first case was reported by Yates and Koss in 1968 but the clear intraepithelial cells in this tumor, which occurred in a 66-year-old man, were negative with mucin stains. Six cases of esophageal Paget's disease have been reported to date (Matsukuma et al. 1995; Karakök et al. 2002; Haleem et al. 2003).

Norihisa et al. (1988) reported an adenosquamous carcinoma of the esophagus, confined to the submucosa, which was accompanied by extensive intraepithelial spread with the histological features of Paget's disease. In this case the esophageal mucosa in the affected area was eroded macroscopically. Figure 13-69 shows this lesion. Large tumor cells with clear cytoplasm infiltrated the epithelium, forming the basal layer type pattern of intraepithelial spreading carcinoma. Several clear tumor cells can be seen in nests within the noncancerous epithelium, with the nonneoplastic basal cell layer occasionally remaining intact (Fig. 13-70). Histologically, some invasive areas of tumor resembled adenosquamous carcinoma, with tubule formation (Fig. 13-71), while others resembled mucoepidermoid carcinoma (Fig. 13-72). The clear cells within the noncancerous epithelium stained positively with PAS and Alcian blue, and were also positive with a CEA immunohistochemical stain. The invasive areas of adenosquamous carcinoma also had mucin-positive cells. As is the case for Paget's disease of the nipple, it may be appropriate to apply the term pagetoid carcinoma to this condition, as it is an invasive carcinoma.

Both adenosquamous and mucoepidermoid carcinomas may have tumor cells with clear cytoplasm in a limited area of the basal layer of the overlying epithelium (see Fig. 13-72), and these cells stain positively for mucin. Sometimes

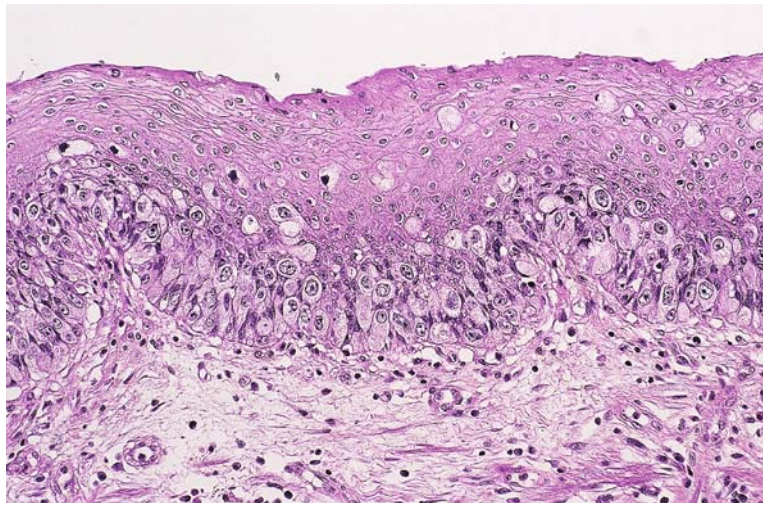


Fig. 13-69. Paget's disease of the esophagus. The basal layer is replaced by intraepithelial carcinoma. Large malignant cells with clear cytoplasm are seen in the basal layer of the epithelium

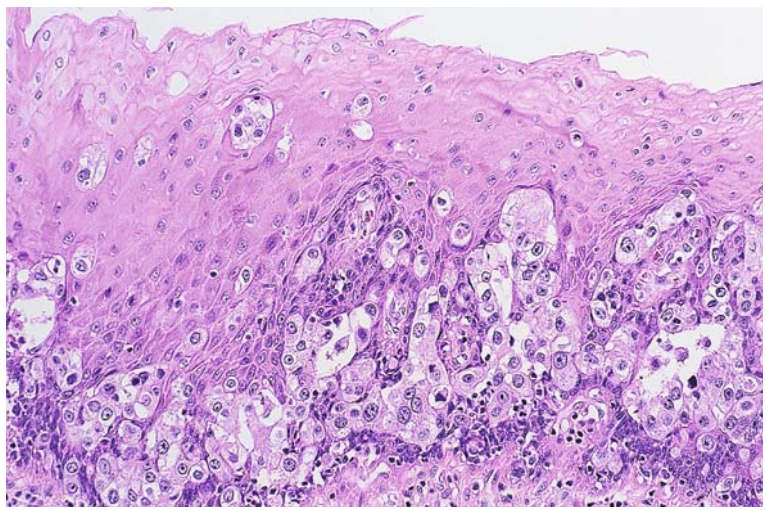


Fig. 13-70. Paget's disease of the esophagus. There are nests of large tumor cells with clear cytoplasm in the noncancerous squamous epithelium. The normal basal layer of the squamous epithelium remains

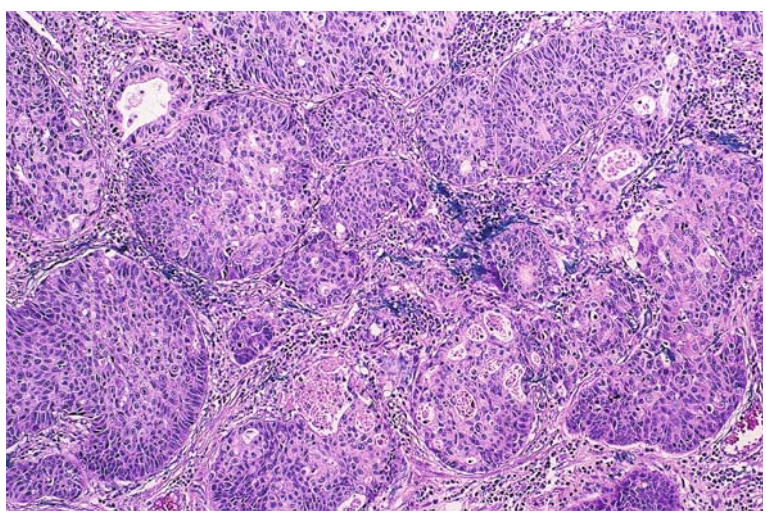


Fig. 13-71. Paget's disease of the esophagus. The invasive tumor in the submucosa is an adenosquamous carcinoma with tubule formation

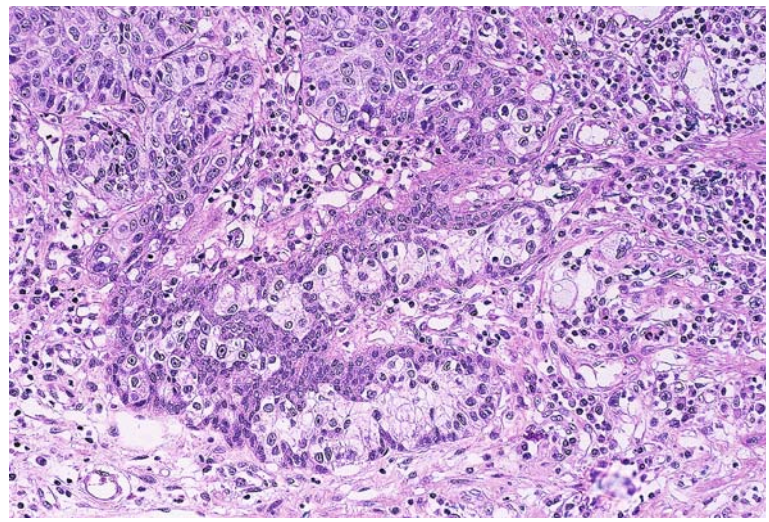


FIG. 13-72. Paget's disease of the esophagus. Invasive tumor in the lamina propria includes mucin-positive cells with clear cytoplasm

squamous cell carcinomas of usual type may also show the intraepithelial spread of clear tumor cells in the basal layer of the overlying epithelium, however, resembling Paget's disease (Chu et al.).

The electron microscopic findings in esophageal Paget's disease have been reported by Matsukuma et al. The clear tumor cells within the squamous epithelium show glandular differentiation, as in Paget's of the nipple and external genitalia, and desmosomes are found between the squamous cells and the clear tumor cells. The presence of these desmosomes indicates that there is adhesive apparatus between the host and tumor cells, and suggests that both host and tumor cells cooperate in its formation.

Chapter 14
Malignant Nonepithelial Tumors of the Esophagus

14.1. Leiomyosarcoma

Shimazu et al. (1983) have stated that leiomyosarcoma of the esophagus was first described in 1902, and that the first Japanese report of this entity was published in 1950.

Leiomyosarcoma is the commonest primary sarcoma of the esophagus but accounts for less than 2% of primary esophageal malignancies. Males are predominant, with a male : female ratio of 2 : 1 (Shimazu et al.). The commonest age is the seventh decade, followed by the sixth decade. The tumor is most commonly located in the lower third of the esophagus. According to Partyka et al. (1981), 43 cases of esophageal leiomyosarcoma have been reported from Europe and America. In Japan, 97 such cases have been reported (Shiraishi et al. 1995).

A collision tumor consisting of microinvasive squamous cell carcinoma and leiomyosarcoma of the esophagus has also been reported (Gaede et al. 1978).

The prognosis of leiomyosarcoma of the esophagus is generally considered to be better than that of squamous cell carcinoma, with a reported cumulative survival rate of 82% (Kodera et al. 1991), but Shimazu et al. (1983), who reviewed 35 Japanese cases, concluded that there were insufficient data to evaluate long-term postoperative results.

Macroscopically, leiomyosarcoma of the esophagus appears as a submucosal tumor (Fig. 14-1) with a white cut surface (Fig. 14-2). Hemorrhage and degeneration may be evident. Some leiomyosarcomas with marked extramural extension are occasionally misdiagnosed as mediastinal tumors. Many leiomyosarcomas are large at the time of surgery, even exceeding 10 cm in diameter (Shimazu et al.).

These tumors may be classified macroscopically into intraluminal (polypoid), intramural, extramu-

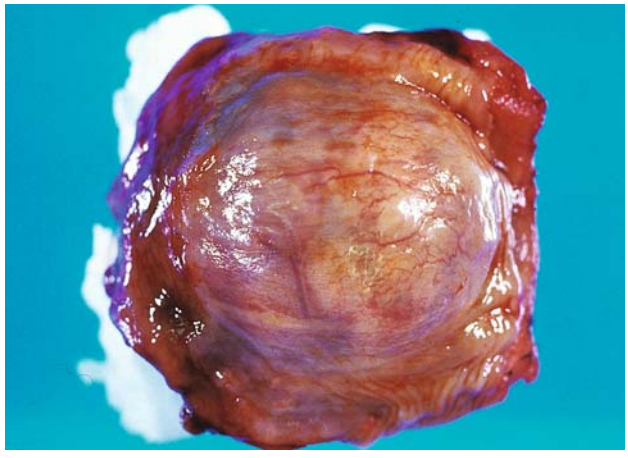


FIG. 14-1. Macroscopic appearance of the mucosal surface of a leiomyosarcoma (advanced protruding polypoid type)

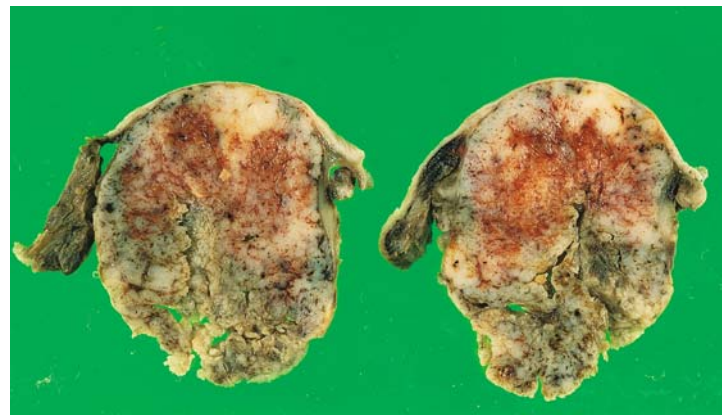


Fig. 14-2. Macroscopic appearance of the cut surface of a leiomyosarcoma. White tumor tissue is evident in the esophageal wall

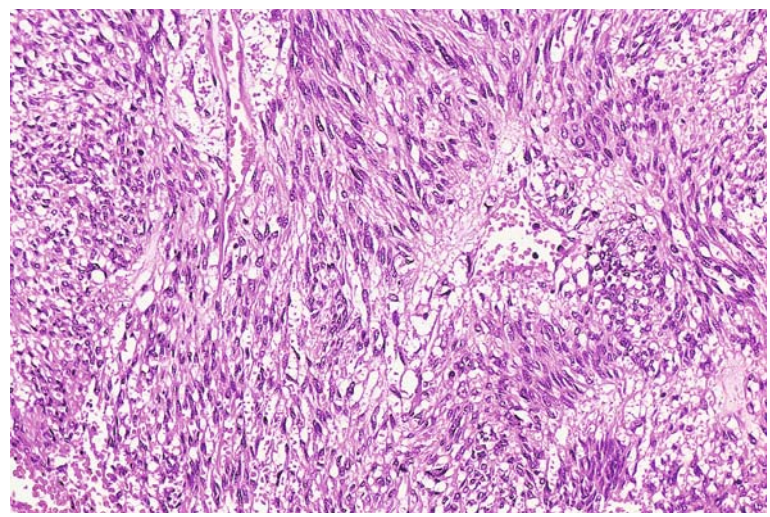


Fig. 14-3. Leiomyosarcoma. The tumor consists of spindle cells with large irregular nuclei

ral, and mixed types. A simple classification of noninfiltrating (polypoid) and infiltrating types is also in use (Buxton; Rainer and Brus). The infiltrating type has a poor prognosis.

Leiomyosarcomas of the esophagus are often ulcerated. When they are not ulcerated, it is often difficult to obtain tumor tissue at biopsy, making diagnosis difficult.

There are very often no lymph node metastases at the time of surgery, and this has led to a consensus view that extensive lymph node dissection is unnecessary when performing esophageal resections for this condition (Shimazu et al.).

Leiomyosarcoma of the esophagus is characterized histologically by a highly cellular proliferation of spindle cells with large nuclei (Fig. 14-3). In contrast to leiomyoma, an extremely large number of mitotic figures may be seen (Fig. 14-4), and in some cases there may be calcification (Itai and Shimazu). The author uses the number of mitotic figures to distinguish leiomyoma and leiomyosarcoma of the esophagus in the same way as for uterine smooth muscle tumors. That is, smooth muscle tumors with 4 or fewer mitoses per 10 high-power fields are considered benign, whereas those with 5 to 9 mitoses have the potential for

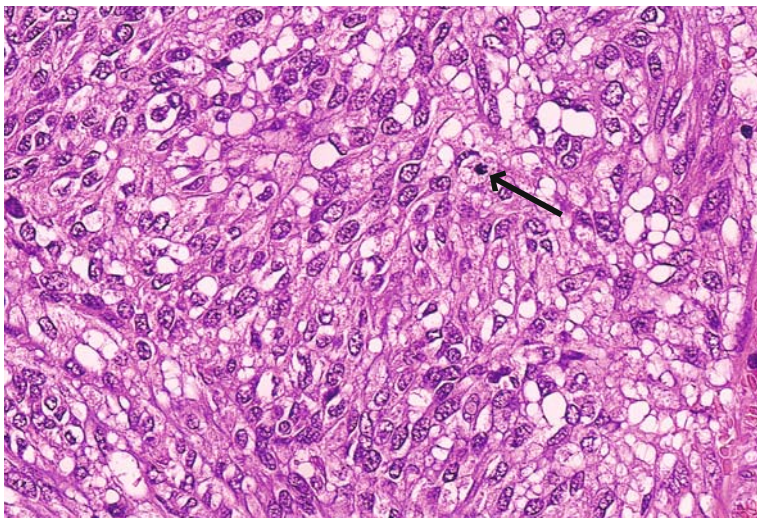


Fig. 14-4. Leiomyosarcoma. Mitotic figures (*arrow*) are seen in the fusiform cells

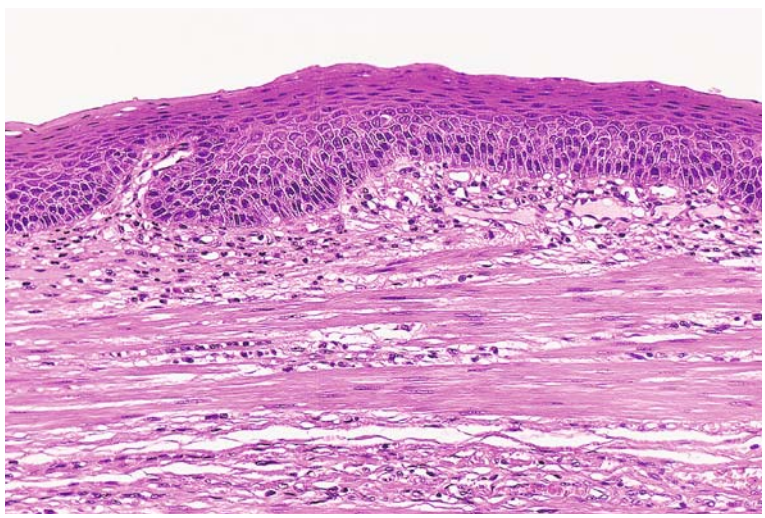


Fig. 14-5. Epithelial dysplasia overlying a leiomyosarcoma. There are atypical basal cells in the squamous epithelium

metastasis and those with 10 or more mitoses are definitely malignant. There are no rational grounds, however, for applying the criteria for uterine leiomyosarcomas to esophageal leiomyosarcomas, and some researchers take the view that the number of mitoses does not reliably distinguish benign from malignant tumors (Gaede et al.). For example, smooth muscle tumors measuring more than 3 cm (Esaki) or more than 5 cm in diameter, or those with hemorrhage or degeneration, are considered by some workers to have malignant potential. Also, there is often great variation in the distribution of mitoses in different parts of a tumor. The number of mitoses found in the leiomyosarcoma shown in Fig. 14-4 was 36 per 10 high-power fields (×200). The patient with this tumor died of hepatic metastases.

The mucosal epithelium overlying the tumor may be dysplastic, as may be the case for the epithelium overlying esophageal leiomyomas (Fig. 14-5). Leiomyosarcomas are usually positive with immunohistochemical stains for actin, desmin, and vimentin, although in some cases the staining may be weak.

Electron microscopy reveals actin filaments with focal densities in the cytoplasm of tumor cells. There is also abundant rough endoplasmic reticulum, and there are many micropinocytotic

vesicles, although these are less numerous than in leiomyomas. It has been reported that no basement membrane or junctional apparatus is seen in leiomyosarcomas, but this is disputed (Gaede et al.). In fact, there is often a discontinuous basement membrane around the tumor cells.

Leiomyosarcomas are distinguishable from neurilemmomas and malignant neurogenic tumors by ultrastructural features such as the presence of actin filaments with focal densities and the absence of complex long cellular processes, and by the results of immunohistochemical stains for neuron-specific enolase (NSE), S-100 protein, and neurofilament. Fibrosarcoma and malignant fibrous histiocytoma can be excluded by the absence of basement membranes on electron microscopy.

14.2. Non-Hodgkin's Lymphoma and Leukemia

The esophagus is occasionally infiltrated by systemic malignant lymphoma; in this regard, it is particularly vulnerable to direct invasion from involved mediastinal lymph nodes. In a study by Givler, there was macroscopic esophageal involvement in 1% of patients with leukemia or systemic lymphoma and histological involvement in 27%. In an autopsy review of 207 cases of leukemia by Fulp et al. (1993), there was leukemic infiltration of the esophagus in 7.2%; the likelihood of esophageal involvement was related to the presence of high leukocyte counts at initial presentation.

The esophagus has a very low incidence of primary malignant lymphoma (less than 1% of extranodal lymphomas), a lower incidence than any other part of the alimentary tract. A total of 21 cases of primary non-Hodgkin's lymphoma of the esophagus have been reported from Japan (Komatsu et al. 1992; Kurihara et al. 1994), and 3 cases have been reported from Western countries (Pearson and Borg-Grech 1991). In addition, there have been several reports of acquired immunodeficiency syndrome (AIDS)-related primary lymphomas of the esophagus (Radin 1993; Heise et al. 1997).

Macroscopically, primary non-Hodgkin's lymphomas of the esophagus usually form a discrete tumor mass or cause marked mural thickening. Figure 14-6 shows the macroscopic appearance of a primary esophageal non-Hodgkin's lymphoma reported by Kikuchi et al.

In all reported cases for which data are available, the lymphomas have been of diffuse type. The pathological criteria for primary non-Hodgkin's lymphoma of the esophagus include no evidence of a primary lesion elsewhere, no lymphocytic leukemia, and the restriction of lymphadenopathy, if any, to regional lymph nodes.

This author has encountered one autopsy case of esophageal involvement by a non-Hodgkin's lymphoma, which manifested as swelling of systemic lymph nodes and infiltrative foci in the esophageal mucosa (Fig. 14-7). The tumor was classified histologically as a diffuse lymphoma of mixed medium-sized and large cell type

FIG. 14-6. Macroscopic appearance of a primary non-Hodgkin's lymphoma of the esophagus at the time of sectioning after fixation (advanced, predominantly subepithelial type). The esophageal wall is diffusely thickened and shows a characteristic subepithelial tumor

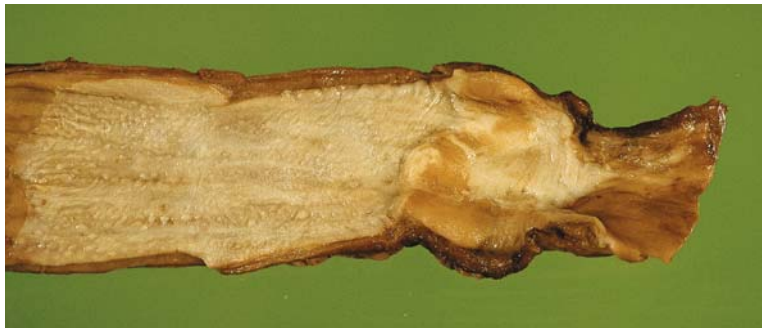


Fig. 14-7. Macroscopic appearance of a non-Hodgkin's lymphoma (advanced, localized and ulcerative type)

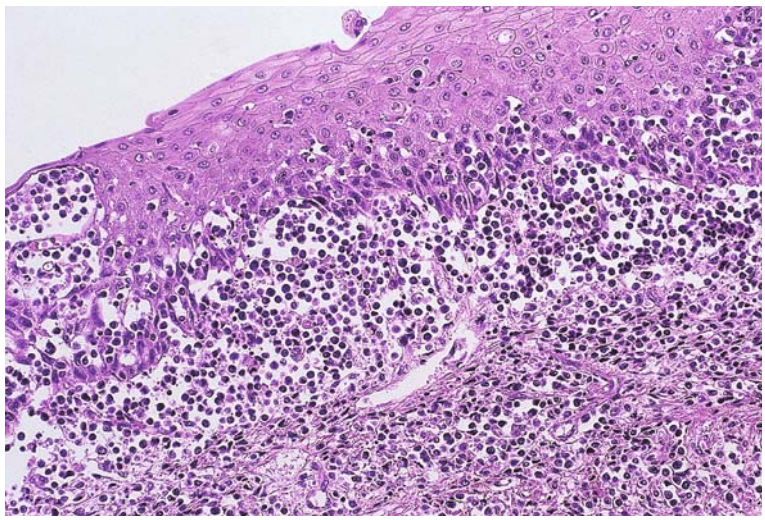


Fig. 14-8. Non-Hodgkin's lymphoma. The tumor cells proliferate within, and elevate, the esophageal epithelium. This is a diffuse lymphoma composed of medium-sized cells

(Fig. 14-8). Malignant lymphomas of the esophagus can be distinguished without difficulty from small cell carcinomas by positive staining for leukocyte common antigen and lack of immunostaining for cytokeratin and epithelial membrane antigen (EMA). Lymphomas are characterized cytologically by the presence of round cells that are dyshesive (Fig. 14-9).

Mycosis fungoides is a type of peripheral T-cell malignant lymphoma that initially arises in the skin and is characterized by a unique process of erythematous (premycotic), mycotic, and tumorous phases. Sézary's syndrome is a variant of mycosis fungoides, characterized by erythroderma with pruritus, and has a leukemic form. Involvement of the gastrointestinal tract has occasionally been reported in both mycosis fungoides and Sézary's syndrome. Esophageal involvement was found at autopsy in 7 of 86 cases of mycosis fungoides in one study; this was much the same as the frequency of involvement of the stomach and other parts of the gastrointestinal tract (Epstein et al.). In 1 reported case of Sézary's syndrome that came to autopsy there was extensive gastrointestinal, including esophageal, involvement (Cohen et al.).

14.3. Hodgkin's Disease

The esophagus is not infrequently involved secondarily in the terminal stages of Hodgkin's disease arising elsewhere, but primary Hodgkin's disease of the esophagus is extremely rare. The frequency of secondary esophageal involvement by Hodgkin's disease is reported to be 5%, according to a review by Surks and Guttman (1966).

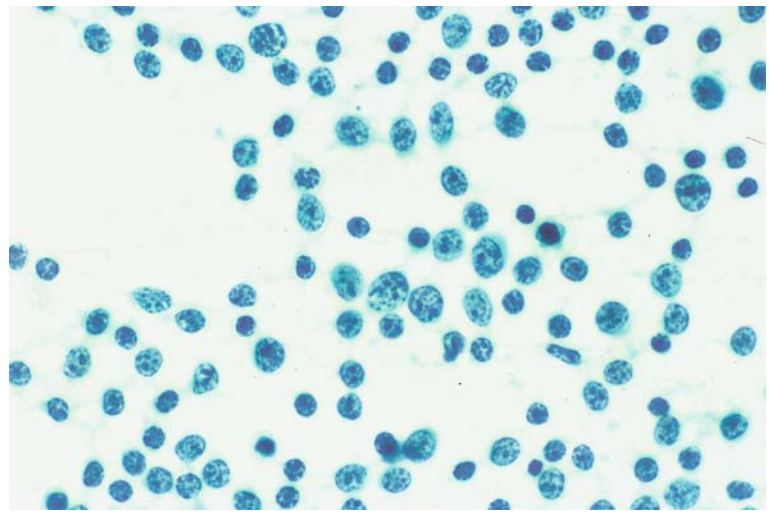


FIG. 14-9. Cytological appearance of a non-Hodgkin's lymphoma (Papanicolaou stain). The tumor is composed of a mixture of medium-sized and large lymphoid cells

As part of a case report of a primary Hodgkin's lymphoma of the esophagus, Stein et al. (1981) reviewed 34 other reported cases. Of these, only 2, including their case, were judged to be examples of primary Hodgkin's lymphoma of the esophagus. The other case had been reported in 1935. More recently, Taal et al. (1993) reported 6 cases of primary Hodgkin's disease of the esophagus. The tumors arose in the lower esophagus in 3 of the 6 cases, and 4 of the 6 patients survived for at least 5 years. Most of the tumors were localized and polypoid, and a few appeared to be submucosal. Three were of the nodular sclerosis subtype.

The 30-year-old man with primary Hodgkin's disease of the esophagus reported by Stein et al. had progressive dysphagia as his chief complaint. The tumor was confined to the wall of the upper esophagus, and there was no mucosal ulcer. Histologically, the tumor showed prominent fibrosis with mixed inflammatory cells and Reed–Sternberg cells and was of nodular sclerosis type. This patient was treated by surgery and radiotherapy and remained well 5 years after presentation.

The cytological features of a case of Hodgkin's disease involving the esophagus have also been reported (Trotman et al.).

14.4. Extramedullary Plasmacytoma of the Esophagus

Although it is said that up to 10% of extramedullary plasmacytomas arise in the gastrointestinal tract (Sharma and Shrivastav 1961), only three cases of primary extramedullary plasmacytoma of the esophagus have been reported (Ahmed et al. 1976; Davies and Boxer 1988; Chetty et al. 2003). Ahmed et al. are considered to have published the first report of a primary plasmacytoma of the esophagus. The patient was a 67-year-old man who had complained of dysphagia and weight loss. The tumor arose in the lower third of the esophagus. There was marked thickening of the esophageal wall, accompanied by ulceration. No metastases were found in the local lymph nodes. The patient was alive 6 months after surgery, but no information about the subsequent course was given. Davies and Boxer described a plasmacytoma of the esophagus that occurred in a 69-year-old man. The tumor was polypoid, measured 4 cm in diameter, and involved the lower third of the esophagus. The third reported case of plasmacytoma of the esophagus occurred in a 58-year-old man (Chetty et al.). The tumor was polypoid with surface ulceration and measured 5 cm in diameter.

14.5. Malignant Granular Cell Tumor

Of all the reported cases of primary granular cell tumor of the esophagus in the literature, nine have been said to have been malignant (Yoshizawa et al. 2004; Isogai et al. 2005). The distinction between benign and malignant granular cell tumors may be difficult, however, and the criteria used for the assessment of malignancy have been unclear in some of the reported cases. An infiltrative growth pattern is not a sufficient criterion for malignancy as this may be seen in benign tumors. Also, the location of the tumor in the esophageal wall is not a reliable indicator of malignancy. Although benign granular cell tumors are usually confined to the lamina propria, cases reported as benign have also involved muscularis mucosae (Gibbons et al. 1980), submucosa (Tune et al. 1981; Patel et al. 1981; Hamada et al. 1994), and adventitia. Metastasis to the liver, lung, pleura, and lymph nodes has occurred from the reported malignant granular cell tumors of the esophagus.

Histological features serving as criteria for malignancy have been considered to be mitotic figures, infiltration into the muscularis propria, vascular permeation, and metastatic foci. The present author considers that at least one of these four features is necessary for a diagnosis of malignancy.

A patient (female, 31 years old) reported by Crawford and De Bakey (1953) had multiple granular cell tumors in various organs before the diagnosis of an esophageal tumor. The esophageal tumor was found to have infiltrated into the trachea and thyroid cartilage. Obiditsch-Mayer and Salzer-Kuntschik reported a case (female, 23 years old) of primary esophageal granular cell tumor that showed prominent tracheal and esophageal infiltration at presentation. Mitotic figures were seen in a tumor from a 70-year-old female patient reported by Ohmori et al. (1987), and both mitotic figures and vascular invasion were seen in a tumor reported by Wyatt et al. (1991).

Another patient (male, 70 years old), reported by Takada et al. (1993), had a polypoid lesion with ulceration in his lower esophagus. This tumor is illustrated in Figs. 14-10 through 14-15. It measured 10 × 5 cm and was mostly covered by squamous epithelium (see Fig. 14-10). The tumor cells invaded as far as the adventitia, but there was no infiltration into neighboring structures, and there were no metastases in lymph nodes or elsewhere. There was vascular permeation, however, indicating that the tumor was malignant. This is presumably the third definite reported case of a primary malignant granular cell tumor of the esophagus, as the possibility of a primary elsewhere had been completely excluded. The patient died of recurrent multiple liver tumors and pleural effusion at the age of 71 (Yoshizawa et al.).

The cut surface was yellow and firm (see Fig. 14-11), with no necrosis or hemorrhage. Histologically, the tumor cells were large, in contrast to those seen in benign granular cell tumors. The tumor cell cytoplasm was more coarsely granular and more strongly eosinophilic than seen in benign granular cell tumors. The nuclei were irregular in size and were atypical, having a few irregular nucleoli. Mitotic figures were present but were infrequent (see Fig. 14-12). In addition, there were tumor cells

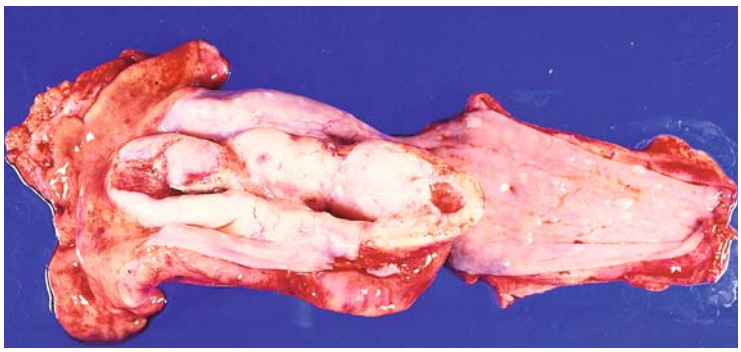


FIG. 14-10. Macroscopic appearance of a malignant granular cell tumor (advanced, ulcerative and localized type)

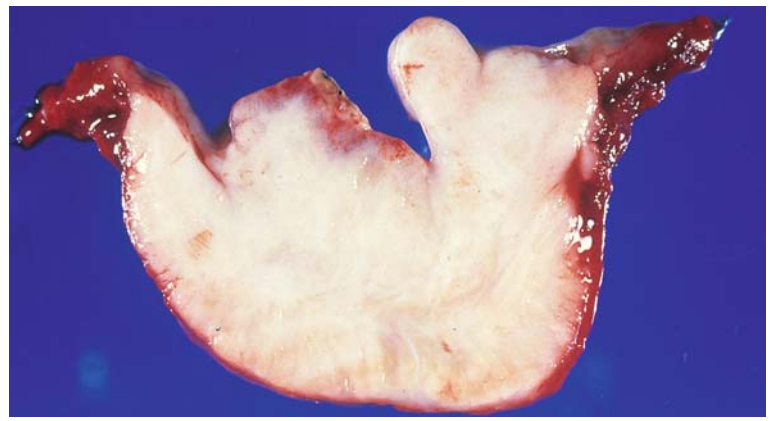


FIG. 14-11. Macroscopic appearance of the cut surface of a malignant granular cell tumor. A yellow and fibrous appearance is evident

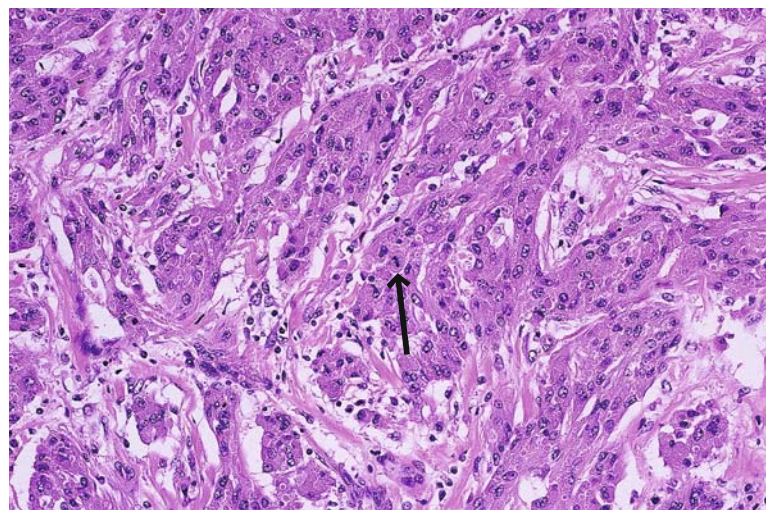


FIG. 14-12. Malignant granular cell tumor. The tumor cells are large with coarse granular and acidophilic cytoplasm. The cell nuclei vary in size and have irregular nucleoli. Mitotic figures are present (*arrow*)

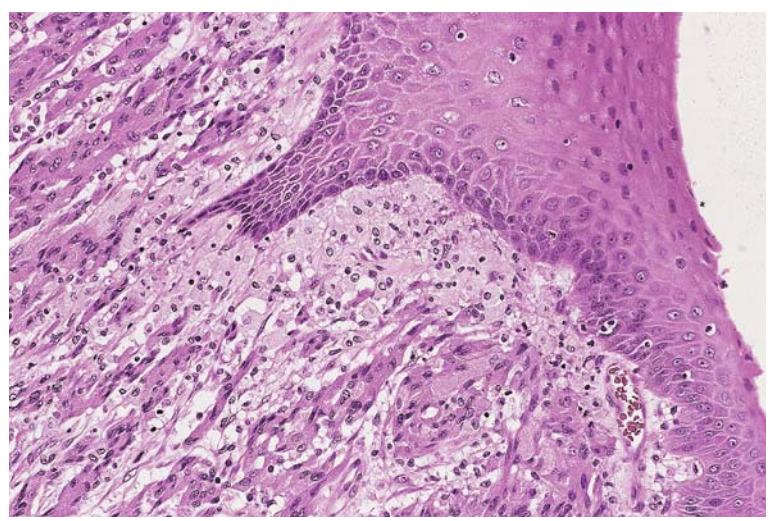


FIG. 14-13. Malignant granular cell tumor. Tumor cells with small nuclei, indistinguishable from the cells of a benign granular cell tumor, are present in the lamina propria just beneath the epithelium

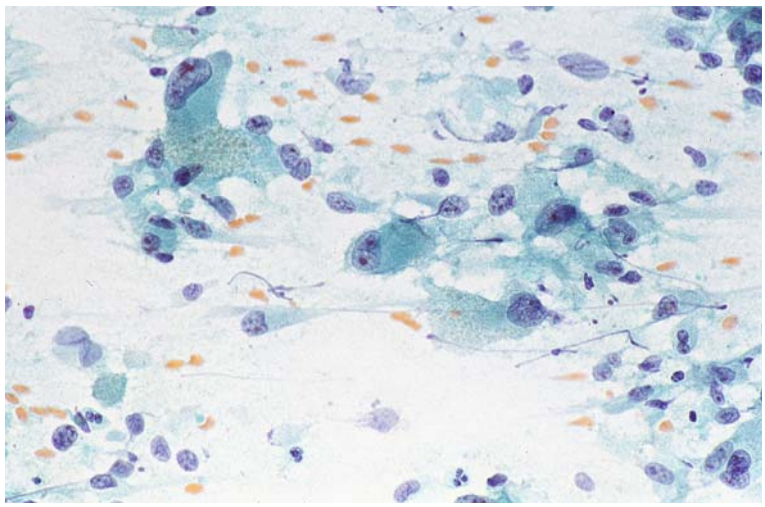


Fig. 14-14. Cytological appearance of a malignant granular cell tumor (Papanicolaou stain). Large cells with acidophilic granular cytoplasm are dispersed singly and in small cohesive groups. They have very pleomorphic nuclei, and some are multinucleate

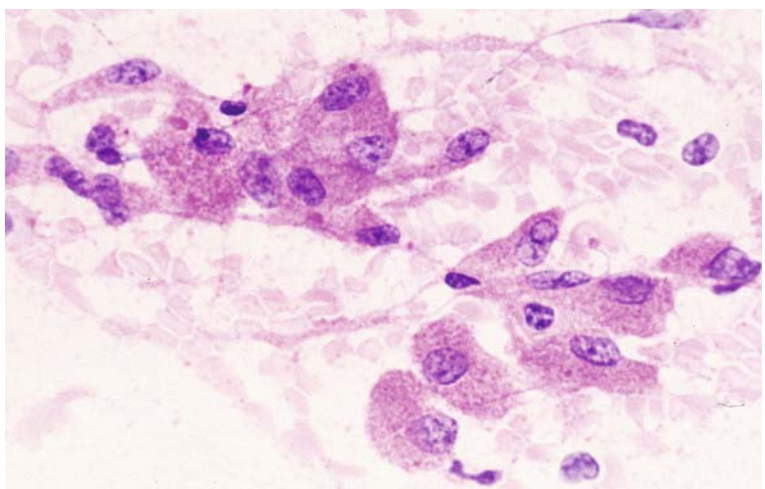


Fig. 14-15. Cytological appearance of a malignant granular cell tumor (periodic acid–Schiff stain). The cytoplasmic granules are PAS positive and diastase resistant

with small nuclei, indistinguishable from the cells of a benign granular cell tumor, in the lamina propria just beneath the epithelium, suggesting that there had been malignant transformation of a benign granular cell tumor (see Fig. 14-13). Pseudoepitheliomatous hyperplasia and atrophy were found in various areas of the overlying epithelium.

As to the cytological features, the large tumor cells with acidophilic granular cytoplasm were dispersed singly and in small groups. Nuclei were very pleomorphic, and some multinucleate tumor cells were seen. There were large nucleoli, some of which had a surrounding halo (see Fig. 14-14). The cytoplasmic granules were PAS positive and diastase resistant (see Fig. 14-15).

14.6. Malignant Neurogenic Tumor

The only case of a malignant neurogenic tumor of the esophagus that the present author has encountered occurred in a 60-year-old man. The tumor was submucosal and formed a broad, pedunculated polyp. It was soft, measured 4.5 cm in diameter, and had a yellowish-white cut surface. Histological examination demonstrated spindle

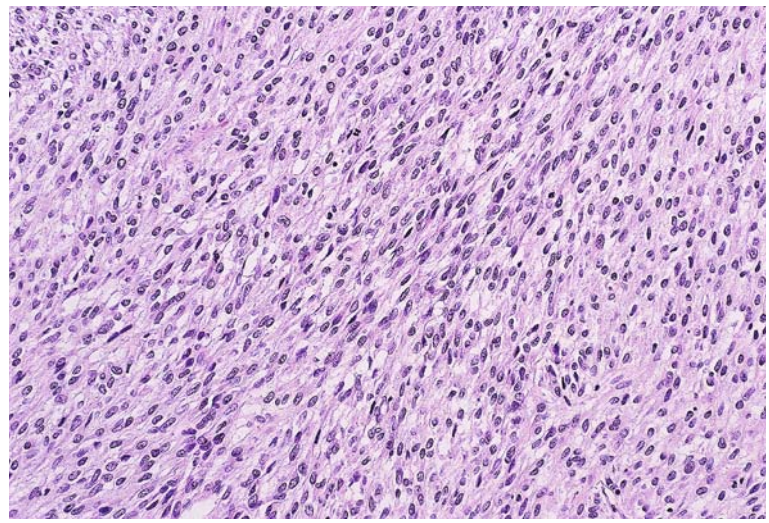


Fig. 14-16. Malignant neurogenic tumor. The tumor consists predominantly of spindle cells

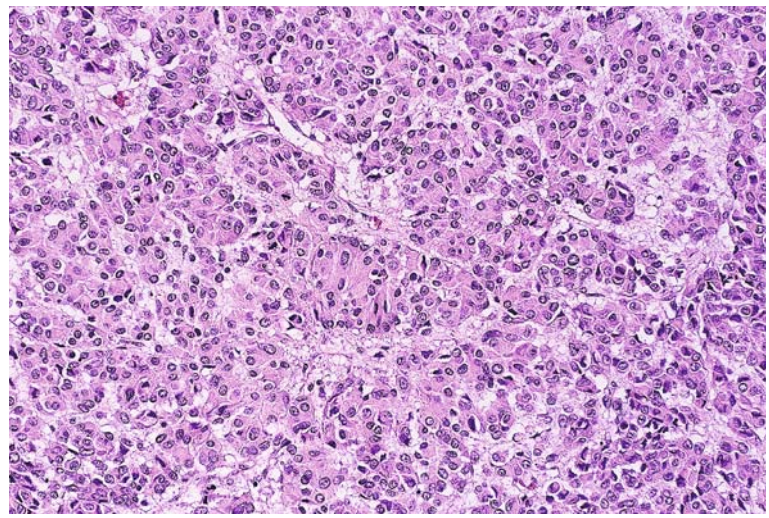


Fig. 14-17. Malignant neurogenic tumor (same case as Fig. 14-16). There is an epithelioid pattern in some areas

cells (Fig. 14-16) and occasionally an epithelioid pattern (Fig. 14-17). There were 16 mitoses per 10 high-power (×200) fields, and the tumor cells were positive for S-100 protein.

A 57-year-old woman with a polypoid tumor that reportedly had histological features of a malignant neurilemmoma has also been reported (Caldwell et al. 1991). This tumor was located in the lower esophagus.

Murase et al. (2001) reviewed 19 cases of schwannoma of the esophagus, including 3 cases of malignant schwannoma. Lymph node metastasis was noted in one of the cases of malignant schwannoma.

14.7. Liposarcoma

Ten cases of primary liposarcoma of the esophagus have been reported (Sunagawa et al. 2003). One of these, reported by Mansour et al. (1983), was a pedunculated tumor of the cervical esophagus that occurred in a 53-year-old man. The patient presented with progressive dysphagia and died 12 months after surgery. The tumor measured 3 × 4 cm and had a protruding polypoid appearance macroscopically. Histologically, it was a myxoid liposarcoma and was covered by flat stratified squamous epithelium.

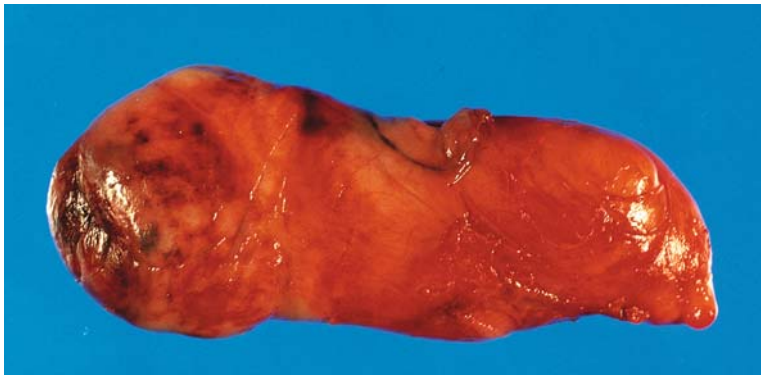


Fig. 14-18. Macroscopic appearance of an esophageal liposarcoma

Another case was reported by Masumori et al. (1991). The patient was a 46-year-old woman. Figure 14-18 shows the macroscopic appearance of the tumor, which was of protruding polypoid type and was located in the cervical esophagus. The resected tumor measured 11 × 4 × 3 cm, and the cut surface was yellow and brown. It was covered by squamous epithelium and histologically was a well-differentiated liposarcoma.

14.8. Angiogenic Sarcoma

There have been several case reports of primary angiogenic sarcoma of the esophagus. Two cases of primary hemangioendothelioma and two cases of primary lymphangioendothelioma of the esophagus were reported by Palanker et al. in 1951. More recently, another case of primary malignant hemangioendothelioma of the esophagus was reported by Llombart-Bosch et al. (1981). The patient was a 42-year-old man who had metastases to mediastinal lymph nodes and died within 2 months of surgery. In this report, both the histological and ultrastructural features of the tumor were described. The tumor cells contained rod-shaped Weibel–Palade bodies, the ultrastructural characteristic of vascular endothelial cells.

There have also been two cases of primary hemangiopericytoma of the esophagus reported. One of these, reported by Fisher (1960), occurred in an 81-year-old woman; the tumor metastasized, and the patient died after radiotherapy. The other, reported by Burke and Ranchod (1981), occurred in a 32-year-old man who was still alive more than 16 months after surgery.

14.9. Rhabdomyosarcoma

According to a report by Vartio et al. (1980), the first reported case of an esophageal rhabdomyosarcoma was by Wolfensberger in 1894. Willén et al. (1989) reviewed 13 cases of primary rhabdomyosarcoma of the esophagus. The male : female ratio was 9 : 3 (sex not specified in 1 case). The major symptoms were dysphagia and odynophagia, and the patient age ranged from 27 to 81 years (mean, 61 years). The tumors were located in the upper esophagus in 1 case, mid-esophagus in 5 cases, and lower esophagus in 6 (unclear in 1 case). Survival for more than 1 year was documented in only 3 of the cases. Macroscopically, 7 of the tumors were polypoid and 5 were ulcerative (the macroscopic appearance was unclear in 1 case). A further case of primary esophageal rhabdomyosarcoma, which occurred in a 55-year-old man, was added by Chetty et al. (1991).

Rhabdomyosarcomas consist of highly pleomorphic cells. Cross-striations were found in the cytoplasm of tumor cells by light microscopy in only 6 of the foregoing 13 cases. Electron microscopy of some recently reported cases has demonstrated Z-banding, a feature of striated muscle cells. In the case reported by Willén et al., the tumor was positive with immunohistochemical stains for desmin, vimentin, and myoglobin.

Rhabdomyosarcomas of the esophagus are thought to arise from undifferentiated mesenchymal cells rather than striated muscle cells, which helps to explain why the reported tumors have been located mainly in the mid- and lower third of the esophagus, where striated muscle fibers are

scarce. It is also possible that rhabdomyosarcomas may sometimes arise by overgrowth of the rhabdomyosarcomatous component of an esophageal carcinosarcoma that has rhabdomyosarcoma as part of its sarcomatous component.

14.10. Osteosarcoma

Only one case of a primary osteosarcoma of the esophagus has been reported, by McIntyre et al. (1982). The patient was a 70-year-old man who died of other disease 3 months after surgery. In this case, there was a polypoid tumor that measured $13 \times 13 \times 5$ cm in the lower esophagus. Histologically, there was prominent proliferation of spindle cells, osteoid formation, and absence of an epithelial component.

14.11. Kaposi's Sarcoma

A Kaposi's sarcoma of the esophagus, which occurred in a 23-year-old Zambian man, was reported in 1980, with detailed esophagographic data (Umerah). This patient also had dermal lesions. The esophageal lesions were described as multiple, with very extensive spread throughout the wall.

One study of 34 AIDS cases from Japan found Kaposi's sarcoma of the esophagus at autopsy in 2 of the 34 (Yamada et al. 1994). In both these cases the patients had had endoscopically evident Kaposi's sarcomas of the stomach during life, but neither had had endoscopic evidence of esophageal disease.

The histological features of Kaposi's sarcoma of the esophagus are the same as those of Kaposi's sarcoma occurring elsewhere; the tumor consists of narrow intercellular spaces containing erythrocytes and a proliferation of spindle-shaped cells that show little atypia (Figs. 14-19, 14-20).

14.12. Synovial Sarcoma

A survey of the literature has revealed seven reported cases of primary synovial sarcoma of the esophagus. The patients have included a 75-year-old woman (Palmer et al. 1983), a 25-year-old man (Amr et al. 1984), a 15-year-old boy (Bloch et al. 1987; Perch et al. 1991), a 29-year-old woman (Caldwell et al. 1991), a 14-year-old girl (Antón-Pacheco et al. 1996), a 20-year-old man (Habu et al. 1998), and a 63-year-old woman (Bonavina et al. 1998). Also, a case of synovial sarcoma that arose in paraesophageal tissue in a 24-year-old man has been reported (Pulpeiro et al. 1988), as has a case of synovial sarcoma that arose at the esophagogastric junction in a 47-year-old man (Billings et al. 2000).

For the first seven cases mentioned above, the postoperative follow-up period extended for more

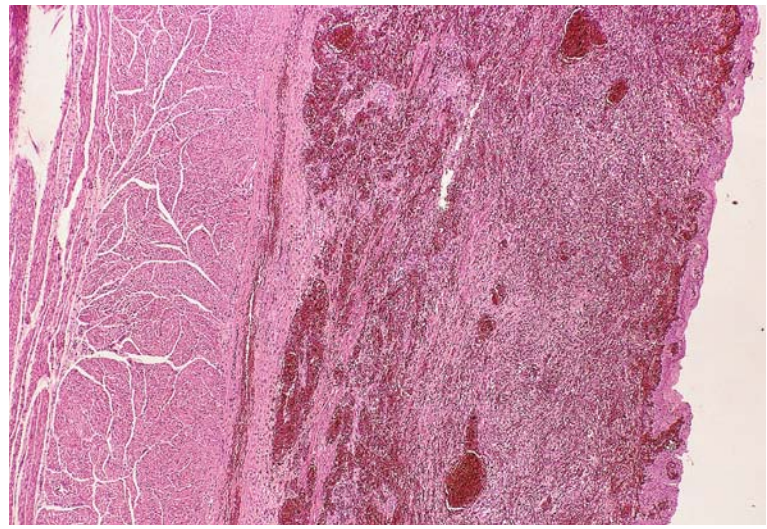


FIG. 14-19. Kaposi's sarcoma of the esophagus. The tumor is seen beneath the esophageal epithelium

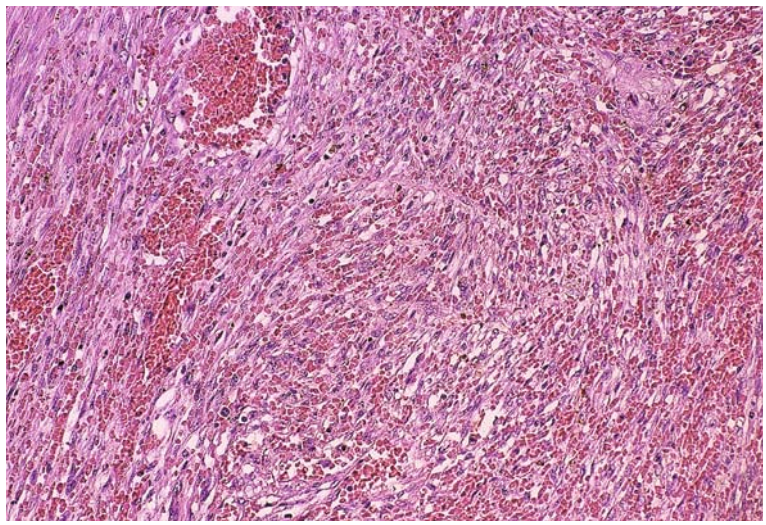


FIG. 14-20. Kaposi's sarcoma of the esophagus. High-magnification view of Fig. 14-19, showing proliferating spindle-shaped cells with erythrocytes in the intercellular spaces

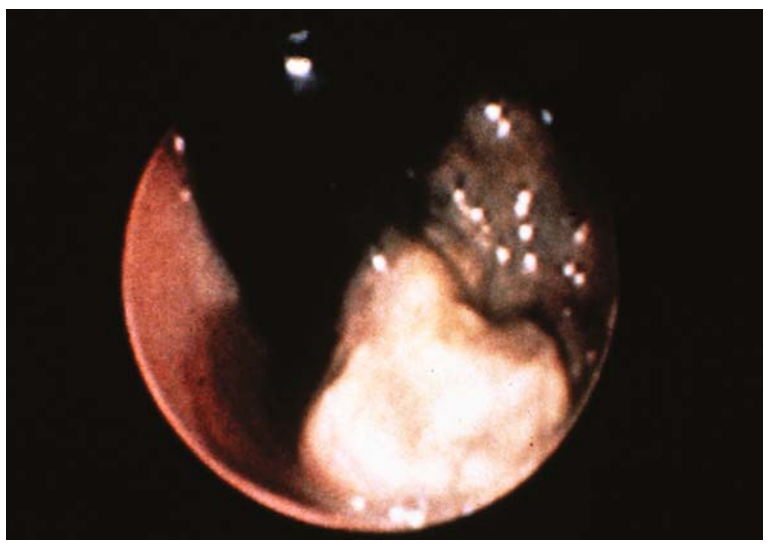


FIG. 14-21. Endoscopic appearance of a synovial sarcoma of the esophagus. A huge polypoid tumor occupies the esophageal lumen

than 1 year in two cases, for more than 2 years in one case, and for more than 3 years in three cases; the remaining patient died within 2 years. Six of the tumors occurred in the cervical or upper esophagus and the seventh occurred in the lower esophagus. These tumors mostly formed large polypoid masses, which measured up to 10 cm in diameter (Figs. 14-21, 14-22).

Synovial sarcomas of the esophagus have the same histological features as those that occur elsewhere, showing a biphasic pattern in which a cuboidal epithelioid component, proliferating in a ductlike manner, is surrounded by a fibrosarcomatous component (Figs. 14-23, 14-24). This author has reviewed two cases of synovial sarcoma of the esophagus, and both tumors had a similar biphasic pattern. One of these two was recently reported by Habu et al. (1998) as the sixth reported case. Figures 14-21 through 14-24 show the endoscopic, macroscopic, and histological features of the case reported by Habu et al.

As to the histogenesis of synovial sarcoma arising in the esophageal wall, where synovial tissue is normally absent, theories have included

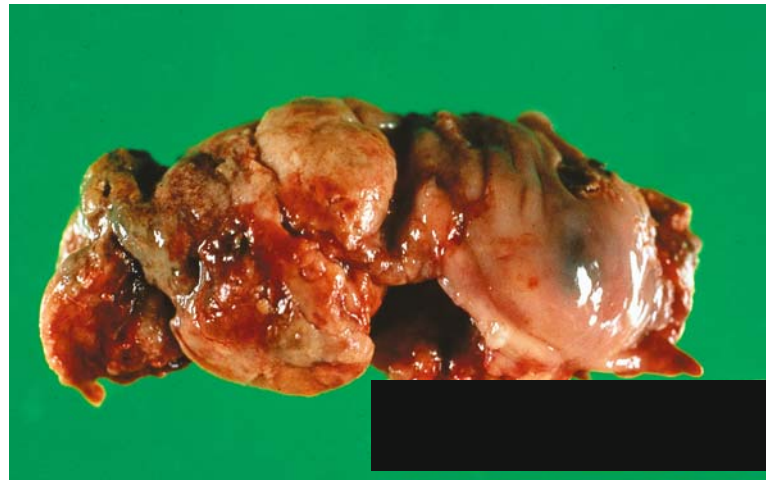


Fig. 14-22. Macroscopic appearance of a synovial sarcoma

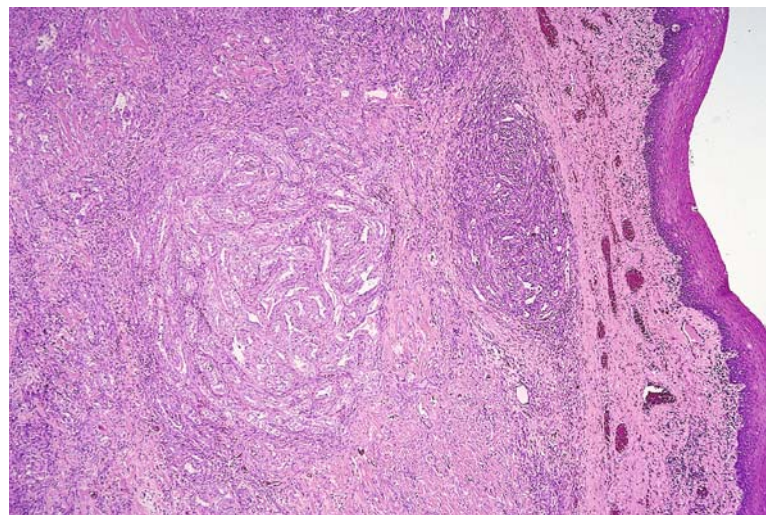


Fig. 14-23. Synovial sarcoma. The tumor has a biphasic pattern and consists of an epithelioid component surrounded by a sarcomatous component

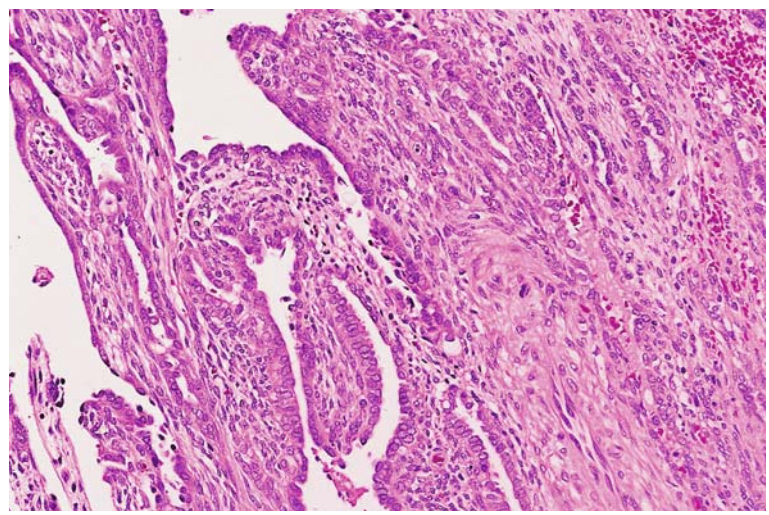


Fig. 14-24. Synovial sarcoma. There is a biphasic pattern in which a cuboidal epithelioid component, proliferating in a ductlike manner, is surrounded by a fibrosarcomatous component

synovioblastic differentiation of mesenchymal cells in connective tissue and origin from local undifferentiated mesenchymal cells.

14.13. Malignant Triton Tumor

One case of a malignant triton tumor arising in the esophagus has been described, in a textbook on the pathology of the esophagus (Enterline and Thompson 1984). This case is also referred to in a report published in 1985. The patient was a 22-year-old man who had complained of dysphagia and weight loss. The tumor was located over a broad area from the cervical to the upper thoracic esophagus and was a polypoid mass attached by a wide base to the esophageal wall. The resected tumor measured 8 cm in diameter and was found to have the histological features of a malignant schwannoma with rhabdomyoblastic differentiation. At the time of the original report, this patient had had a recurrence-free survival of more than 23 months after incomplete resection and radiotherapy; he was later reported to be alive and well, 7 years following treatment (Perch et al. 1991).

14.14. Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the human gastrointestinal tract, but they are rare in the esophagus. A report from the United States (Tran et al. 2005) indicated that 1% to 3% of GISTs arose in the esophagus. Iwashita et al. (2001) reviewed 105 Japanese cases of GIST of the esophagus and did not encounter a single primary esophageal case. Fukushima et al. (2006) reviewed 17 Japanese cases of primary GIST of the esophagus and rapid accumulation of the case reports is observed.

A radiation induced GIST of the esophagus has been reported (Miller et al. 2000).

GIST is considered to arise from the interstitial cells of Cajal, or their precursors, in the wall of the gastrointestinal tract. There is expression of the tyrosine kinase receptor Kit in most GISTs. Most GISTs show a mutation at exon 11 of c-*kit*, but some show a mutation at exon 9 and/or 13.

Most GISTs stain positive for CD34 and overexpress c-*kit* oncoprotein (CD117). The distinction of GISTs from other tumors is very important, not only because GISTs have a high risk of malignant behavior, also because they are usually responsive to a targeted molecular therapy STI-571 (imatinib mesylate).

Macroscopically, GISTs are gray white on cut section. Necrosis, hemorrhage, and ulceration may be seen in the high-risk type. Histologically, they consist of a spindle cell proliferation and have a similar appearance to GISTs elsewhere in the gastrointestinal tract. They are classified into low-, intermediate-, and high-risk groups on the basis of the mitotic index of the tumor cells (Fletcher et al. 2002). Small GISTs (less than 2 or 5 cm in diameter) with a low mitotic index have a good prognosis.

No reports discussing the specific histological or clinical features of primary GISTs of the esophagus have been published.

14.15. Fibrosarcoma

One case of a fibrosarcoma arising in the esophagus has been reported (Lin et al. 1995).

14.16. Malignant Rhabdoid Tumor

Two cases of malignant rhabdoid tumor of the esophagus have been reported (Ng et al. 2003).

14.17. Extraskeletal Ewing's Sarcoma

One case of esophageal Ewing's sarcoma, which occurred in a 56-year-old man, has been reported (Maesawa et al. 2002). The tumor was a nodular mass, $34 \times 20 \times 18$ cm.

Chapter 15
Carcinosarcoma and Pseudosarcoma

15.1. Carcinosarcoma and Pseudosarcoma

Tumors consisting of carcinomatous and sarcoma-like components are called carcinosarcomas. The first case of a carcinosarcoma of the esophagus was reported by von Hansemann in 1904, although carcinosarcomas of other organs had been reported earlier. As early as 1938 Saphir and Vass discussed the development of the sarcoma-like component and referred to the term sarcomatoid carcinoma. The term pseudosarcoma was first used in relation to the esophagus by Stout and Lattes (1957). They concluded that the sarcoma-like component was the result of a benign stromal reaction, even though it appeared histologically to be malignant. A large number of such cases have been reported, and carcinosarcoma and pseudosarcoma account for 0.3% to 2.3% of all reported primary esophageal malignancies.

The prevailing view is that carcinosarcoma and pseudosarcoma fall into the same category. Although there are still unanswered questions, the idea that the sarcoma-like component represents mesenchymal transformation or spindle cell metaplasia (mesenchymal metaplasia) of the epithelial component is becoming the consensus view, as stated in many reports.

These tumors are considered to grow more rapidly than usual squamous cell carcinomas; for example, the doubling time was 2.2 months in one reported case (Sasajima et al. 1988). The 3-year survival of patients with esophageal carcinosarcomas in one series, however, was 68%, higher than the survival rate for patients with squamous cell carcinomas (Iyomasa et al.).

Two cases of granulocyte colony-stimulating factor producing carcinosarcoma of the esophagus have been reported (Oshiro et al. 1999). A case of esophageal carcinosarcoma with intramural metastasis was reported (Sanada et al. 2006).

15.2. Macroscopic Features

Almost all reported cases of carcinosarcoma have been macroscopically polypoid, rarely with accompanying macroscopic ulceration (Iyomasa et al.) (Figs. 15-1 through 15-3). Hamabe et al. (1985) reported that 93% of a series of 67 carcinosarcomas were polypoid macroscopically. A broad adjacent carcinomatous portion may occasionally be ulcerated, forming a complex macroscopic appearance. Macroscopic examination occasionally reveals the presence of an intraepithelial carcinoma or a superficially invasive carcinoma around the tumor base on the esophageal wall. In a series of 102 esophageal carcinosarcomas reported by Kitagawa et al. (1989), 54% occurred in the midesophagus, 34% in the lower esophagus, and 8% in the upper esophagus.

15.3. Microscopic Features

Both carcinomatous and sarcoma-like components may be found in metastatic foci in lymph nodes and other organs. The fact that sarcoma-like components are often seen in lymph node metastases has long been considered a reasonable basis for the view that these components are neoplastic and malignant.

Also, there have been some cases in which the histological features of carcinosarcoma were only

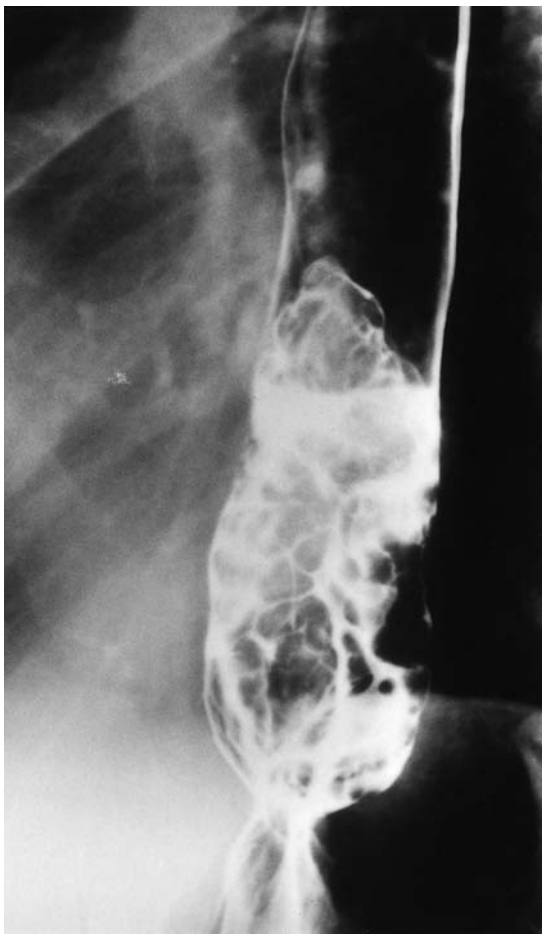


FIG. 15-1. Esophagogram from a patient with an esophageal carcinosarcoma

evident in metastatic foci, with the primary tumor being a squamous cell carcinoma (Terada et al. 1990).

In biopsy specimens, the sarcoma-like cells sometimes stain weakly positive with Alcian blue, indicating a need for caution when trying to distinguish this entity from poorly differentiated adenocarcinoma. There is often a thick necrotic layer overlying the tumor in biopsy specimens (Figs. 15-4, 15-5).

Epithelial dysplasia has been found in a few cases in mucosa in the vicinity of carcinosarcomas (Matsusaka et al. 1976; Takubo et al. 1982). The reported carcinomatous components in esophageal carcinosarcomas have included squamous cell carcinoma (Figs. 15-6, 15-7), basaloid squamous carcinoma (Fig. 15-8), adenocarcinoma, and neuroendocrine carcinoma (Kanamoto et al. 2000). Histologically, squamous cell carcinoma in situ with or without early stromal invasion is very often found in mucosa around the tumor base.

In the 8th and 9th editions of the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*, published in Japan, it was proposed that "carcinosarcoma" be further classified into so-called carcinosarcoma, pseudosarcoma, and true carcinosarcoma. If the sarcomatous component has foci showing muscular, cartilaginous, or osseous differentiation (Fig. 15-9), the tumor is regarded as a true carcinosarcoma. In addition,

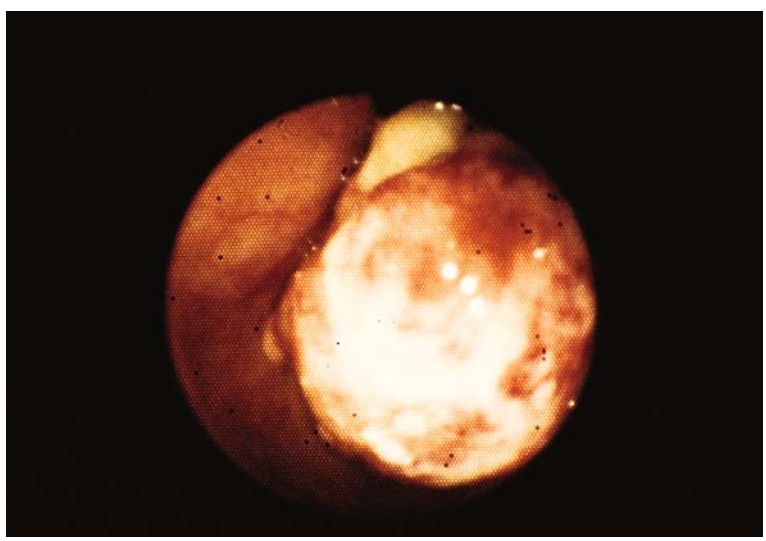


FIG. 15-2. Esophagoscopic appearance of an esophageal carcinosarcoma

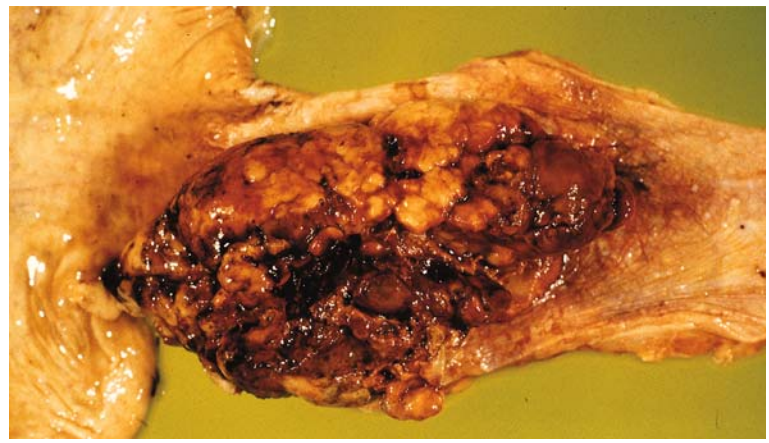


FIG. 15-3. Macroscopic appearance of a carcinosarcoma (advanced protruding polypoid type)

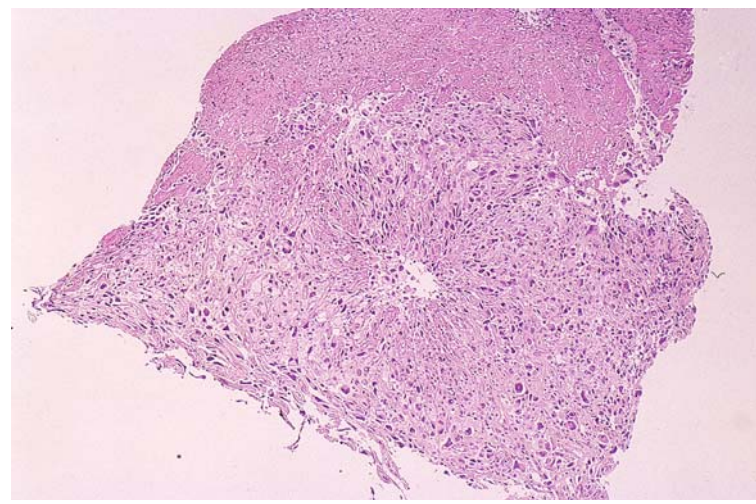


FIG. 15-4. Biopsy specimen of a carcinosarcoma. There is a thick necrotic layer overlying the sarcoma-like component

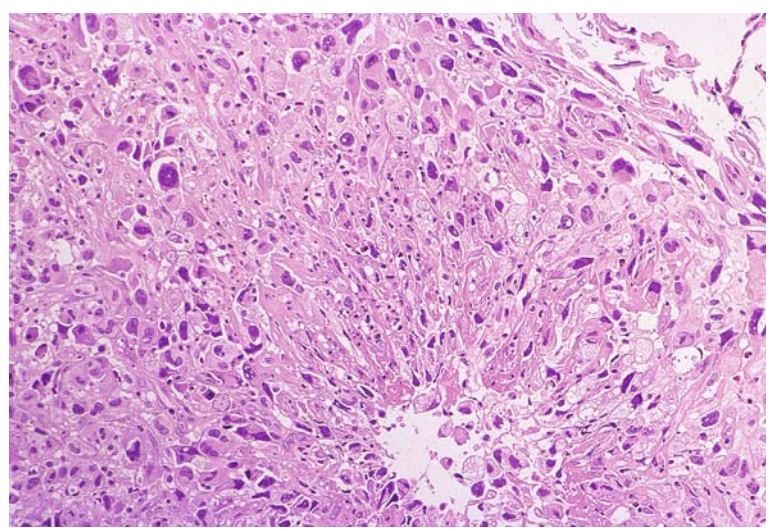


FIG. 15-5. High-magnification view of Fig. 15-4. The sarcoma-like component consists of bizarre giant cells

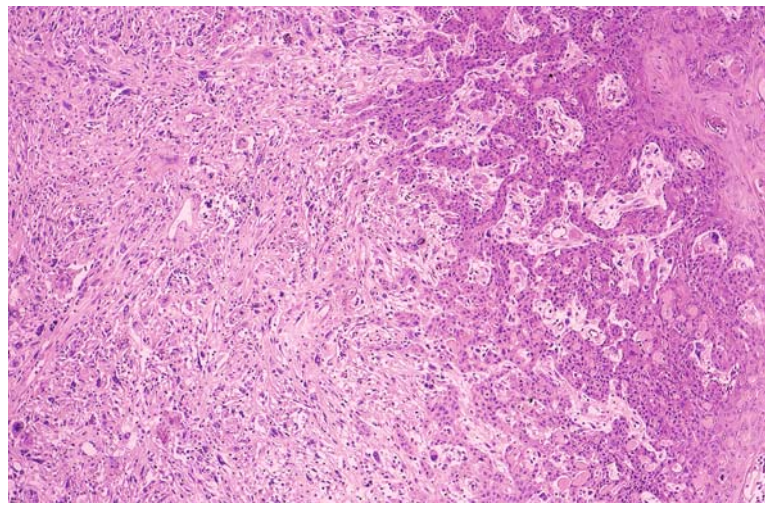


Fig. 15-6. Carcinosarcoma. An area of transition between well-differentiated squamous cell carcinoma and sarcoma-like tissue

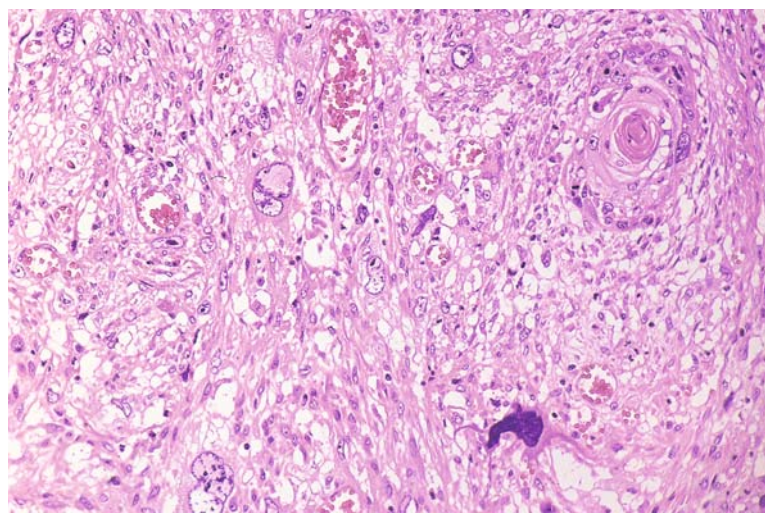


Fig. 15-7. Carcinosarcoma. A nest of well-differentiated squamous cell carcinoma is seen within sarcoma-like tissue

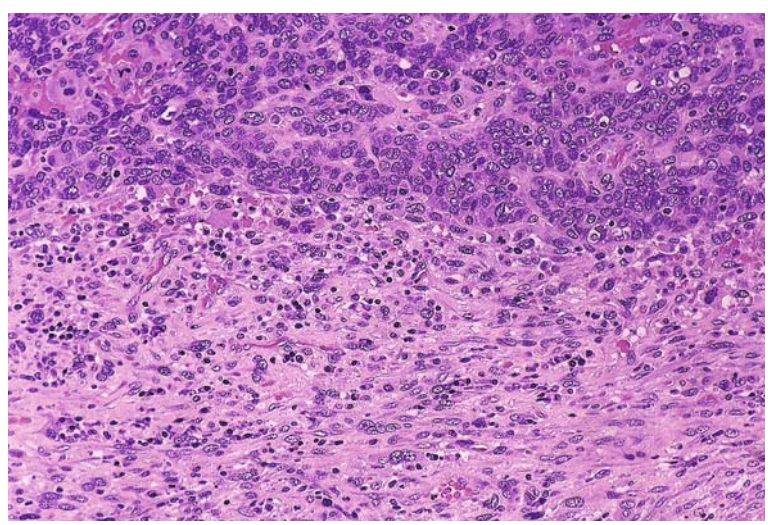


Fig. 15-8. Carcinosarcoma. Basaloid squamous carcinoma and sarcoma-like tissue are evident

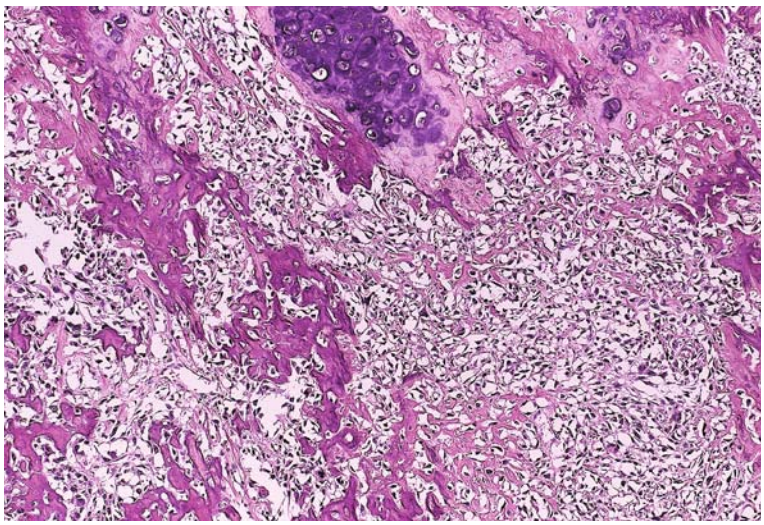


Fig. 15-9. Sarcoma-like component of carcinosarcoma. Osteoid and cartilaginous tissue are present in the sarcoma-like component

the sarcoma-like component may take the form of a malignant fibrous histiocytoma or a fibrosarcoma. When there are areas of transition between the carcinomatous and sarcoma-like components (see Fig. 15-6), or when the sarcoma-like component stains positively for epithelial markers (e.g., keratin, epithelial membrane antigen), the tumor is classified as a so-called carcinosarcoma. When the stromal component has no atypical cells and has few mitoses (i.e., shows no evidence of malignancy), the tumor is classified as a pseudosarcoma (this is not pseudosarcoma in the sense described by Stout and Lattes). The present author, however, has not encountered any such cases of pseudosarcoma as so defined, and this entity may in fact be a carcinoma arising in association with an inflammatory fibroid polyp or a fibrovascular polyp.

Also, although so-called carcinosarcoma has transitional areas between the carcinomatous and sarcoma-like components, the sarcoma-like component often stains negatively for epithelial markers. There is, therefore, controversy regarding these three subtypes of "carcinosarcoma." In this author's experience, cells in the sarcoma-like component that are positive for epithelial markers are generally polygonal, rather than spindle shaped, and often resemble epithelial cells. In addition, there have been conflicting reports about the staining reactions of the sarcoma-like components with epithelial markers, some studies reporting positive results (Gal et al.) and others negative results (Linder et al.; Wang et al.). Moreover, with regard to true carcinosarcomas, which contain foci of rhabdomyosarcoma, osteosarcoma, or chondrosarcoma in the sarcomatous component, histological transition has been reported between spindle cell sarcoma-like tissue, which surrounds foci of osteosarcoma or chondrosarcoma, and the carcinomatous component (Matsui et al. 1995).

In this regard, the present author currently groups these tumors collectively as carcinosarcomas, without further classification, but specifies the histological types of carcinomatous and sarcoma-like components, and comments on the presence or absence of transitional areas. The subclassification of carcinosarcomas proposed in the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* (8th and 9th editions), as already detailed, represents a problem that requires further consideration.

15.4. Cytological Features

In cytological smears of carcinosarcoma the epithelial component, if present in the specimen, shows the same cytological features as those seen in usual squamous cell carcinoma (Fig. 15-10). The sarcoma-like component, however, occurs as

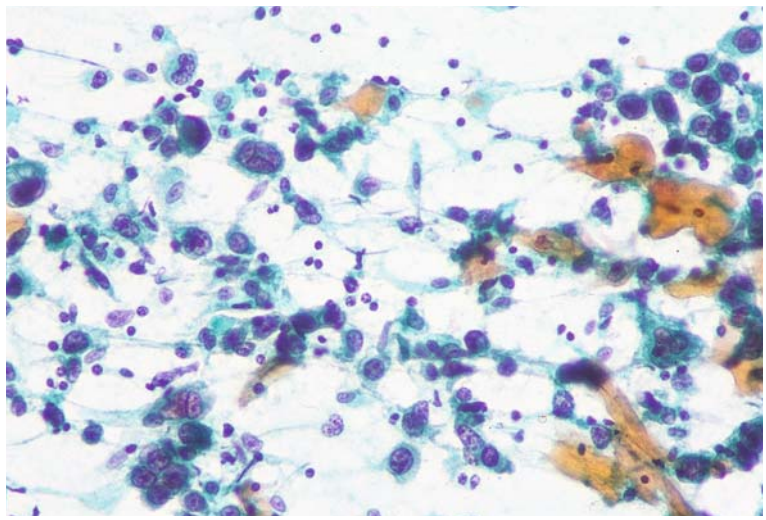


FIG. 15-10. Cytological appearance of a carcinosarcoma (Papanicolaou stain). Bizarre sarcoma-like cells and keratinizing malignant squamous cells are evident. Multinucleate giant cells are also present

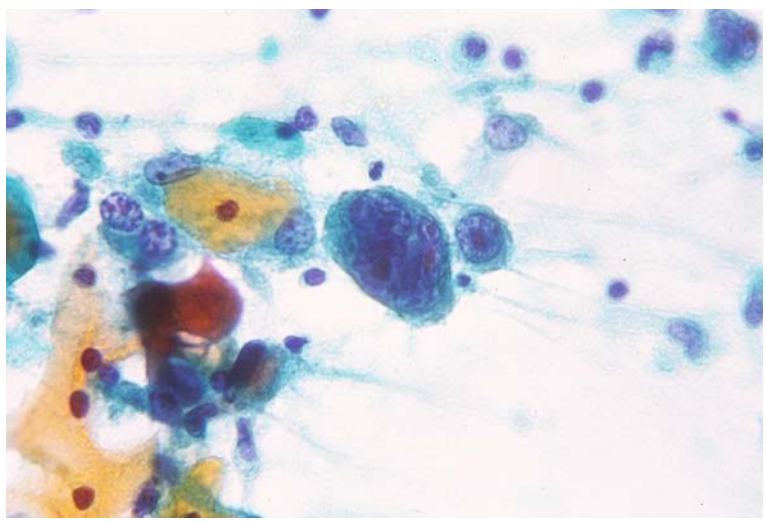


FIG. 15-11. Cytological appearance of a carcinosarcoma (Papanicolaou stain). Multinucleate sarcoma-like cells and keratinizing malignant squamous cells are evident. Perinucleolar haloes are seen in the nuclei of multinucleate sarcoma-like cells

irregular clusters of cells and scattered singly dispersed cells. The sarcoma-like cells are often very large and spindle shaped or polygonal (see Figs. 15-10, 15-11). They are rather thick, and stain light green with the Papanicolaou stain, occasionally appearing to have fibrous material in their cytoplasm. The nuclei are round or oval and highly variable in size, and there is uneven thickening of nuclear membranes. Many multinucleate and mononuclear giant cells are seen. Granular or coarse chromatin is distributed unevenly, and intranuclear pseudoinclusion bodies, resulting from invaginations of the cytoplasm, are occasionally found. Nucleoli are irregular in shape and size, and sometimes have surrounding haloes. The cytological appearance of the sarcoma-like component is that of an extremely pleomorphic sarcoma, and the sarcoma-like cells alone provide no features to suggest a diagnosis of carcinosarcoma (Fig. 15-12), but when the aforementioned cells are seen in cytology specimens from a polypoid tumor of the esophagus, it may be considered that the tumor is very likely to be a carcinosarcoma.

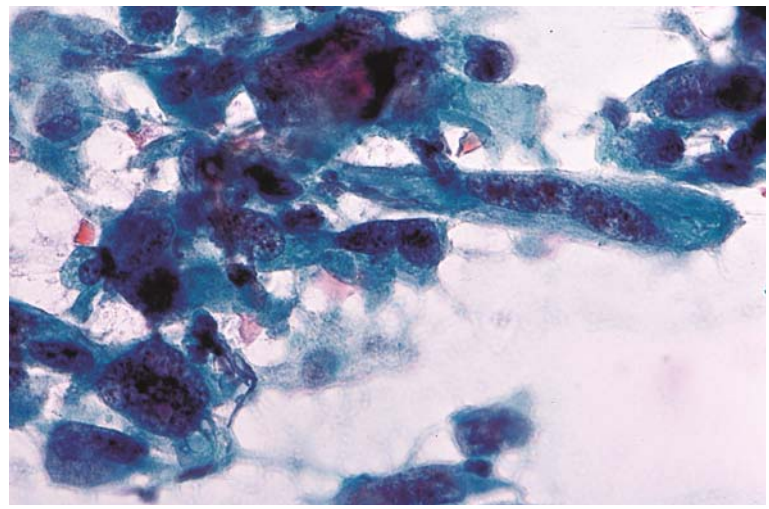


Fig. 15-12. Cytological appearance of a carcinosarcoma (Papanicolaou stain). The cytoplasm of a spindle shaped cell appears to contain fibrous material

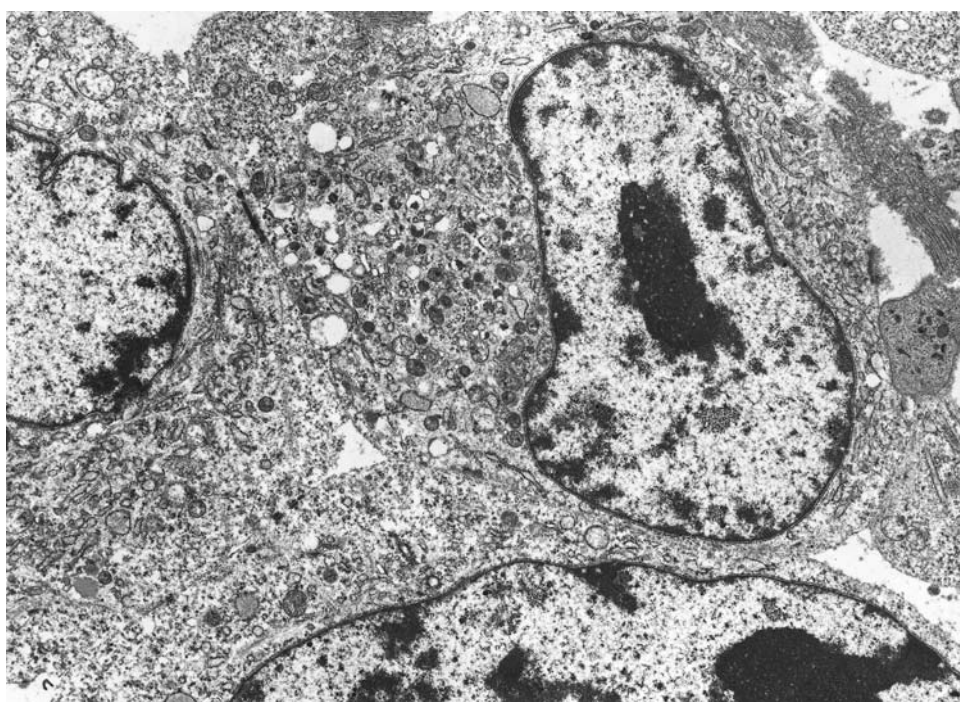


Fig. 15-13. Electron micrograph of a carcinosarcoma. Desmosome-like structures are evident between the tumor cells

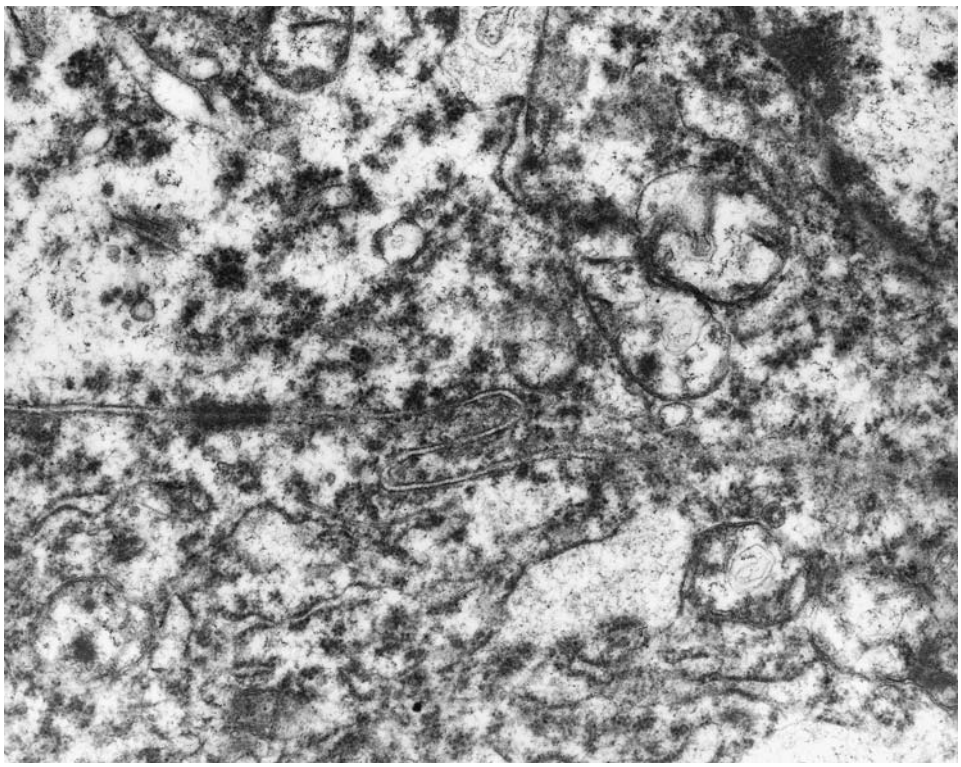


Fig. 15-14. Electron micrograph of a carcinosarcoma. A desmosome-like structure is evident

15.5. Ultrastructural Features

Some reports on carcinosarcoma of the esophagus have referred to ultrastructural evidence of desmosomes between or within tumor cells in the sarcoma-like tissue, suggesting that these cells have arisen from epithelium, but the electron micrographs published in such reports have rarely shown well-developed desmosomes. As poorly developed desmosome-like structures may sometimes also be seen between mesenchymal cells, electron micrographs of carcinosarcomas should be taken at a sufficiently high magnification to allow careful observation of the cell junctions. The tumor cells contain smooth or rough endoplasmic reticulum, but have few keratin filaments. This author has not found any basement membrane material around the sarcoma-like cells in cases that he has examined (Figs. 15-13, 15-14).

Chapter 16
Malignant Melanoma and Related Entities

16.1. Malignant Melanoma of the Esophagus

Although primary malignant melanoma of the esophagus is even less common than carcinosarcoma of the esophagus, this entity has become relatively well understood. More than 300 case reports have been published in the literature since 1906, including 193 cases from Japan (Baur 1906; Kreuser 1979; Guzman et al.; Sabanathan and Eng 1990; Yamaguchi et al. 2004). Esophageal malignant melanoma occurs about twice as frequently in men as in women (2.2:1), and the mean age is 60.4 years (Yamaguchi et al.). The tumors have been reported to be located in the mid- and lower esophagus in 86% of cases (Chalkiadakis et al. 1985). The prognosis was previously considered to be extremely poor. From earlier papers, the only reported case of long-term survival was one in which the tumor had reached the submucosa but had not metastasized to lymph nodes (Matsubara et al.), and Caldwell et al. reported 8 patients with malignant melanoma of the esophagus, none of whom survived for more than 4 years. Recent papers, however, have reported a much better prognosis. Volpin et al. (2002) reported a 5-year survival of 37% in 25 surgically resected cases between 1989 and 2000. In 72 Japanese cases from 1993 to 2003, Yamaguchi et al. reported a 5-year survival of 31%; 59% of the 72 tumors were in stages 0, I, or II, and the authors considered that the better prognosis was the result of their relatively early detection. The overall survival and stage survival rates reported by Yamaguchi et al. (2004) are shown in Figs. 16-1 and 16-2. In the series by Yamaguchi et al. there was no significant difference in outcome between patients who had, or had not, been given preoperative radiotherapy.

Macroscopically, primary malignant melanomas of the esophagus frequently appear as large protruding tumors (Figs. 16-3 through 16-5), resembling carcinosarcomas. Melanomas, however, usually have darkly pigmented areas (Fig. 16-6) and do not show the intraepithelial spread of

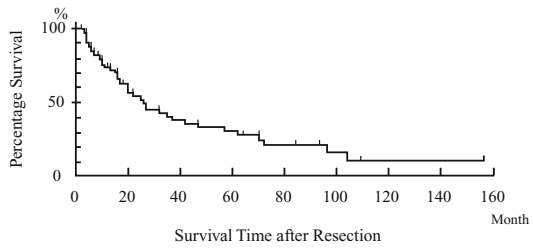


FIG. 16-1. Analysis of the crude survival following esophagectomy of 72 patients with esophageal malignant melanoma. The overall 5-year survival of the 72 patients was 40.8%. (Cited from Yamaguchi et al. Jpn J Gastroenterol 101, p. 1091)

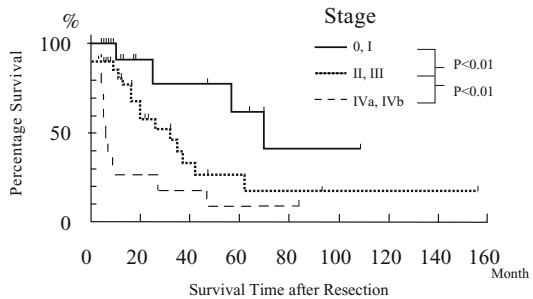


FIG. 16-2. Analysis of the crude survival following esophagectomy of 72 patients with esophageal malignant melanoma, separated according to stage of disease into three groups. The 5-year survival for stages 0 and I patients was 62.9%, for stages II and III was 26.5%, and for stages IVa and IVb was 8.9% (Cited from Yamaguchi et al. Jpn J Gastroenterol 101, p. 1091)

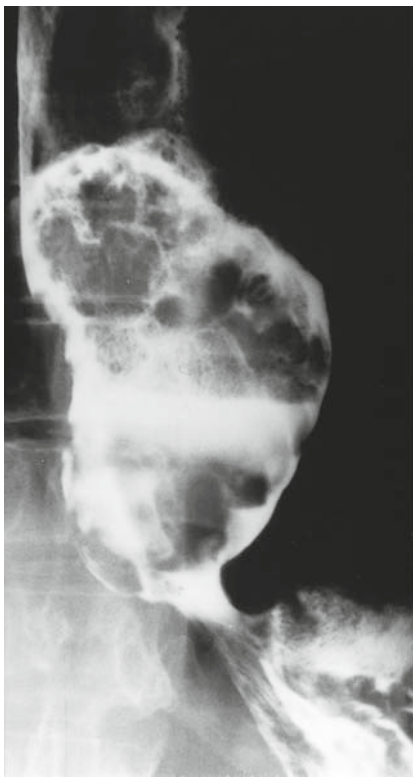


FIG. 16-3. Esophagogram from a patient with an esophageal malignant melanoma

squamous cell carcinoma that is usually observed in the esophageal mucosa in cases of carcinosarcoma. It is therefore possible to distinguish melanomas and carcinosarcomas macroscopically.

A case of flat melanoma showed an area of irregular blackish pigmentation (Mikami et al. 2001). A case of flat melanoma with invasion to the lamina propria mucosa has been reported and, in Japan, six cases of superficial type melanoma of the esophagus were reported between 1999 and 2003 (Kimura et al. 2005).

Endoscopically, about 85% of esophageal malignant melanomas are recognizable by the presence of darkly pigmented areas, but melanomas and carcinosarcomas can be distinguished more accurately at endoscopy by the presence or absence of intraepithelial spreading squamous cell carcinoma in adjacent mucosa, as demonstrated by Lugol's iodine staining. It is common for malignant melanomas to be black or blackish purple in color on cross section, but pink to dark brown coloration is also possible, depending on the amount of melanin present.

Radial growth (atypical junctional activity) of pigmented tumor cells (see Figs. 16-6, 16-7) may be seen in mucosa surrounding the tumor. Moreover, pale brown colored benign melanosis may also be seen in the mucosal epithelium near the tumor

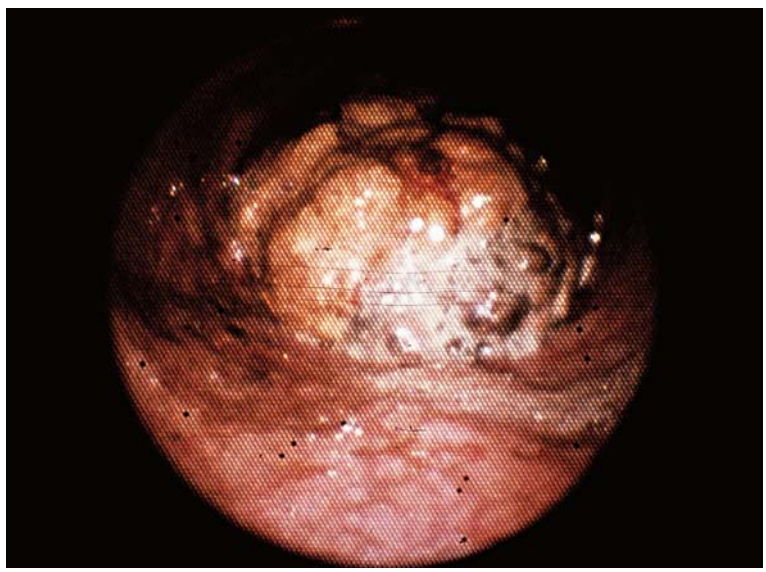


FIG. 16-4. Esophagoscopic appearance of an esophageal malignant melanoma. *Black areas* are evident on the tumor surface

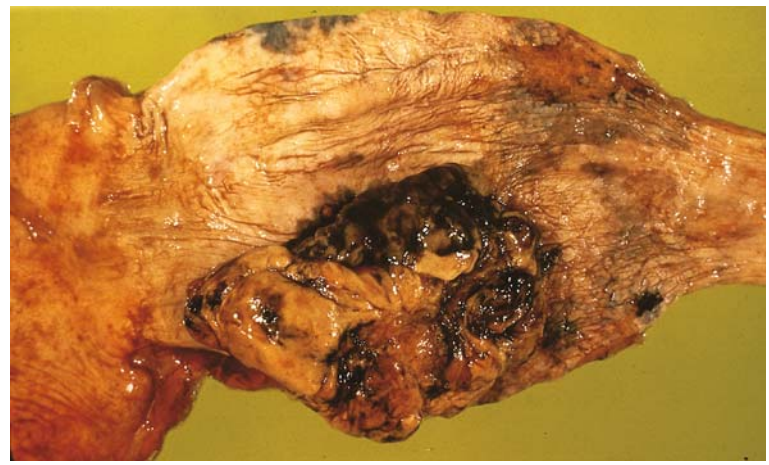


Fig. 16-5. Macroscopic appearance of a malignant melanoma (advanced protruding polypoid type). Darkly pigmented areas are evident

Fig. 16-6. Macroscopic appearance of the radial growth of a malignant melanoma. Infiltration into surrounding mucosa from the darkly pigmented area (*arrow*, radial growth) of the tumor is evident. A wide area of melanosis, pale brown in color, is seen in the mucosa proximal to the tumor

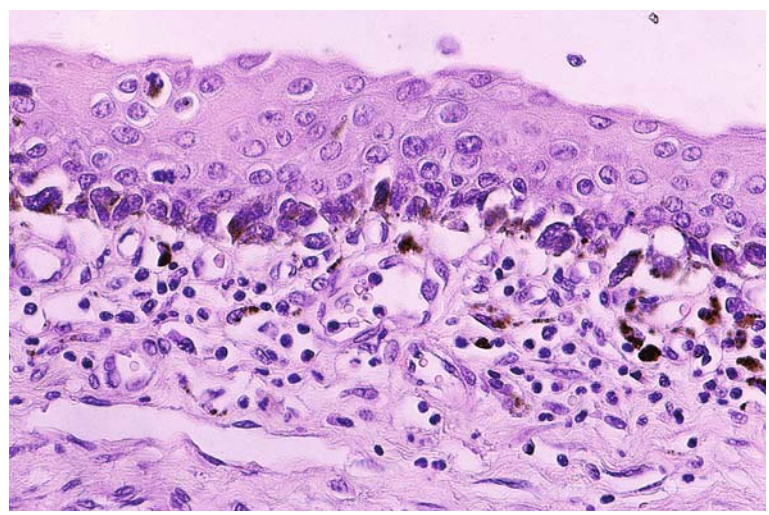


Fig. 16-7. Radial growth. There are malignant melanoma cells in the basal layer of the mucosal epithelium. Macrophages with coarse granules are seen in the muscularis mucosae

(see Figs. 16-5, 16-6); this is the result of increased pigmentation of basal epithelial cells, usually with an associated increase in the number of benign melanocytes in the basal layer.

As with malignant melanomas of the skin, esophageal malignant melanomas consist of polygonal or spindle-shaped tumor cells (Figs. 16-8, 16-9). The cells show a sheet-like growth in most cases, occasionally with an onion skin-like appearance (see Fig. 16-8). Neural differentiation, to melanotic schwannoma, has been reported in esophageal melanoma (Brown et al.). There are also often areas consisting of spindle-shaped tumor cells with an associated prominent stromal reaction. The cell cytoplasm contains fine black melanin granules, and the large round nuclei have very prominent single nucleoli. The nuclei also sometimes have pseudoinclusion bodies, which represent invaginations of the cytoplasm; this is thought to be caused by an abnormality of cell growth. Macrophages may be seen around the tumor; these have small round nuclei and intracytoplasmic granules that are larger than the pigment granules found in the cytoplasm of tumor cells.

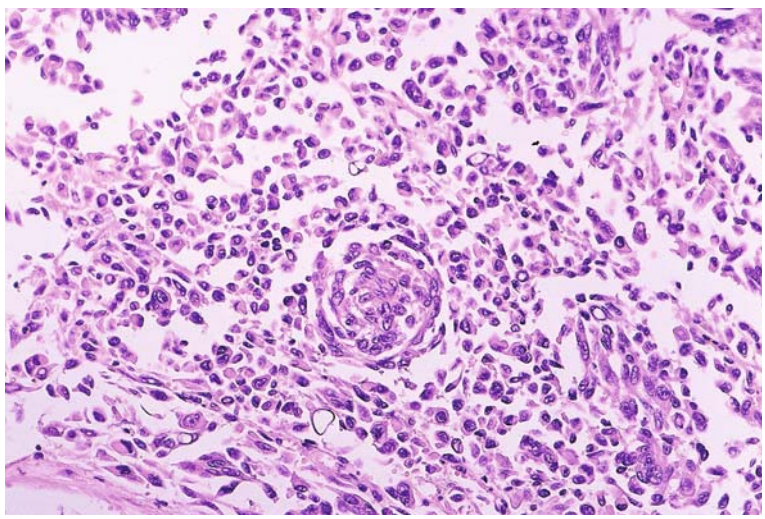


FIG. 16-8. Malignant melanoma. There is an onion skin-like appearance of spindle-shaped cells surrounded by epithelioid cells

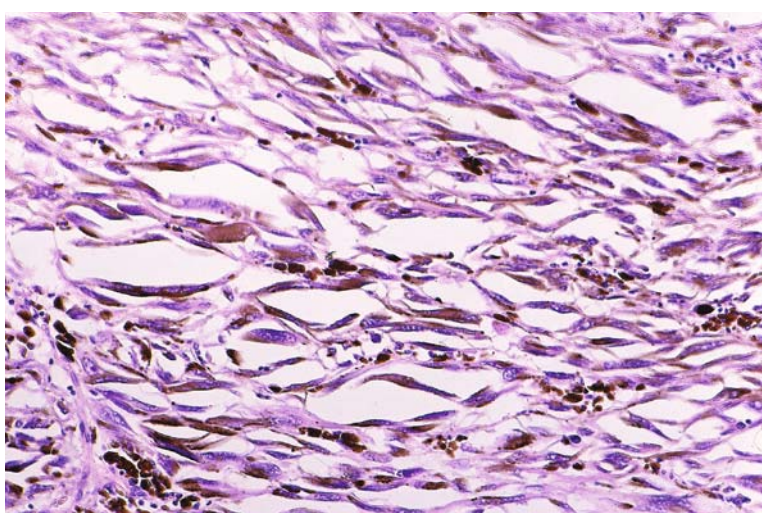


FIG. 16-9. Malignant melanoma. Spindle-shaped tumor cells contain fine melanin granules

The tumor cells stain positively with the DOPA reaction and also by the Fontana–Masson method (Fig. 16-10). The cells showing radial growth are also often positive with these reactions, but spindle-shaped tumor cells in areas rich in stroma are sometimes negative.

A primary lesion can be distinguished from metastatic melanoma by the presence of mucosal spread of tumor cells between the epithelium and lamina propria, similar to radial growth at the epidermodermal junction in malignant melanomas of the skin (Allen and Spitz). Although the mucosal spread of melanoma cells is often called atypical junctional activity, it is better referred to as the radial growth of melanoma. Radial growth may also extend toward deeper tissue along the excretory ducts of the esophageal glands proper, and this is called ductal involvement by melanoma (Fig. 16-11).

Although it is usually expected that no radial growth will be evident in advanced cases of melanoma, this is not the case for esophageal melanomas. The present author has encountered six primary malignant melanomas in resected

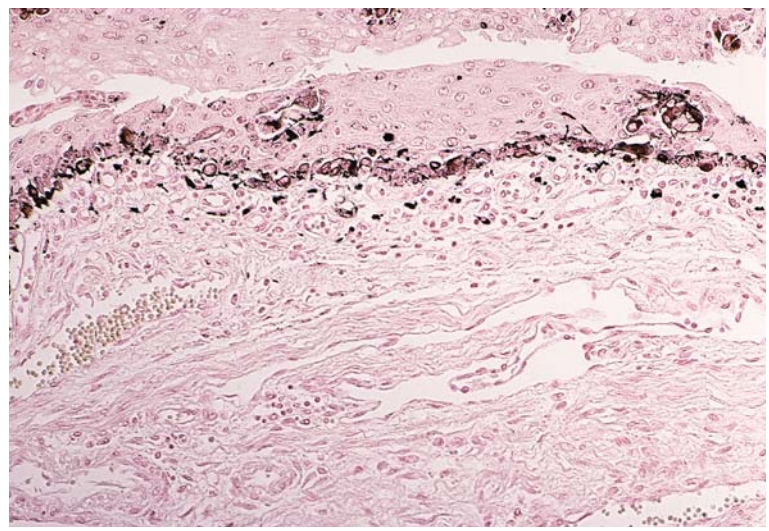


Fig. 16-10. An area of radial growth of malignant melanoma (Fontana–Masson method)

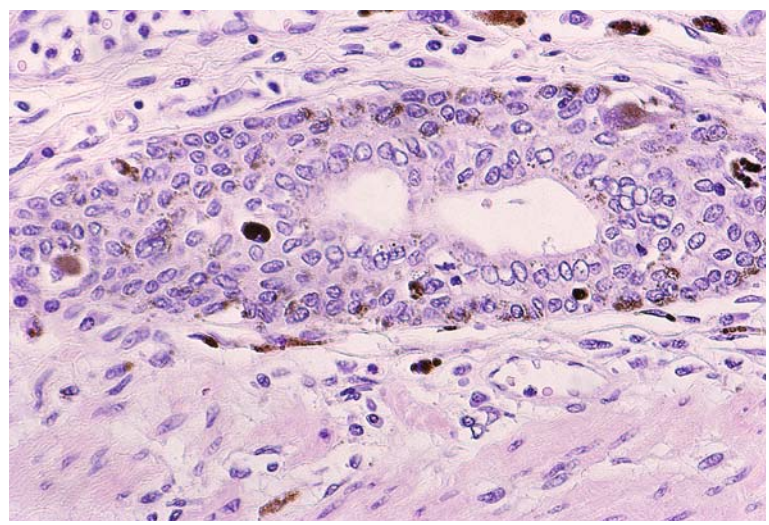


Fig. 16-11. Ductal involvement by malignant melanoma. Infiltration of melanoma into the excretory duct of an esophageal gland proper. Melanoma cells are seen in the ductal epithelium

esophagi, all of which showed radial growth. When there is no radial growth, a lesion is judged to be primary or metastatic by its clinical course.

Mucosal, plantar, and subungual malignant melanomas have recently been classified separately from conventional malignant melanoma of the skin, in view of their poor prognosis and differences in histology. It has been reported that the radial growth of melanoma arising in mucosa more closely resembles the radial growth of lentigo maligna melanoma than that of superficial spreading melanoma; the tumor cells are more infiltrative in mucosal melanoma than in lentigo maligna melanoma, however, and single tumor cells may be seen infiltrating the surrounding squamous epithelium. This pattern is called single cell infiltration (Fig. 16-12), and represents one of the characteristic features of primary malignant melanoma of mucosal, plantar, palmar, and subungual sites.

Malignant melanomas show very little response to radiation therapy but it is known that, after radiotherapy or chemotherapy, tumor cells may occasionally be seen to have more numerous cytoplasmic melanin granules.

Because pale brown melanosis (see Figs. 16-5, 16-6, 16-13) is sometimes found macroscopically in

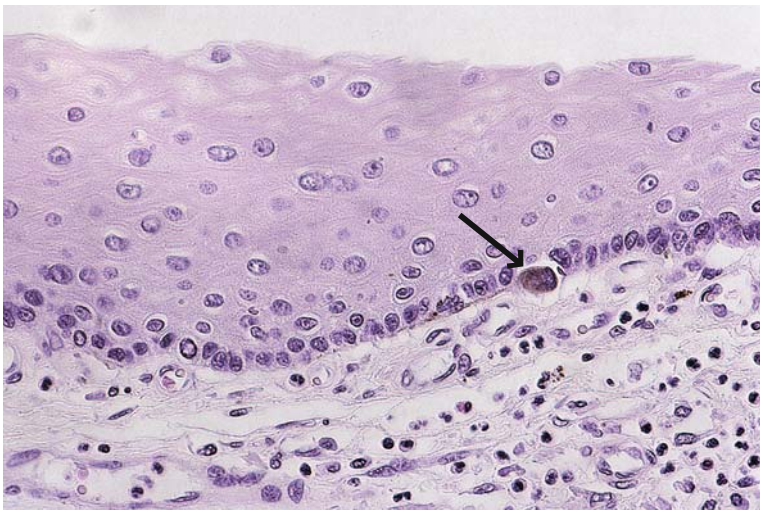


FIG. 16-12. Single cell infiltration of malignant melanoma. There is infiltration of a melanoma cell (*arrow*) along the basal layer of the mucosal epithelium

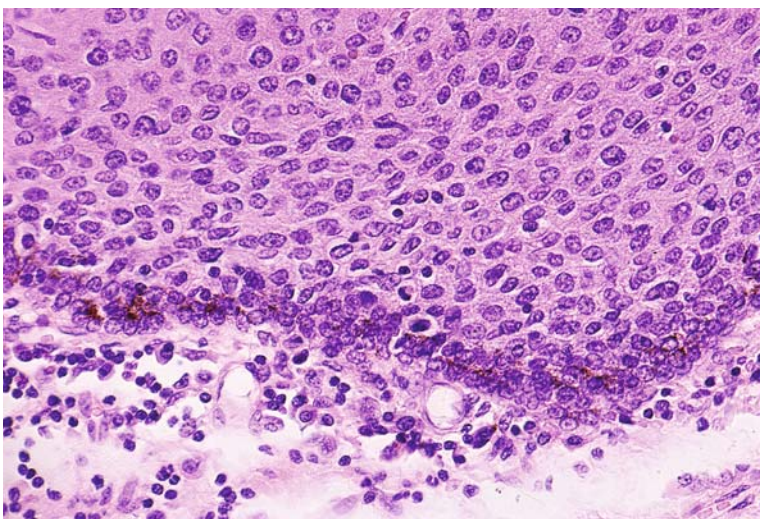


FIG. 16-13. Benign melanosis surrounding radial growth. The basal layer is brown in color

mucosa surrounding the radial growth of tumor cells, melanosis is thought to be a probable precursor of malignant melanoma of the esophagus (see Section 2.2.1.7.1. Melanosis and Melanocytosis).

Melanoma cells show strong positivity with immunohistochemical stains for S-100 protein, neuron-specific enolase (NSE), vimentin, and melanoma-associated antigen (NKI/C3; Bio-Science). These stains are useful for diagnosing amelanotic melanomas in which the tumor cells show no evident melanin granules, but even in cases of amelanotic melanoma the identification of radial growth allows a histological diagnosis of malignant melanoma to be made without difficulty.

The cytological features of esophageal malignant melanoma are the same as those of malignant melanoma of the skin or other sites. The tumor cells are singly dispersed and scattered, or occasionally appear as loosely cohesive groups. "Cell-in-cell" figures, characteristic of epithelial cells, are often seen (Fig. 16-14). The tumor cells are polygonal or spindle shaped and have fine intracytoplasmic granules with a blackish-brown color on Papanicolaou staining (blackish-purple on Giemsa staining) (Fig. 16-15). The cytoplasm is rather foamy, in contrast to that of malignant squamous cells. Each tumor cell usually has a single large, round nucleus. The nuclei have single, very large, rather irregular acidophilic nucleoli

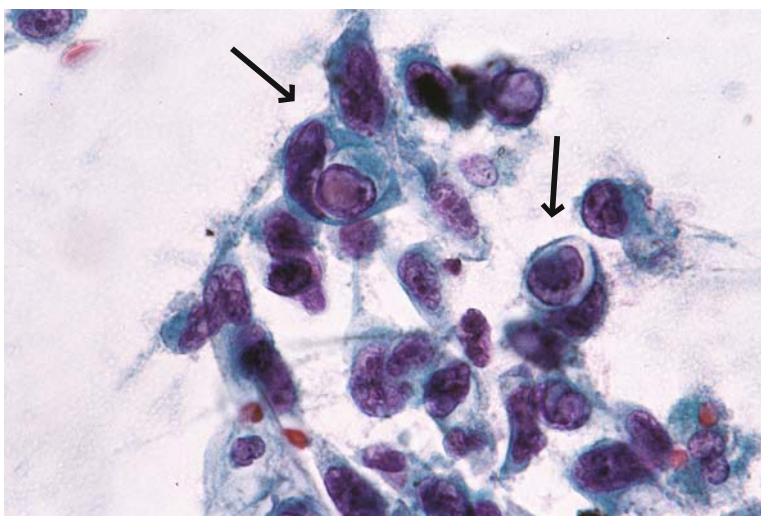


Fig. 16-14. Cytological appearance of a malignant melanoma of the esophagus (Papanicolaou stain). A "cell-in-cell" appearance (*arrows*) is seen

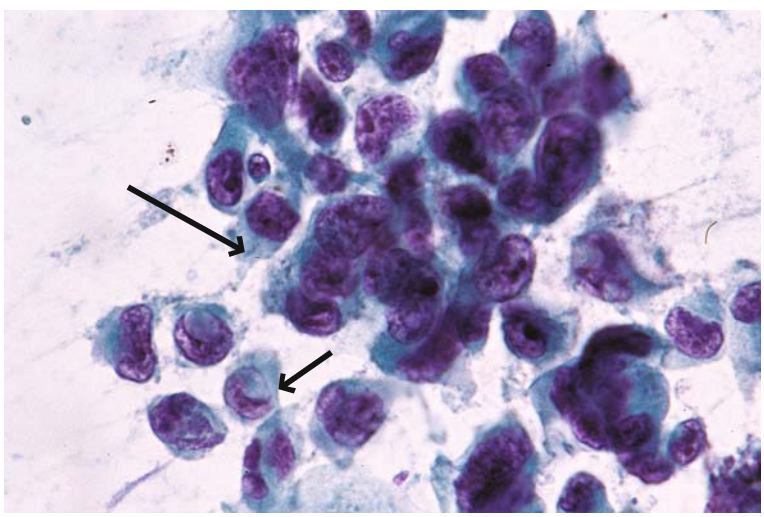


Fig. 16-15. Cytological appearance of a malignant melanoma of the esophagus (Papanicolaou stain). The tumor cells are loosely cohesive and contain melanin granules (*long arrow*) in their cytoplasm. The smear has a brown background. The tumor cell nuclei have pseudoinclusion bodies (*short arrow*) and prominent nucleoli

and, occasionally, intranuclear pseudoinclusion bodies (invaginations of the cytoplasm) (Aldovini et al.). Some tumor cells may have two or more eccentric nuclei. Macrophages with coarse granules may sometimes be found among the tumor cells. The detection of fine black cytoplasmic granules allows a diagnosis of malignant melanoma to be easily made. The presence of very large nucleoli and intranuclear pseudoinclusion bodies, in the absence of pigment granules, is suggestive of melanoma.

Electron microscopy shows intracellular melanosomes at various maturation stages; these are useful diagnostically. Melanosomes are also observed in the cytoplasm of the intranuclear pseudoinclusion bodies. Junctional apparatus is rarely found between melanoma cells, but interrupted basement membranes may be seen.

16.2. Metastatic Melanoma

In addition to primary malignant melanoma, some cases of secondary malignant melanoma of the esophagus, metastatic from the skin, have been reported, although metastasis of melanoma to the esophagus is considered to be rare (Wood and Wood). The incidence of metastasis of cutaneous malignant melanoma to the esophagus was reported to be 4% in a series of 125 autopsy cases of cutaneous melanoma reported by Das Gupta and Brasfield (1964), but there has been a wide variation in incidence in different reports. In another report, all patients with esophageal metastases from cutaneous melanoma died within 1 year (Schneider et al. 1993).

Metastatic melanomas of the esophagus usually have darkly pigmented areas that are evident endoscopically (Kadakia et al. 1992). Metastatic melanomas may be distinguished from primary malignant melanomas histologically by the absence of radial growth of tumor cells.

16.3. Anthracosis of the Esophagus

Anthracosis of the esophagus, or anthracosis of paraesophageal lymph nodes affecting the esophageal wall, has been reported in three papers (Murata et al. 2002; Vakharia et al. 1990; Shinoda et al. 1989). The lesion is benign, and it is very important to distinguish from malignant melanoma. In one reported case, it was associated with a traction diverticulum (Fig. 16-16), and there was a pigmented peribronchial lymph node adjacent to the lesion (Murata et al). The second case was associated with Barrett's esophagus (Vakharia et al.). In the third case, a swollen and pigmented lymph node at the tracheal bifurcation had become exposed to the esophageal

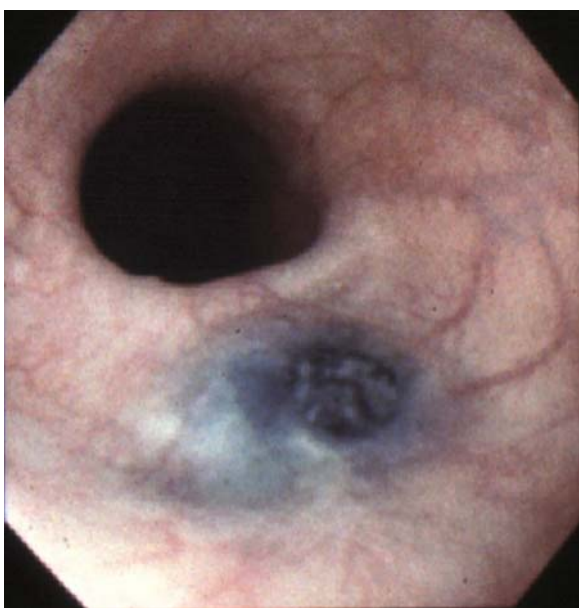


FIG. 16-16. Endoscopic appearance of anthracosis of the esophagus. There is an area of black mucosa with a smooth surface in a traction diverticulum

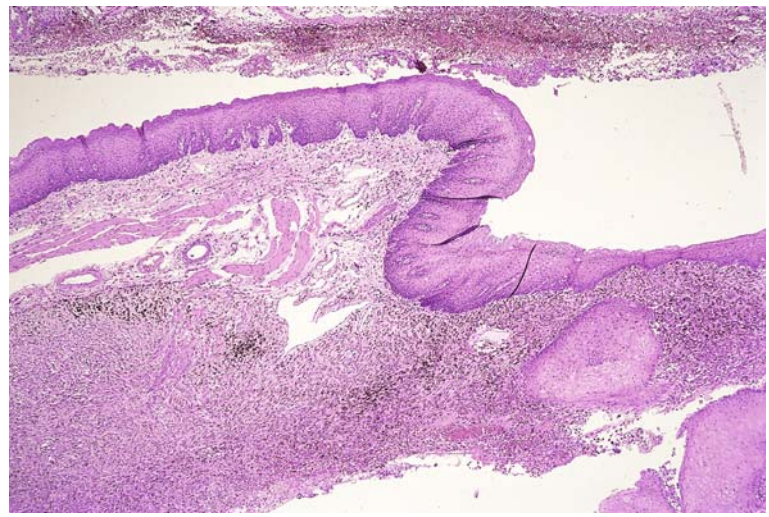


FIG. 16-17. Anthracosis of the esophagus. Many black pigment-laden cells are irregularly distributed under the squamous epithelium

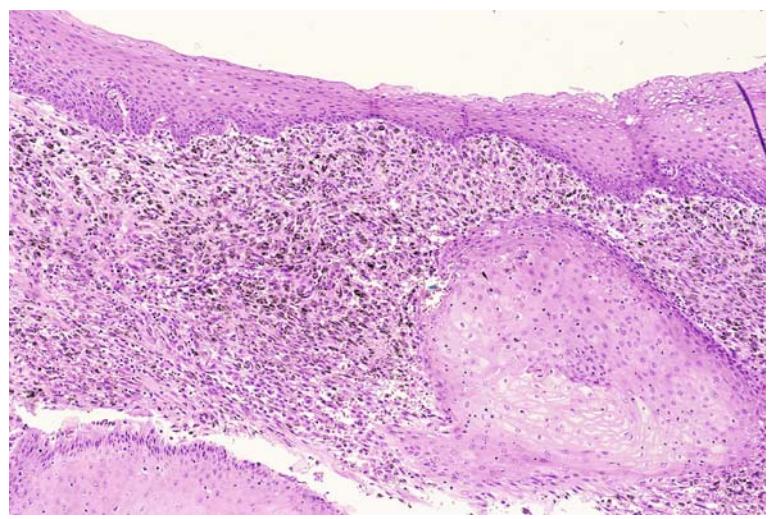


FIG. 16-18. Anthracosis of the esophagus. There are black pigment-laden macrophages without mitoses

lumen (Shinoda et al.); this lesion appeared as a tumor mass with a shallow ulcer on endoscopy and esophagography.

Endoscopically, anthracosis of the esophagus appears as a flat, elevated, or ulcerated black lesion and is usually thought to be a malignant melanoma or submucosal hematoma.

Biopsy specimens reveal many black pigment-laden macrophages in the mucosa and submucosa, with associated fibrosis (Figs.16-17, 16-18). The black pigments are resistant to bleaching. With immunohistochemical stains, the cells are vimentin and CD68 positive, and are negative with S-100 and other melanoma stains.

Chapter 17
Metastatic Carcinoma of the Esophagus

Secondary carcinoma of the esophagus occurs as a result of direct invasion from a primary tumor of an adjacent structure, invasion from metastatic foci in mediastinal lymph nodes, or metastatic hematogenous spread.

Systematic studies of autopsy cases of metastatic carcinoma have found the frequency of metastasis to the esophagus to be 3.1% (Abrams et al.) and 3.2% (Toreson). According to Abrams et al. this frequency is comparable to that of metastatic carcinoma to the skin (4.4%), heart (3.8%), urinary bladder (3.6%), thyroid gland (1.9%), and pituitary gland (1.8%). This finding reflects the fact that the esophagus is one of the sites least likely to be affected by metastatic carcinoma from other organs. The esophagus ranks 21st in the order of structures affected by metastatic carcinoma, excluding lymph nodes.

In relationship to primary site, the incidence of metastasis to the esophagus at autopsy was 8.7% in patients with pulmonary carcinoma, 4.2% in patients with mammary carcinoma, and 3.4% in patients with gastric carcinoma (Abrams et al.). Reports from Europe and America have indicated that hematogenous metastasis to the esophagus most frequently occurs from mammary carcinoma and pulmonary carcinoma.

In a review of autopsy data on gastrointestinal metastases from malignant tumors of the lung, the esophagus was the most common site for metastatic spread, esophageal metastasis being present in 7.8% of patients with lung cancer at autopsy (Antler et al.). In contrast, there have been hardly any reported instances of esophageal metastasis from primary rectal, pancreatic, or ovarian carcinomas.

FIG. 17-1. Macroscopic appearance of recurrent lesions in the esophagus after gastrectomy for a well-differentiated papillary adenocarcinoma (protruding cauliflower type)

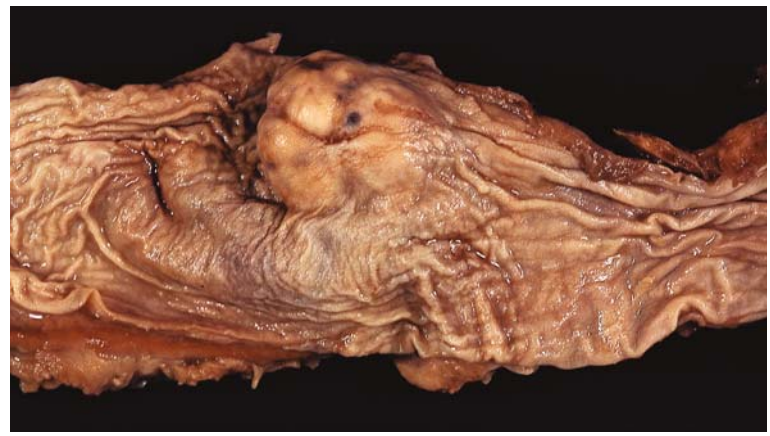


FIG. 17-2. Macroscopic appearance of a metastatic deposit of small cell carcinoma of the lung in the upper esophageal wall (protruding predominantly subepithelial type)

Direct invasion of the esophagus may occur from primary carcinomas of the gastric cardia, hypopharynx, larynx, lung, and thyroid (Hale et al.; Melliere et al. 1993). Secondary invasion of the esophagus from lymph node metastases occurs predominantly in patients with pulmonary and mammary carcinomas.

Figure 17-1 shows recurrent lesions that developed in the esophagus after resection of a primary gastric carcinoma, and Fig. 17-2 shows a metastatic deposit of small cell carcinoma of the lung, forming a nodular tumor mass in the upper esophagus. Secondary tumors usually have a polypoid appearance, similar to that shown in Figs. 17-1 and 17-2, but diffuse thickening of the esophageal wall was reported in a considerable number of metastatic breast carcinomas (Koike et al. 2005).

Metastasis to the esophagus from cutaneous malignant melanoma is described in Chapter 16 (p. 278).

Additional Readings

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1.2.3.1. Congenital Esophageal Duplication Cyst
1.2.3.2. Gastroenteric Cyst
1.2.3.3. Bronchogenic Cyst
1.2.3.4. Other Cysts
1.2.3.4.1. Retention Cyst

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2.2.1.7. Melanosis, Argyrophil Cells, Argentaffin Cells, Langerhans' Cells, and Merkel Cells

2.2.1.7.1. Melanosis and Melanocytosis

2.2.1.7.2. Argyrophil Cells and Argentaffin Cells

2.2.1.7.3. Langerhans' Cells

2.2.1.7.4. Merkel Cells

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2.2.1.8.2. Esophageal Glands Proper
2.2.1.8.2.1. Mucous Cells
2.2.1.8.2.2. Serous Cells
2.2.1.8.2.3. Oncocytes
2.2.1.8.2.4. Myoepithelial Cells
2.2.1.8.2.5. Ductal Epithelium

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2.2.1.9. Lamina Propria Mucosae, Lamina Propria
2.2.1.9.1. Intrapapillary Vessels, Intrapapillary Capillary Loops
2.2.1.10. Lamina Muscularis Mucosae, Muscularis Mucosae
2.2.1.10.1. Biopsy Sites

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2.2.2. Tunica Submucosa
2.2.3. Tunica Muscularis Propria
2.2.4. Tunica Adventitia

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2.2.6. Other Ectopic Tissues
2.2.6.1. Ectopic Thyroid Gland
2.2.6.2. Ectopic Hepatic Tissue and Ectopic Pancreatic Tissue
2.2.6.3. Ectopic Parathyroid Gland

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Chapter 4. Achalasia and Esophageal Motor Dysfunction
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Chapter 5. Infective Esophagitis

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Chapter 7. Esophagitis and Esophageal Ulcer
7.1. Gastroesophageal Reflux Disease, Reflux Esophagitis, and Esophageal Ulcer
7.1.1. Perforation of Benign Esophageal Ulcer
7.1.2. Minimal Change Esophagitis
7.1.3. Endoscopy-Negative Gastroesophageal Reflux Disease
7.1.4. Endoscopic Stages of Reflux Esophagitis
7.1.5. Histological Findings in Reflux Esophagitis

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Chapter 10. Benign Nonepithelial Tumors and Tumor-Like Conditions of the Esophagus

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10.9.1. Diffuse Esophageal Leiomyomatosis

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10.13. Granular Cell Tumor

10.13.1. Pseudoepitheliomatous (Pseudocarcinomatous) Hyperplasia of the Esophagus

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10.16. Glomus Tumor

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Chapter 11. Squamous Epithelial Dysplasia and Squamous Cell Carcinoma

11.1. Squamous Epithelial Dysplasia

11.1.1. Definition of Squamous Epithelial Dysplasia

11.1.2. High-Grade Dysplasia and Squamous Cell Carcinoma in Situ

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11.2.8. Intraepithelial Spread and Ductal Involvement
11.2.8.1. Intraepithelial Spread in Esophageal Mucosa
11.2.8.2. Intraepithelial Spread in Gastric Mucosa
11.2.8.3. Ductal Involvement

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11.2.12. Multiple Carcinoma of the Esophagus and Synchronous Primary Carcinoma of the Esophagus and Other Sites

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11.2.14. Death Caused by Recurrence of Esophageal Carcinoma
11.2.15. Direct Invasion by Esophageal Carcinoma
11.2.15.1. Direct Invasion of Stomach
11.2.15.2. Direct Invasion of Lung
11.2.16. Hematogenous Spread
11.2.16.1. Hematogenous Spread at Diagnosis and Surgery
11.2.16.2. Hematogenous Spread at Autopsy
11.2.17. Lymph Node Metastasis
11.2.17.1. Depth of Tumor Invasion and Nodal Metastasis
11.2.17.1.1. Endoscopic Mucosal Resection, Endoscopic Submucosal Dissection, and Lymph Node Metastasis in Mucosal Carcinoma
11.2.17.2. Latent Lymph Node Metastases from Cancer of Other Organs Detected at Surgery for Esophageal Cancer

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Chapter 12. Barrett's Esophagus and Primary Adenocarcinoma of the Esophagus

12.1. Barrett's Esophagus

12.1.1. Definitions of Barrett's Esophagus and Columnar-Lined Esophagus

12.1.2. Definition of the Esophagogastric Junction and Longitudinal (Palisade) Vessels

12.1.3. Macroscopic Appearance of Barrett's Esophagus

12.1.4. Histological Appearance

12.1.4.1. Double Muscularis Mucosae in Barrett's Esophagus

12.1.4.2. Squamous Reepithelialization and Pseudoregression of Barrett's Esophagus

12.1.4.3. Esophageal Glands Proper and Squamous Islands in Barrett's Esophagus

12.1.4.3.1. Targeted Biopsy of Squamous Islands in Barrett's Esophagus

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12.1.5. Barrett's Esophagus After Gastrectomy, Esophagectomy, and Surgery for Achalasia

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12.2.1. Barrett's Adenocarcinoma

12.2.1.1. Definition of Barrett's Adenocarcinoma

12.2.1.2. General Considerations

12.2.1.2.1. Background Mucosa of Barrett's Adenocarcinoma

12.2.1.3. Histological Appearances

12.2.1.3.1. High-Grade Dysplasia, Intramucosal Adenocarcinoma, and the Vienna Classification

12.2.1.3.2. Low-Grade Dysplasia

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12.2.1.5. Lymph Node Metastasis in Esophageal Adenocarcinoma

12.2.1.5.1. Photodynamic Therapy, Endoscopic Mucosal Resection, and Endoscopic Submucosal Dissection of Mucosal Adenocarcinoma

12.2.1.5.2. Lymphovascular Invasion in Esophageal Adenocarcinoma

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12.2.1.8. Squamous Cell Carcinoma, Basaloid Squamous Carcinoma, Adenosquamous Carcinoma, Mucoepidermoid Carcinoma, Adenocarcinoma with Lymphoid Stroma, Carcinosarcoma, Choriocarcinoma, Alpha-Fetoprotein-Producing Carcinoma, and Carcinoid Tumor Complicating Barrett's Esophagus

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12.2.3. Adenocarcinoma Arising from Esophageal Cardiac Glands

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12.2.4. Adenocarcinoma Arising from Esophageal Glands Proper

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Chapter 13. Carcinomas Other Than Squamous Cell Carcinoma and Adenocarcinoma

13.1. Adenosquamous Carcinoma (Coexistence of Adenocarcinoma and Squamous Cell Carcinoma)

13.2. Mucoepidermoid Carcinoma

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13.4. Undifferentiated Carcinoma

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13.5. Basaloid Squamous Carcinoma, Basaloid Carcinoma

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13.6. Other Tumor Types

13.6.1. Carcinoid Tumor

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13.6.2. Choriocarcinoma

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13.6.3. Paget's Disease

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Chapter 14. Malignant Nonepithelial Tumors of the Esophagus

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Chapter 15. Carcinosarcoma and Pseudosarcoma
15.1. Carcinosarcoma and Pseudosarcoma
15.2. Macroscopic Features
15.3. Microscopic Features
15.4. Cytological Features
15.5. Ultrastructural Features

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Chapter 16. Malignant Melanoma and Related Entities

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