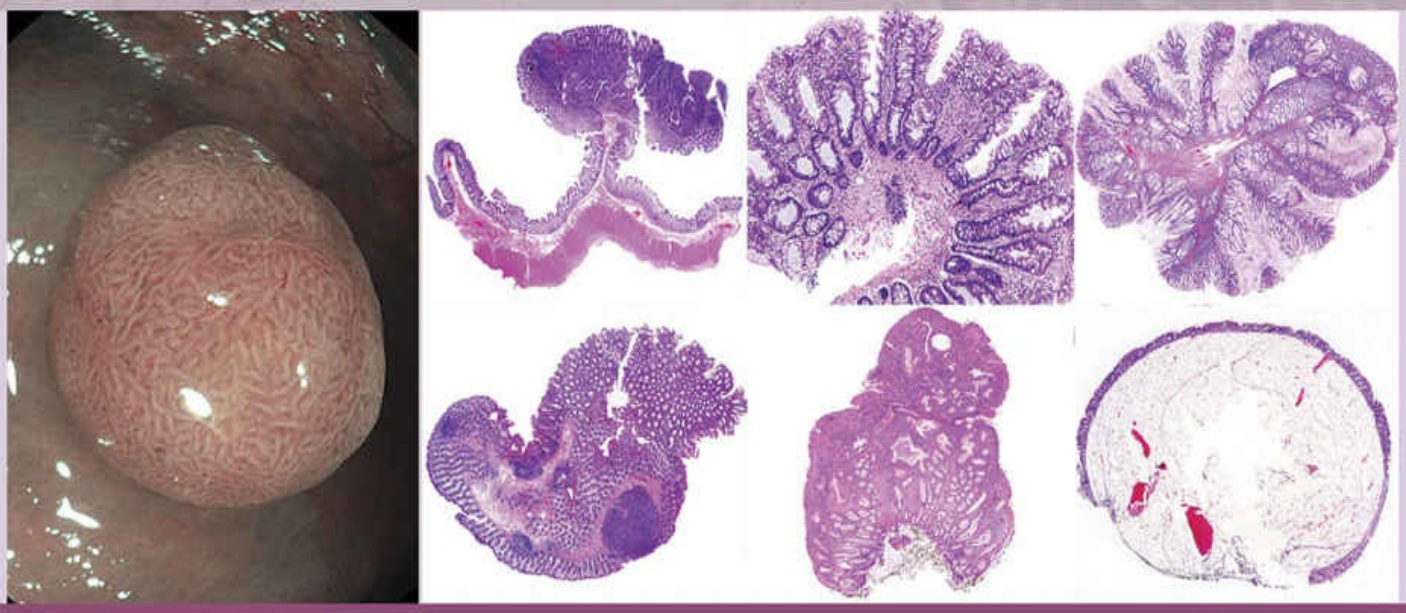
A Pattern Based Approach to
Neoplastic Biopsies

Atlas of GASTROINTESTINAL PATHOLOGY



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Atlas of Gastrointestinal Pathology A Pattern Based Approach to Neoplastic Biopsies

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Dedication

To my family:

Matt: For being my rock.

Madeline: Stay brave. Stay curious.

Tommy: Yes, I'd rather be outside, too.

Dora M. Lam-Himlin, MD

To all the colleagues who love gastrointestinal pathology as much as we do.

Elizabeth A. Montgomery, MD

To my loving family:

Mary and Andy: Mike and I didn't realize how much we needed parents, until we became parents ourselves. Thank you for always being there for us, and for reminding us about the importance of family, love, and laughter.

Mom: Thank you for being my first best friend, believing in me always, and teaching me the value of hard work. Our Wednesday afternoon brownies are some of my favorite memories.

Jackson and Madelyn: Objects in the mirror are sometimes closer than they appear. If it is important, NEVER give up—hunker down and dig in!

Mike: The keys to a good road trip are fun, excitement, danger, and Johnny Cash.

OGN: This book and my career would not be possible without you. Although I don't deserve you, I thank the heavens for you every day. Here's to Baltimore, the Incatrail, and all of tomorrow's mischievous adventures.

Christina A. Arnold, MD

Preface

Diagnosis and reporting of neoplastic GI biopsies is a complex moving target, as evidenced by evolving nomenclature, updates in society guidelines, recognition of new therapeutic targets, and increasing requirements for prognostic elements and ancillary testing interpretation. This follow-up textbook on GI neoplasia is the highly anticipated companion volume to *Atlas of Gastrointestinal Pathology: A Pattern Based Approach to Non-Neoplastic Biopsies*. This new book applies the now-familiar method of pattern based learning to GI neoplasia and provides a systematic algorithm for tackling common and uncommon interpretation challenges. Mirroring the previous text, this book highlights tell-tale "red flags" found in the clinical chart, hidden clues in the slides, and how to discern an exact diagnosis despite sometimes disabling artifacts.

New topics covered include a simple approach to the endoscopic mucosal resection (EMR) specimen, the latest definition of Barrett esophagus and its reporting, an algorithmic approach to serrated polyps, instructions for decoding the alphabet soup of colorectal cancer molecular testing, the latest consensus guidelines on approaching anal dysplasia and dysplasia arising in inflammatory bowel disease, and a handy guide to syndromic polyps with emphasis on morphology, clinical considerations, genetics, and practical reporting.

The illustrations extend beyond a handful of classic examples for each entity, and more than 1600 images cover the full morphologic spectrum of the major patterns of GI neoplasia. The sessile serrated adenoma/polyp, for example, is illustrated in more than 50 figures that include direct comparisons with differential diagnoses and borderline cases, and each image is captioned with a careful description. The corresponding text details information on how to classify the polyp, minimum diagnostic criteria, clinical implications of surveillance intervals, and sample sign-out notes.

In this book, disease processes are grouped by their histologic patterns—an approach that echoes the first volume and closely approximates the method by which experienced pathologists mentally approach daily sign-out. Organized by these major patterns, each chapter details neoplastic considerations for the esophagus, stomach, small intestine, colon, anus, and soft tissue.

The text is high yield and focused on checklists, key features, diagnostic pearls and pitfalls, frequently asked questions, and sample notes—see the following descriptions. We hope this

collective experience leaves the reader with a familiarity of the major patterns of GI neoplasia and confidence in navigating through the clinicopathologic clues and pitfalls to arrive swiftly at the correct diagnosis. Select structural elements are briefly introduced as follows.

- Each chapter opens with a "Chapter Outline" that outlines the enclosed structure and allows the reader to quickly hone in on select patterns and pertinent differential diagnostic considerations. Similar checklists are found throughout the chapter to neatly organize complicated topics.
- "The Unremarkable X": Normal histology is sometimes overlooked in textbooks because it is assumed to be widely understood, much to the frustration of junior trainees. A firm understanding of normal is essential to recognizing subtle injury patterns. As such, each chapter begins with a brief discussion of normal histology to contrast to the succeeding mucosal injury patterns and to highlight helpful diagnostic clues.
- The "Pearls & Pitfalls" boxes include lessons from real life sign-out experience with an emphasis on important diagnostic clues, mimics, and hazards.
- The "Frequently Asked Questions" sections stem from our busy consult service and teaching sessions. In these sections, we discuss real-life diagnostic dilemmas and offer diagnostic tips and tools to sort through commonly encountered sign-out challenges.
- All major topics close with a "Key Features" section that summarizes the essential elements of the subtopic for handy reference.
- A "Sample Note" section accompanies the more challenging topics. In these sections, an example pathology report is included with the top-line diagnosis, pertinent discussion, and salient references. These notes offer a template of how to synthesize complicated topics and are based on real-life cases and interactions with clinicians. The select references are included for those interested in further reading but also can be included in pathology reports to help guide clinical management.
- Each chapter features a corresponding "Quiz" section in the appendix to emphasize important teaching points. These sections offer the reader experience and confidence with high-yield teaching topics. Questions are in the format of the board type examinations and can also serve as useful board preparatory materials.

Acknowledgments

We thank our institutions, colleagues, and trainees for invaluable resources and support. We are indebted to our inquisitive trainees and clinicians whose fresh perspectives and lively discussions drove the direction of this book. We particularly thank our families for understanding the numerous late night, early morning, and weekend marathon writing sessions.

We thank our Acquisition Editor, Ryan Shaw, for taking a chance on this project, and our Editorial Coordinator, Lindsay Ries, for working diligently with us to ensure timely completion. We thank Frank M. Corl, MS, for the custom medical illustrations; Rick Marshall for computer assistance in identifying pertinent teaching material; and Shawn Scully for photography editing on select topics.

Lastly, we thank the production team led by Ramkumar Soundararajan for their careful attention to detail.

1

Esophagus

The Unremarkable Esophagus

Normal esophageal mucosa is a common sample in the practice of gastrointestinal pathology, and most of us are familiar with squamous mucosa on biopsies. Mucosa consists of epithelium (stratified squamous), lamina propria, and muscularis mucosae. Beneath those structures are the submucosa and muscularis propria. Assessing resections and endoscopic mucosal resections (EMRs) helps us learn about these layers.

The layers matter and there are some pitfalls! Cancers that invade only the lamina propria are staged as T1a, whereas those that extend into the submucosa are T1b neoplasms.[1] There are some issues that can arise and result in confusion. In general, mucosal biopsies grasp some epithelium and a little bit of lamina propria. Many biopsies contain only squamous epithelium and lack even lamina propria; normal squamous mucosa is slippery, and it is difficult for the endoscopist to easily grasp it to obtain a large "bite," so abundant lamina propria and/or muscularis mucosae tend to be present in biopsies from damaged mucosa. Most biopsies do not grasp submucosa.

Note the indicated layers in the samples in Figs. 1.1 and 1.2. The layer just under the epithelium is the lamina propria rather than the submucosa. This is easy to spot on well-oriented samples such as the one seen in Fig. 1.1 but not so obvious at times on samples such as those seen in Fig. 1.2. Furthermore, once the esophagus is damaged and the epithelium is replaced by columnar epithelium, as in Fig. 1.3, the muscularis mucosae becomes thick and disorganized, sometimes even forming two (duplicated) or three (triplicated) layers with bits of lamina propria between them.[2] The tissue between these sloppy smooth layers is

all lamina propria, not submucosa! The irregularities in the muscularis mucosae following mucosal damage are further discussed in the section concerning EMRs. In Fig. 1.3, there is a clue (in addition to the squamous epithelium) that the sample is from the esophagus; an esophageal submucosal gland is present at the lower right of the image, and a duct that is intended to lead from the submucosal gland to the surface is indicated. The presence of esophageal submucosal glands and ducts in a sample confirms that the sample is derived from the esophagus, but this is not a common finding in mucosal biopsies.

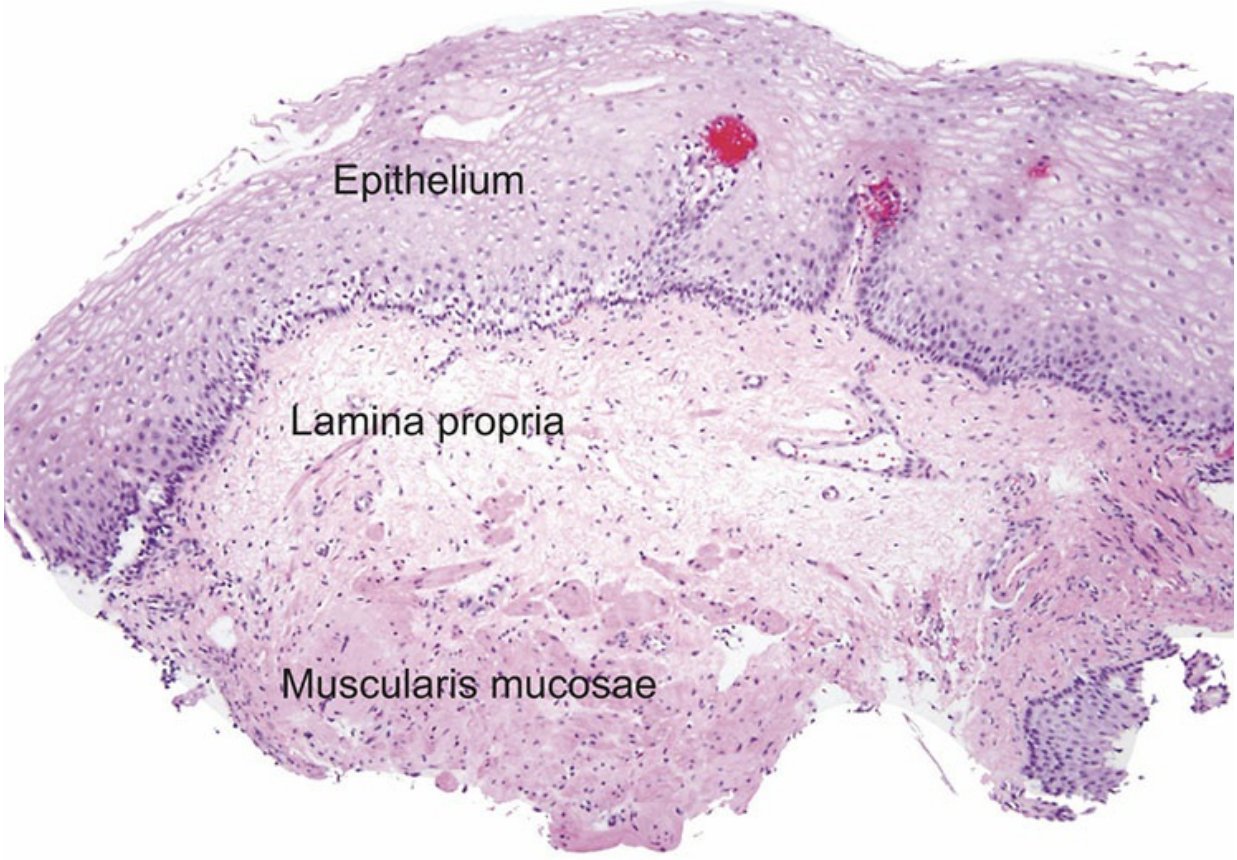

FIGURE 1-1 Esophageal mucosal biopsy. This sample is slightly tangentially embedded. Note that the biopsy contains all three layers of the mucosa, namely, the squamous epithelium, the loose lamina propria with a few delicate blood vessels, and the muscularis mucosae (this is Latin for the muscle of the mucosa). The epithelium has only a few layers of the darker basal cells, and the more superficial cells are pink (eosinophilic), with their long axes arranged parallel to the basement membrane, which is normal

polarity for squamous epithelium. For columnar epithelium, the long axes of the nuclei are normally arranged perpendicular to the basement membrane. This sample is essentially normal and fairly well oriented.

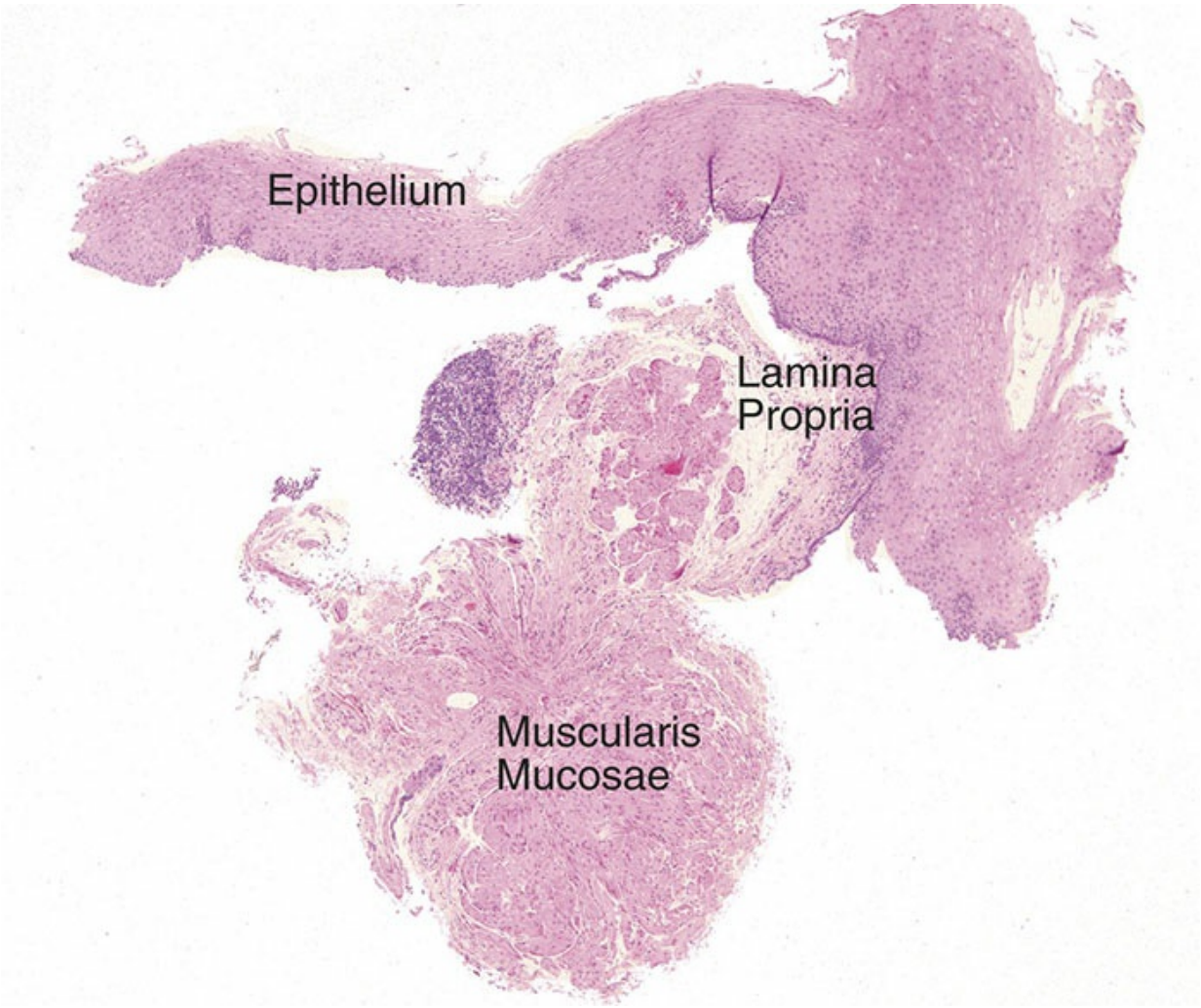

FIGURE 1-2 Esophageal mucosal biopsy. This mucosal biopsy has been embedded in a disorderly fashion such that it is a bit trickier to interpret than the sample shown in Fig. 1.1 There is a lymphoid aggregate at the left. The muscularis mucosae is tangentially embedded and appears thick, but this is not muscularis propria. The loose connective tissue at the upper right is lamina propria rather than submucosa.

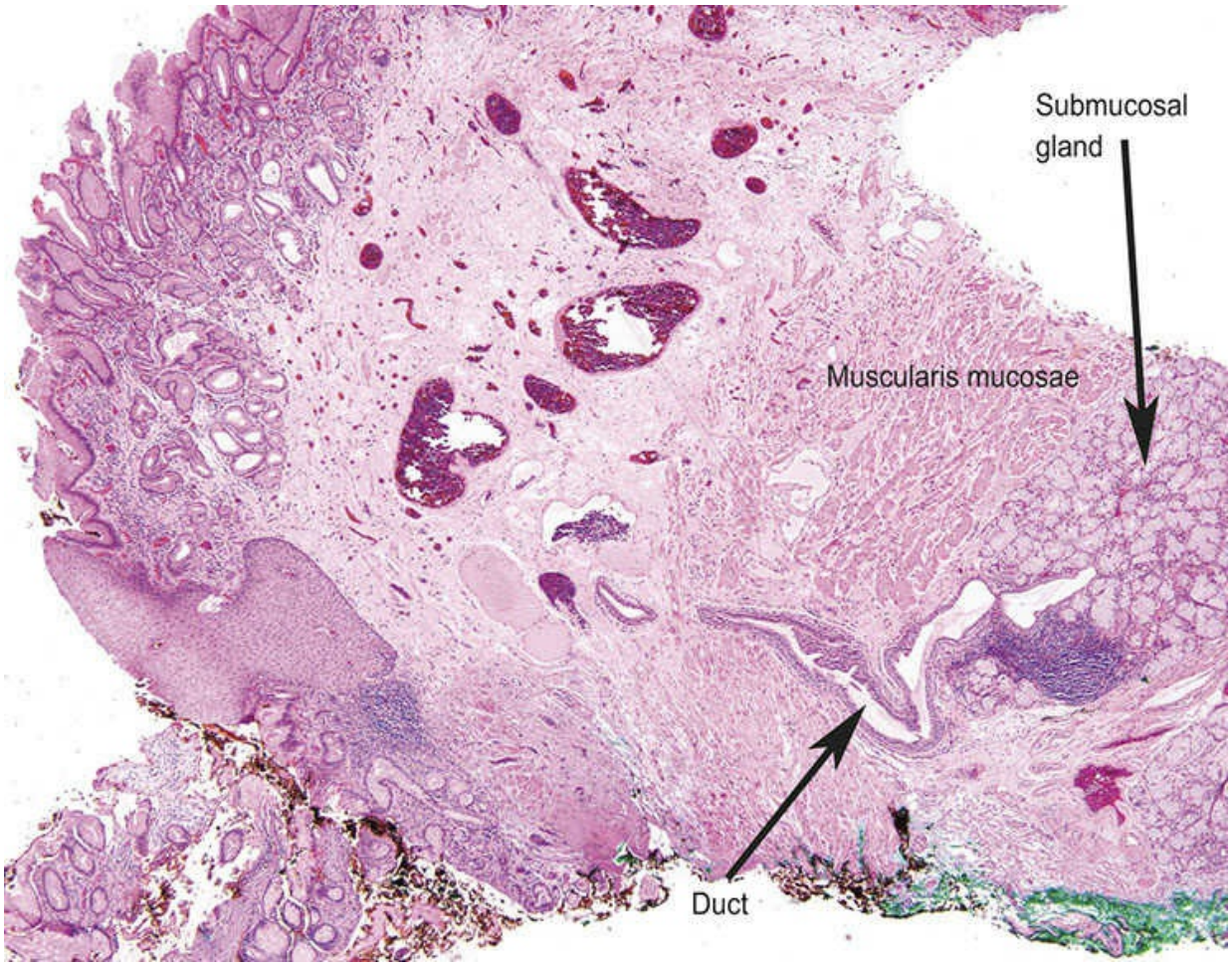

FIGURE 1-3 Endoscopic mucosal resection. Even though this specimen is not well oriented, it shows the layers that can be seen. Submucosa appears at the lower right of the field, and a submucosal gland is indicated. To the left of the submucosal gland, a thickened portion of muscularis mucosae courses across the sample. A duct, which transports secretions from the submucosal gland to lubricate the surface, is seen piercing through the muscularis mucosae. The zone to the left beneath the mucosa is the lamina propria and not the submucosa. Epithelium is seen at the left. Note that in the columnar cardiac mucosa portion, lamina propria invests individual glands, whereas it is under the squamous epithelium in the zone with squamous epithelium.

The presence of so-called multilayered epithelium,[3,4] discussed later, is also a clue that a specimen is derived from the esophagus. Figure 1.4 shows a mucosal biopsy that contains a submucosal gland, but this is unusual.

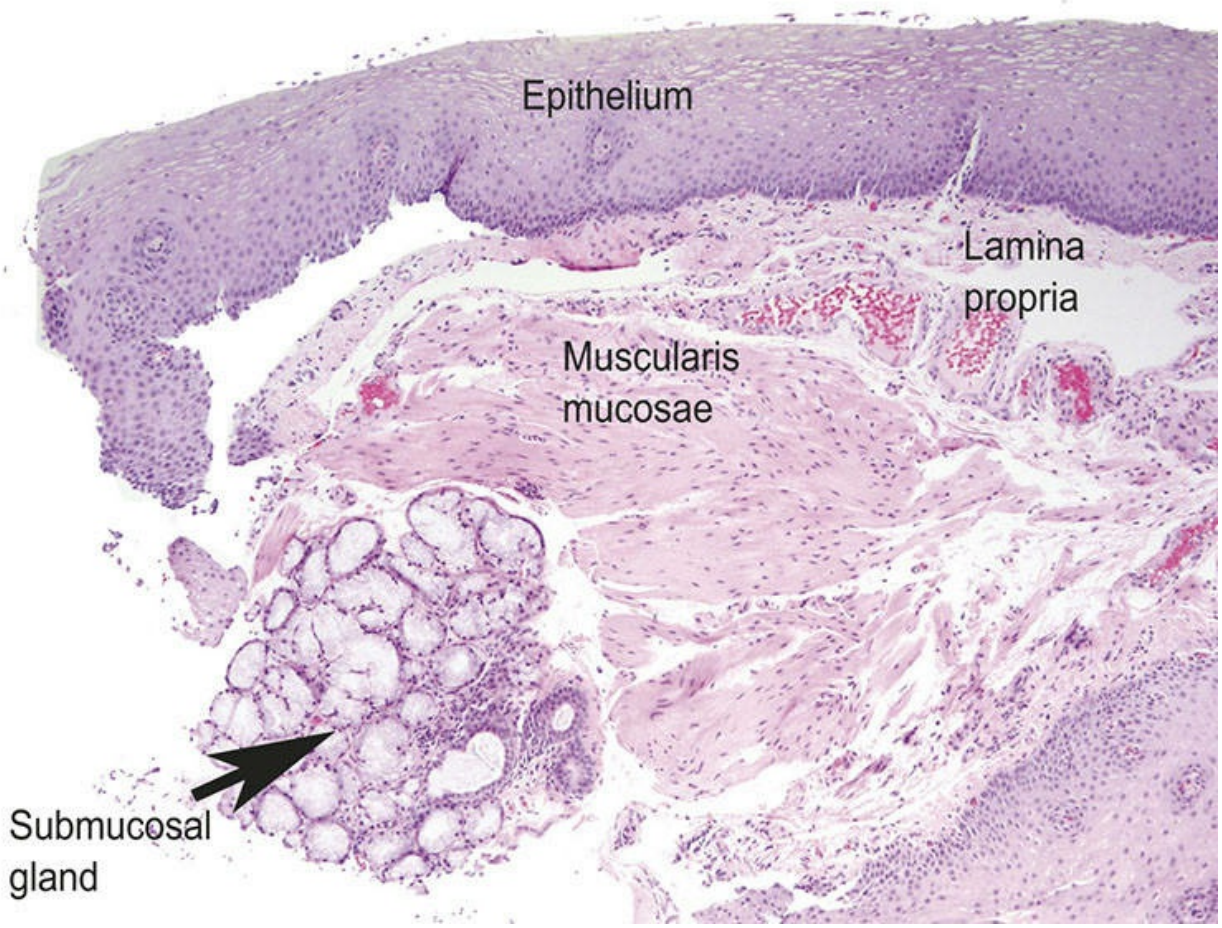

FIGURE 1-4 Biopsy of esophagus. This is an unusual case in that a submucosal gland is present such that a small portion of submucosa is clearly present in the specimen. However, the loose connective tissue in between the epithelium and the muscularis mucosae is lamina propria rather than submucosa.

Pancreatic acinar cell heterotopia is also common in esophageal biopsies and resections and is an incidental finding. The resection images shown in Figs. 1.5 and 1.6 highlight this finding and compare it with the appearance of submucosal glands. Pancreatic acinar heterotopia of the esophagus is generally encountered in the mucosa, whereas submucosal glands, of course, are in the submucosa.

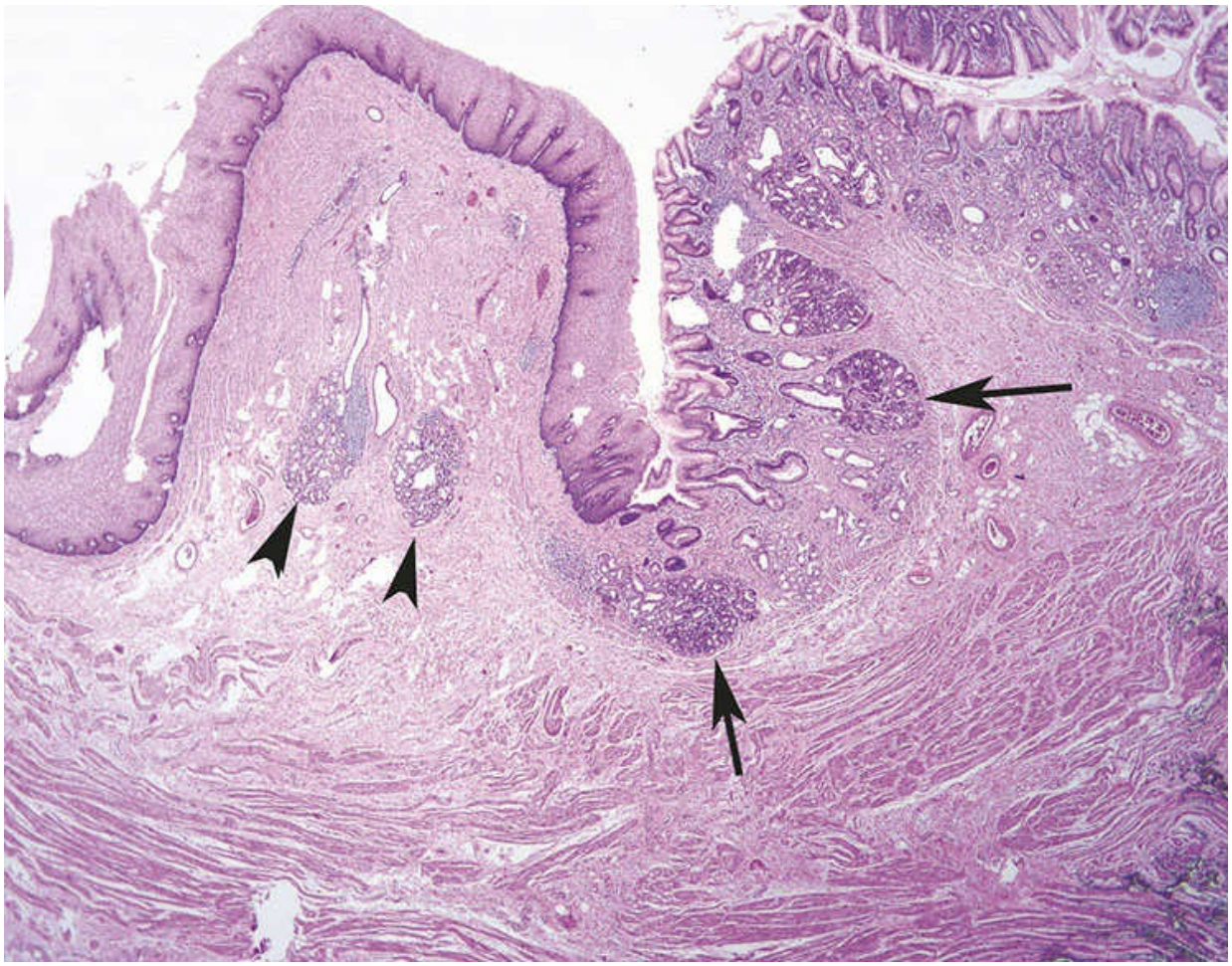

FIGURE 1-5 Gastroesophageal junctional tissue, resection specimen. In this resection specimen, the muscularis propria curves across the bottom of the field, and an area of squamous epithelium at the left coats the lamina propria, muscularis mucosae, and submucosa, where two submucosal glands are marked with *arrowheads*. At the center and right, the mucosa is of the cardiac type and cardiac glands are present as well as foci of pancreatic heterotopia that are within the mucosa, and a delicate cord of muscularis mucosae is beneath these foci of pancreatic heterotopia marked by the *arrows*.

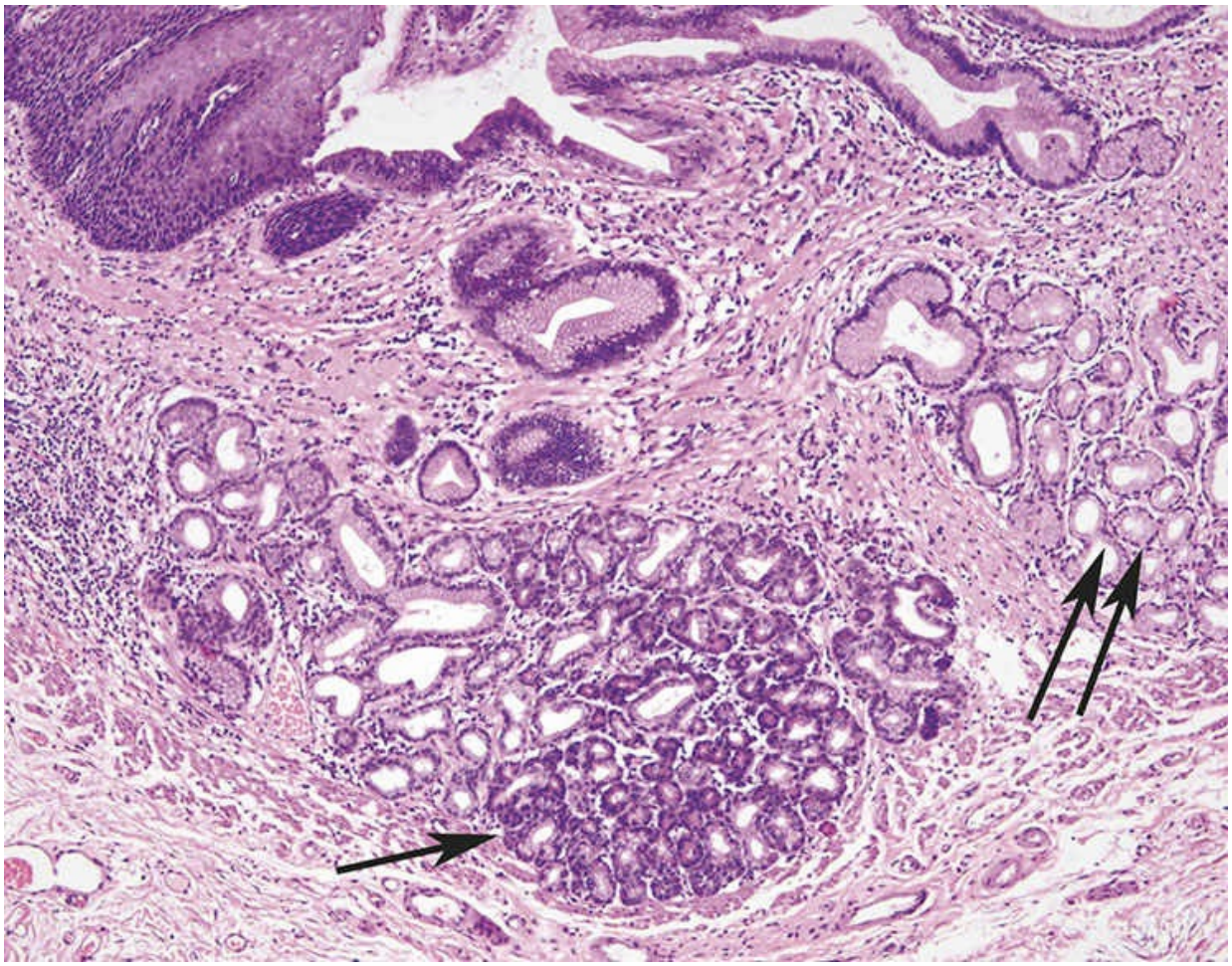

FIGURE 1-6 Gastroesophageal junctional tissue. This is a high--magnification image of one of the foci of pancreatic heterotopia that are indicated in Fig. 1.5. A nodule of pancreatic heterotopia is indicated by a *single arrow* and wisps of muscularis mucosae are beneath it. The *double arrow*s mark gastric cardiac glands, which produce mucin.

Some Esophageal Polyps

Granular Cell Tumor

Granular cell tumors of the esophagus account for about 1% to 2% of all granular cell tumors,[5] and the esophagus is the most common gastrointestinal tract site.[6] Most esophageal granular cell tumors arise in the distal esophagus and about 5% to 10% are multicentric. There is a female predominance, and these tumors are more common in African-Americans than in whites. Occasional large examples require radical surgery, and malignant examples are rare.[7,8] Most esophageal granular cell

tumors appear as well-marginated masses on imaging studies such that they are interpreted as gastrointestinal stromal tumors (GISTs). The important thing with granular cell tumors is that they can be foolers. Do not be the next victim!

It is not clear why granular cell tumors are prone to elicit a pseudoepitheliomatous reactive response in the overlying squamous epithelium (Fig. 1.7). "Epithelioma" is an old term for carcinoma, so "pseudoepitheliomatous hyperplasia" simply means "pseudocarcinomatous hyperplasia." This benign response of squamous epithelium occasionally leads to a misinterpretation of squamous cell carcinoma if the granular cell tumor is not spotted. This phenomenon also applies to anal canal granular cell tumors. Of course, pseudoepitheliomatous hyperplasia can be found on top of carcinomas as well as other processes. Figs. 1.8 and 1.9 show pseudoepitheliomatous (squamous) hyperplasia overlying an adenocarcinoma of the esophagus.

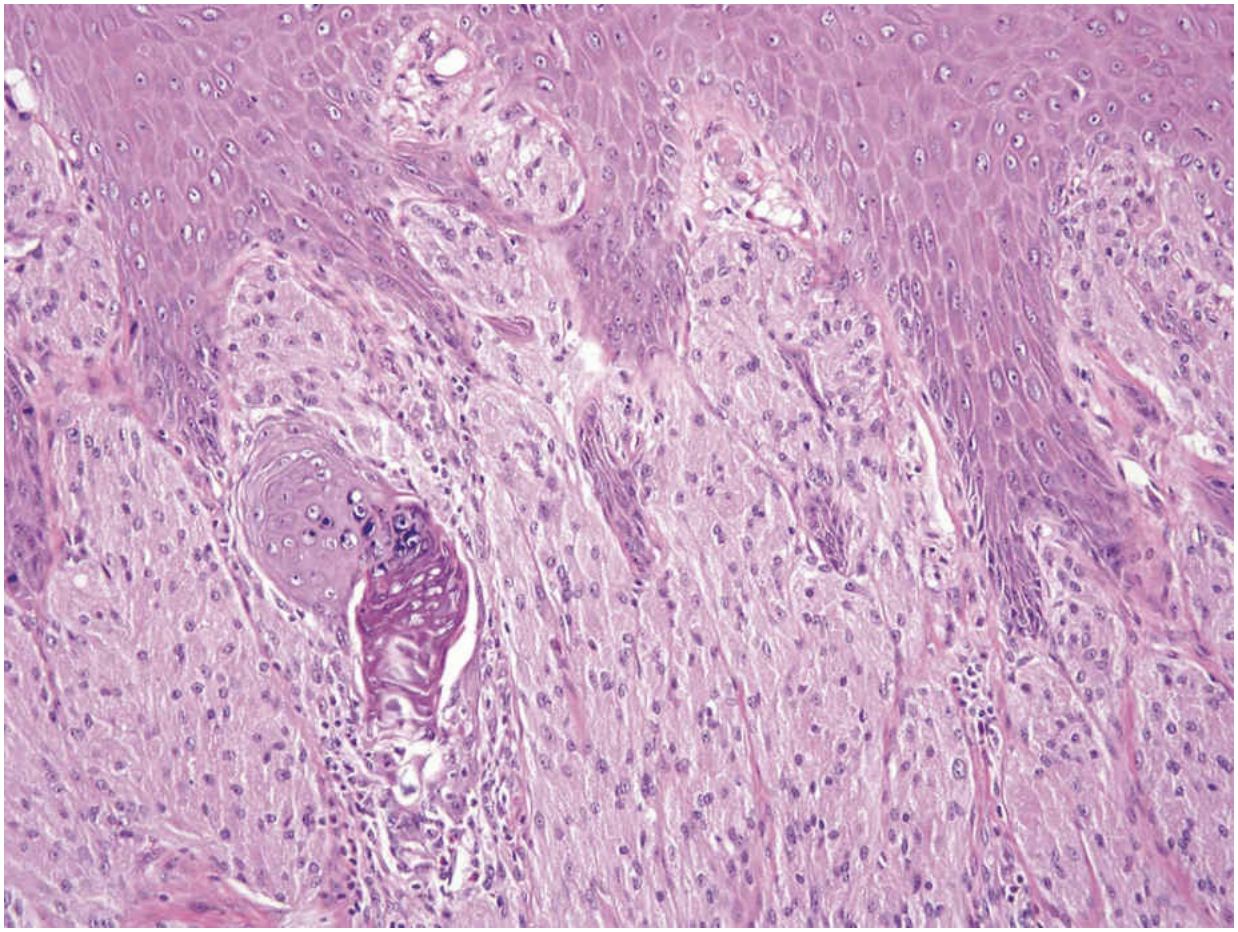

FIGURE 1-7 Granular cell tumor. The tumor consists of plump eosinophilic cells with granular cytoplasm and small nuclei. This type of tumor is notorious for stimulating hyperplasia of the overlying squamous epithelium (so-called pseudoepitheliomatous hyperplasia), which can be mistaken for carcinoma.

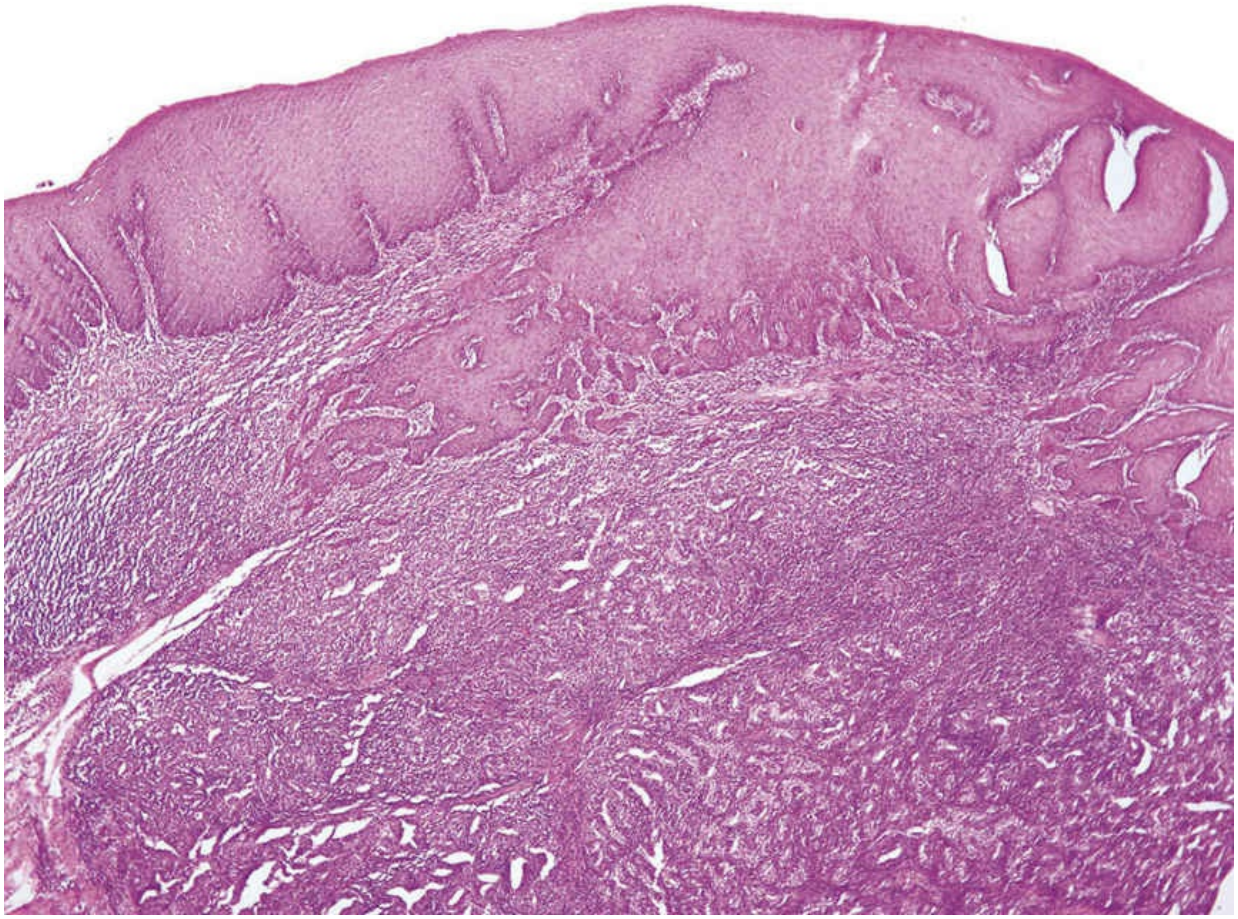

FIGURE 1-8 Pseudoepitheliomatous hyperplasia associated with an adenocarcinoma. The adenocarcinoma at the bottom of the field has undermined the squamous epithelium at the top of the field. The squamous process is benign and reactive.

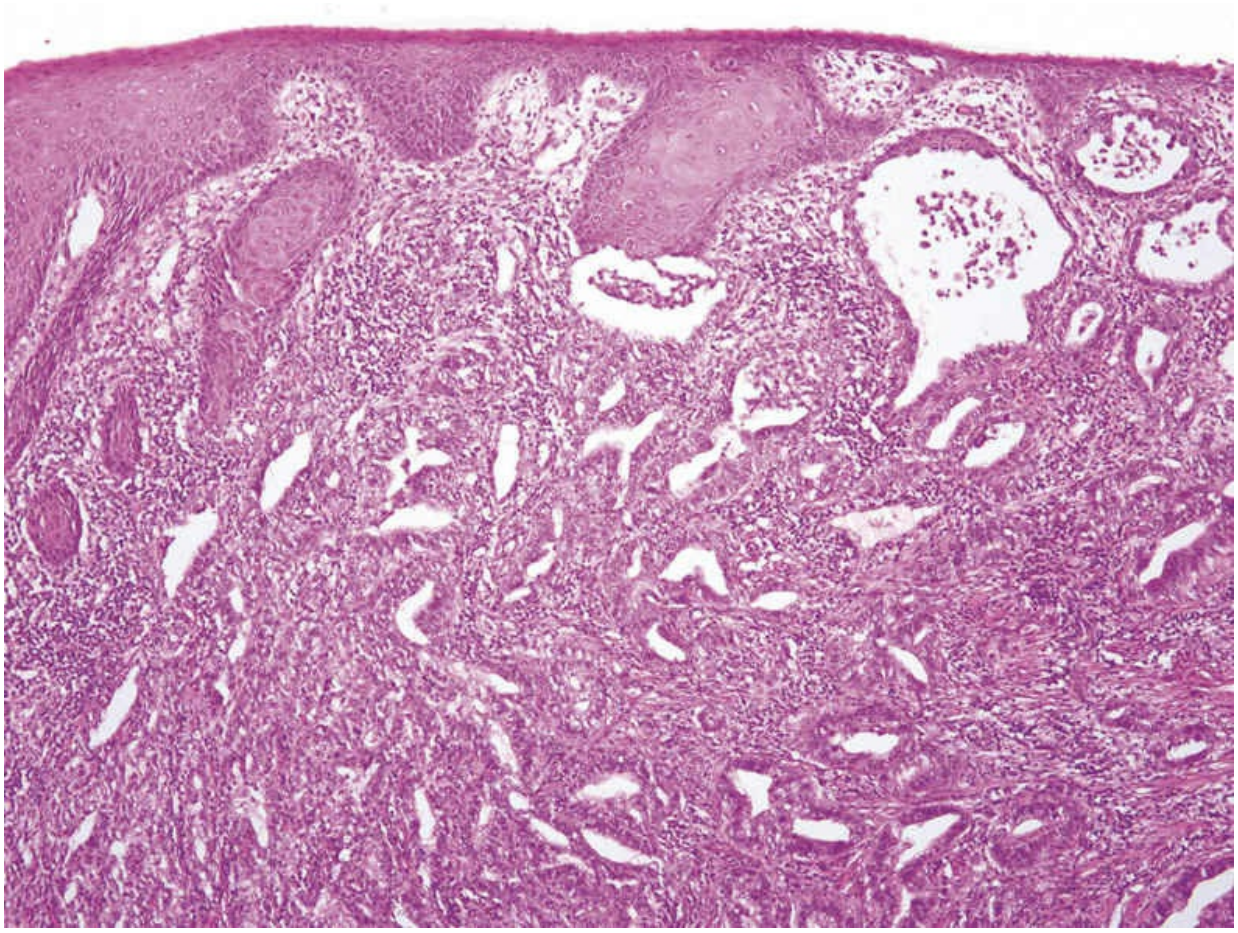

FIGURE 1-9 Pseudoepitheliomatous hyperplasia associated with an adenocarcinoma. This is a high-magnification image of the same lesion as that seen in Fig. 1.8. The surface squamous component is benign and simply reacting to the adenocarcinoma beneath it.

Like granular cell tumors in the skin and elsewhere, esophageal granular cell tumors show strong S100 protein expression (Fig. 1.10). Remember that a high-quality S100 protein preparation should display both nuclear and cytoplasmic labeling.

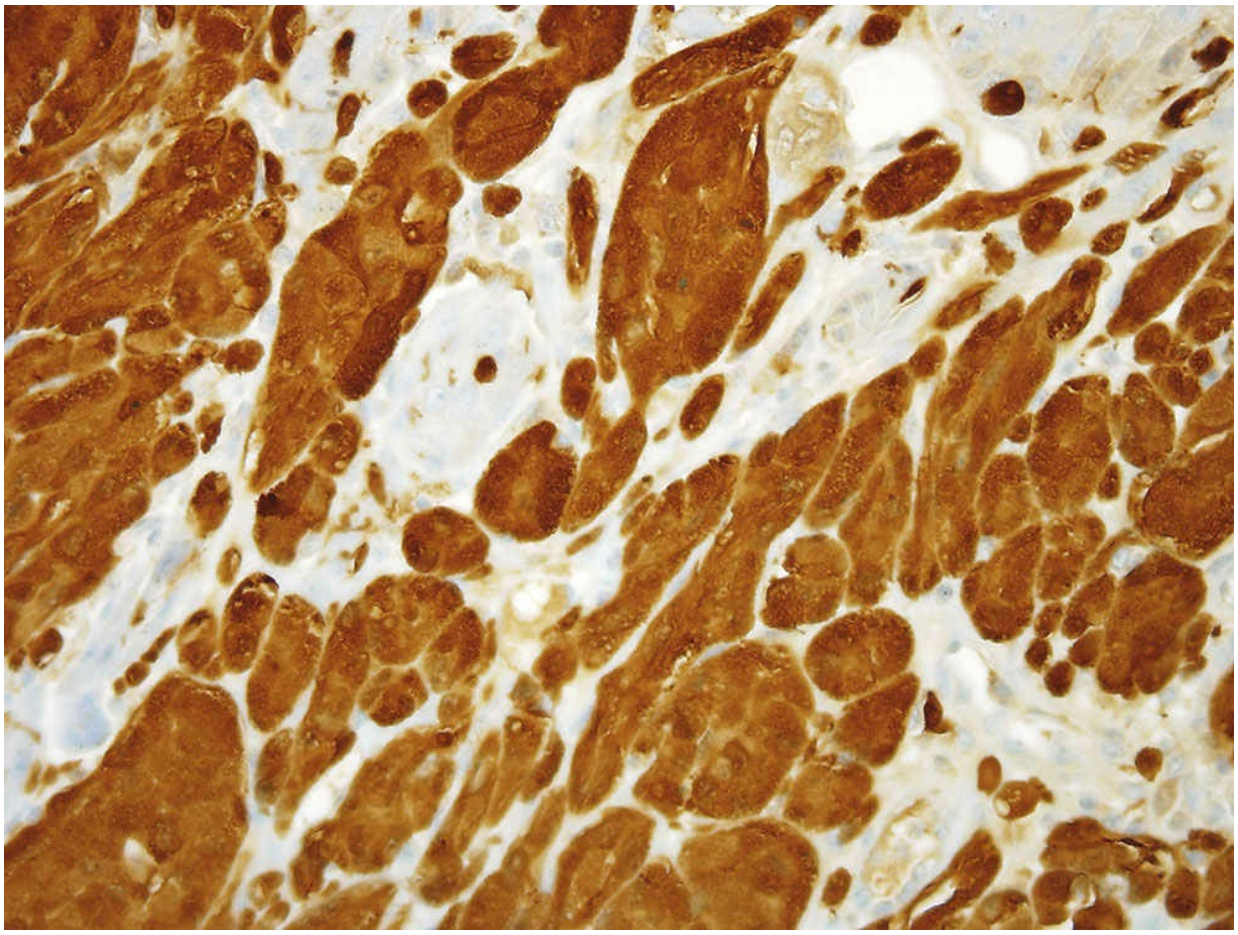

FIGURE 1-10 Granular cell tumor. This stunning S100 protein immunohistochemical stain shows striking nuclear and cytoplasmic expression.

Leiomyoma

Leiomyoma is by far the most common spindle cell tumor of the esophagus, but it is still uncommon. Esophageal leiomyomas arise in young patients (well, at least compared with one of the authors—median age, 35 years),[9] with a male predominance. They consist of cells with eosinophilic cytoplasm (Fig. 1.11) and express desmin and alpha-smooth muscle actin, but not CD117 and CD34. The important pitfall to be aware of in diagnosing gastrointestinal tract leiomyomas is that, if one performs immunolabeling for CD117 and DOG1, these stains label Cajal cells that are either entrapped in or proliferating along with the lesion (Fig. 1.12). For this reason, confident morphologists avoid these stains. Esophageal leiomyomas are easy to diagnose on staining with hematoxylin and eosin (H&E)—they are hypocellular, pink, and benign.

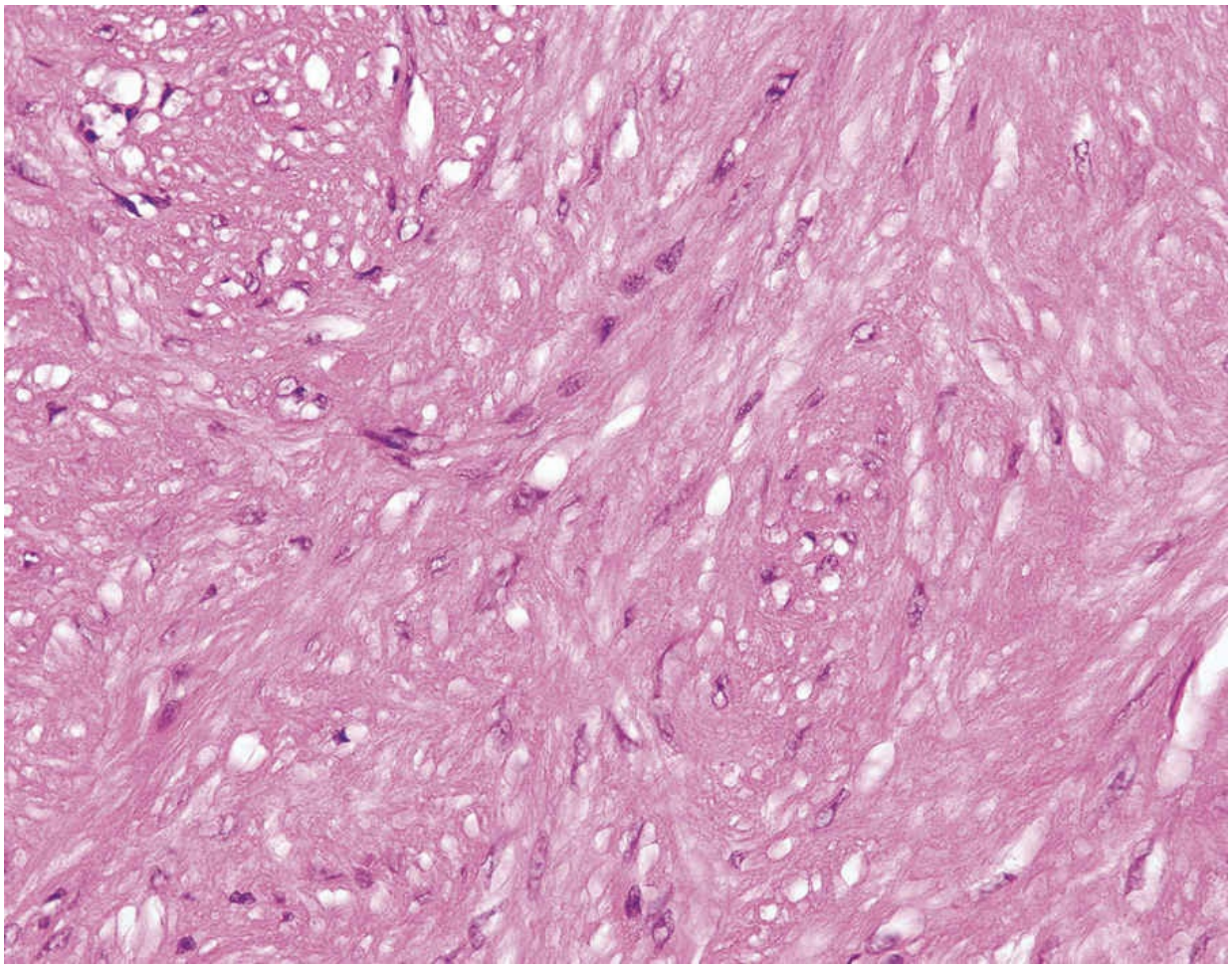

FIGURE 1-11 Esophageal leiomyoma. The lesional cells are brightly eosinophilic, and the tumor has low cellularity. The cytoplasm is fibrillary, and paranuclear vacuoles are present.

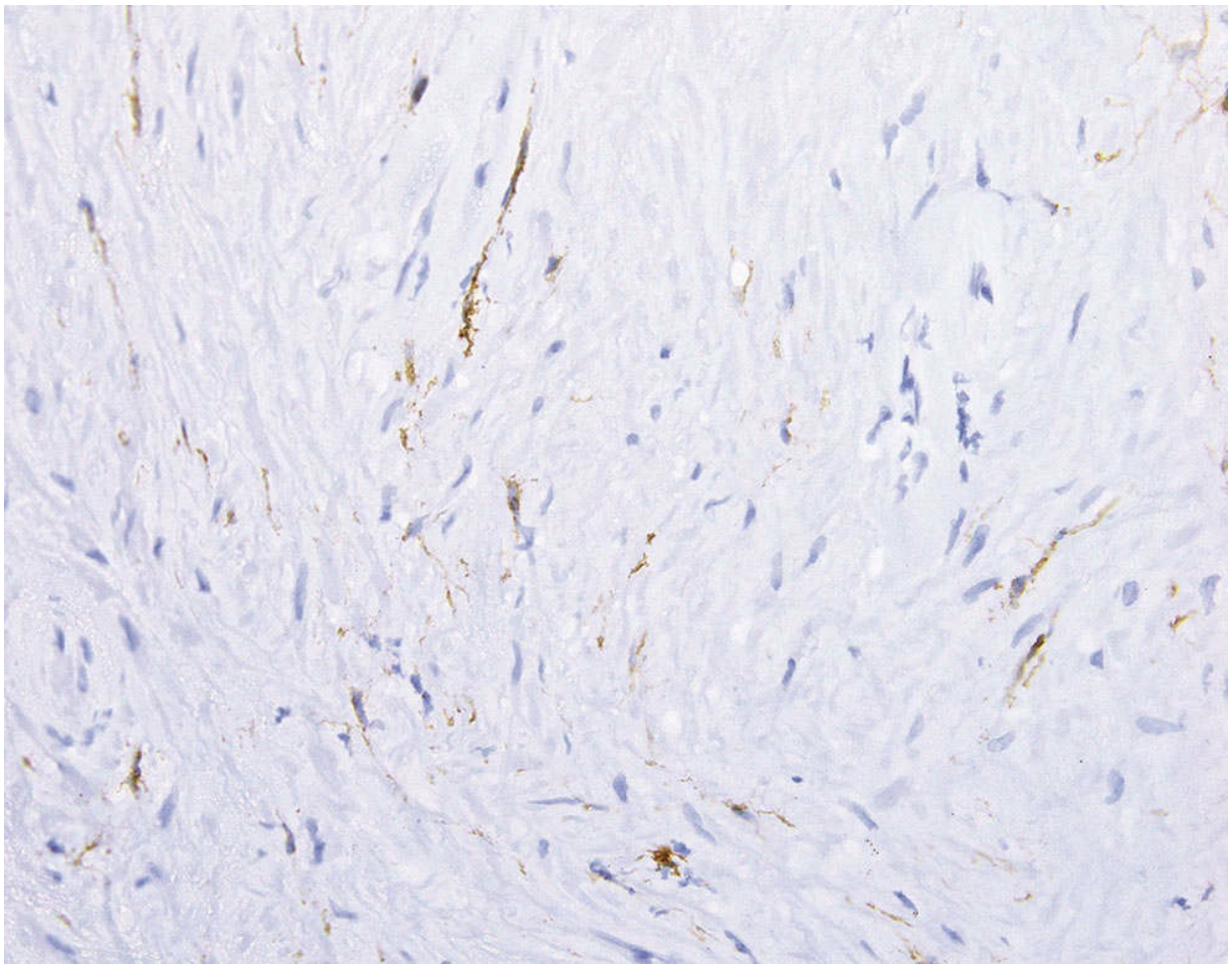

FIGURE 1-12 Esophageal leiomyoma. This is a CD117/KIT stain. Do not be fooled by the scattered labeled cells. Whether these are entrapped Cajal cells or an integral part of the leiomyoma is not clear, but they should not result in an interpretation of gastrointestinal stromal tumor.

Gastrointestinal Stromal Tumors of the Esophagus

GISTs predominate in the stomach and intestines, but they are vanishingly rare in the esophagus. Even the combined files of the former Armed Forces Institute of Pathology and the Haartman Institute of the University of Helsinki yielded only 17 examples of esophageal GISTs![9] They arose in the lower third of the esophagi of adults (12 men and 5 women), with a median age of 63 years). Patients most commonly presented with dysphagia. Compared with leiomyomas, GISTs have an overall basophilic appearance and combinations of solid, myxoid, and perivascular collarlike patterns (Figs. 1.13–1.15). GISTs are discussed in "Stomach" and "Mesenchymal Lesions" chapters in more detail, but those

in the esophagus are truly rare.

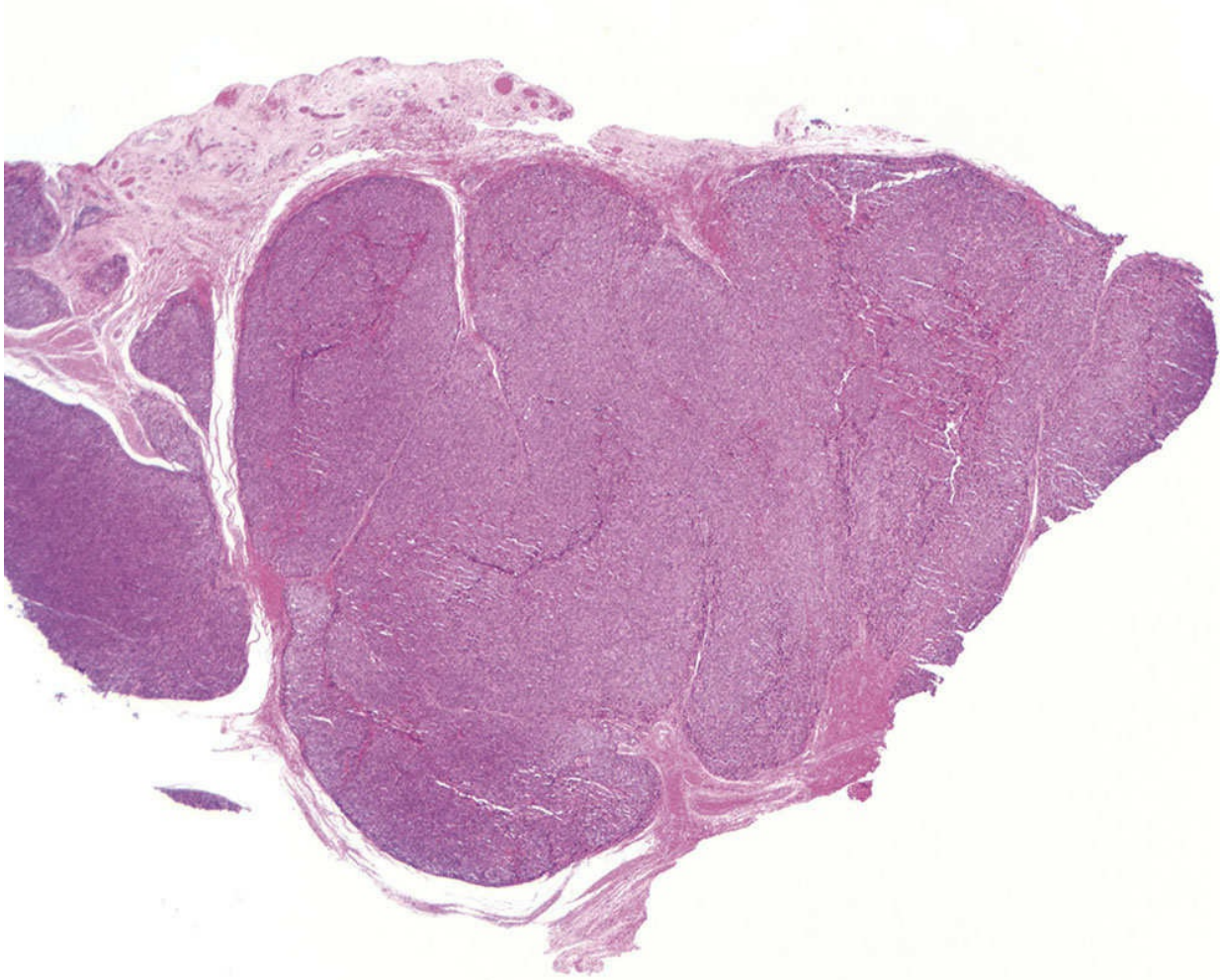

FIGURE 1-13 Esophageal gastrointestinal stromal tumor. These lesions are rare in contrast to gastric gastrointestinal stromal tumor. Note the prominent cellularity, a striking difference from the cellularity of the leiomyoma in Figs. 1.11 and 1.12.