Lizhi Zhang
Vishal S. Chandan
Tsung-Teh Wu
Editors

Surgical Pathology of Non-neoplastic Gastrointestinal Diseases

Springer

Surgical Pathology of Non-neoplastic Gastrointestinal Diseases

Lizhi Zhang • Vishal S. Chandan • Tsung-Teh Wu
Editors

Surgical Pathology of Non-neoplastic Gastrointestinal Diseases

Springer

Editors
Lizhi Zhang
Mayo Clinic
Rochester, MN
USA

Vishal S. Chandan
University of California Irvine
Irvine, CA
USA

Tsung-Teh Wu
Mayo Clinic
Rochester, MN
USA

ISBN 978-3-030-15572-8 ISBN 978-3-030-15573-5 (eBook)
https://doi.org/10.1007/978-3-030-15573-5

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

In the last few years, there have been significant additions and advances in both our knowledge and our concepts regarding many nonneoplastic gastrointestinal (GI) tract entities. The advances in endoscopic techniques have led to an increased number of GI tract biopsies being performed. New surgical techniques have also led to increased GI surgeries being performed with minimal morbidity. The pathology of these GI entities is intriguing, varied, and very important for most surgical pathologists. The proper diagnosis and classification of nonneoplastic GI pathology are vital for correct patient management decisions.

This book has been written for a broad target audience with the aim of it being of interest and benefit to pathologists who are already in practice to those who are just beginning their training in pathology. All of the authors are practicing GI/liver pathologists or gastroenterologists at the Mayo Clinic, where we are very fortunate to see an extensive number and a wide variety of cases in GI pathology. We are also grateful for the wealth of consult cases shared with us over the years by pathologists like you, and many of the rare cases illustrated in this book came from you! The chapters in this book reflect the current literature on the topics in the field of nonneoplastic GI pathology with important inputs from personal experiences of the authors.

This book includes chapters that provide an in-depth coverage of topics in GI pathology which we believe the readers will find useful. Each major/common entity within the chapters is described in detail with its definition, clinical features, pathological features (covering both the gross and microscopic details), differential diagnosis, and treatment/prognosis. All the chapters also highlight the use of special/immunohistochemical stains and other supporting studies as needed with a focus on providing a practical differential diagnosis rather than just a list of potential associations. This book has also been extensively illustrated with both gross and microscopic images to be an integral part of the information provided in the text.

We would also like to acknowledge the exceptional administrative support of Crystal Holtz, Amanda Rudat, Alison Smarzyk, Laurie Frazier, Monica Kendall, and Courtney Hyland for this book.

Finally, this book has been written for surgical pathologists by surgical pathologists who have a passion for GI pathology. We enjoy and love to read, talk, write, and sign out GI pathology cases. We hope that our zest for GI pathology comes through in this book and we would be able to contribute in some way to your understanding and enjoyment of GI pathology.

Rochester, MN, USA — Lizhi Zhang, MD
Irvine, CA, USA — Vishal S. Chandan, MD
Rochester, MN, USA — Tsung-Teh Wu, MD, PhD

Contents

Contributors

Editors

Lizhi Zhang, MD Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Vishal S. Chandan, MD Department of Pathology, University of California – Irvine, Irvine, CA, USA

Tsung-Teh Wu, MD, PhD Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Authors

Ferga C. Gleeson, MD Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Murli Krishna, MD Department of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville, FL, USA

Jason T. Lewis, MD Department of Laboratory Medicine and Pathology, Mayo Clinic Florida, Jacksonville, FL, USA

Taofic Mounajjed, MD Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Bobbi S. Pritt, MD, MSc Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Samar Said, MD Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Audrey N. Schuetz, MD, MPH Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Sejal Subhash Shah, MD Department of Pathology, Kaiser Permanente Southern California, Irvine, CA, USA

Thomas C. Smyrk, MD Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Michael Torbenson, MD Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Saba Yasir, MBBS Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Part I

Introduction

Normal Histology of Gastrointestinal Tract

1

Vishal S. Chandan

Esophagus

Anatomy

The esophagus is a hollow muscular tube that connects the pharynx to the stomach. It begins in the neck region at the cricoid cartilage, traverses through the thorax in the posterior mediastinum, and extends past the diaphragm up to the stomach. In an adult, it measures approximately 25 cm in length. At endoscopy, usually the length of the esophagus is measured as the anatomic distance from the incisor teeth. This corresponds to the esophagus beginning at 15–18 cm from the incisor teeth and extending to the gastroesophageal junction (GEJ) which is located at approximately 40 cm. The adult human esophagus can be divided into cervical, thoracic, and abdominal parts. The upper esophageal sphincter is usually referred to as a 3 cm segment of the proximal esophagus at the level of the cricopharyngeus muscle. The lower esophageal sphincter is usually referred to as a 2–4 cm segment just proximal to the anatomic GEJ, at the level of the diaphragm. Of note, there are no well-established anatomic landmarks that outline these sphincters in relation to the esophageal musculature, though they may be recognized during endoscopy.

The normal esophagus has several points of constriction along its course. They are at the cricoid origin of the esophagus, at the aortic arch, at the crossing of the left main bronchus and left atrium, and at the passage through the diaphragm. These constrictions are clinically relevant as food or medication pills can become lodged at these sites of luminal narrowing resulting in contact mucosal injury to the esophagus [1, 2].

V. S. Chandan (✉)
Department of Pathology, University of California – Irvine, Irvine, CA, USA
e-mail: vchandan@uci.edu

The GEJ is defined as the upper limit of the proximal gastric folds. The anatomic landmarks that can define the GEJ include the peritoneal reflection from the stomach onto the diaphragm or the incisura. Of note, the mucosal GEJ does not correspond to the muscular GEJ. The proximal margin of the gastric folds has been shown to closely correlate with the muscular GEJ and may provide a reasonable and reproducible anatomic landmark for the muscular GEJ [3]. The Z line represents the mucosal squamocolumnar junction seen at endoscopy or on gross examination.

Normal Histology

The esophageal wall consists of four layers: mucosa, submucosa, muscularis propria, and adventitia (Fig. 1.1). The esophagus does not have a distinct serosal lining. Hence, esophageal tumors tend to spread more easily and are difficult to treat surgically. The absence of a serosal layer also makes esophageal luminal disruptions more difficult to repair at surgery.

The mucosa consists of nonkeratinizing stratified squamous epithelium, lamina propria, and muscularis mucosae (Fig. 1.2). Almost the entire length of the esophagus is lined by squamous epithelium which can be divided into basal, prickle, and superficial layers (Fig. 1.3). The basal layer is usually 1 to 3 cells thick and occupies about 5–15% of the epithelial thickness. The prickle and superficial cell layers which lie above the basal layer are rich in glycogen and become flatter toward the surface. The most distal segment of the esophagus which is immediately below the squamous mucosa is normally lined by gastric cardiac-type mucosa and varies in length from a millimeter to about a centimeter. Rare endocrine cells and melanocytes may also exist within the squamous mucosa. Occasional intraepithelial lymphocytes can be seen as a normal finding and usually located in the suprabasal portion of the epithelium. Sometimes, the nuclei of the lymphocytes can become convoluted and may cause confusion with the nuclei of neutrophils (Fig. 1.4).

L. Zhang et al. (eds.), *Surgical Pathology of Non-neoplastic Gastrointestinal Diseases*,
https://doi.org/10.1007/978-3-030-15573-5_1

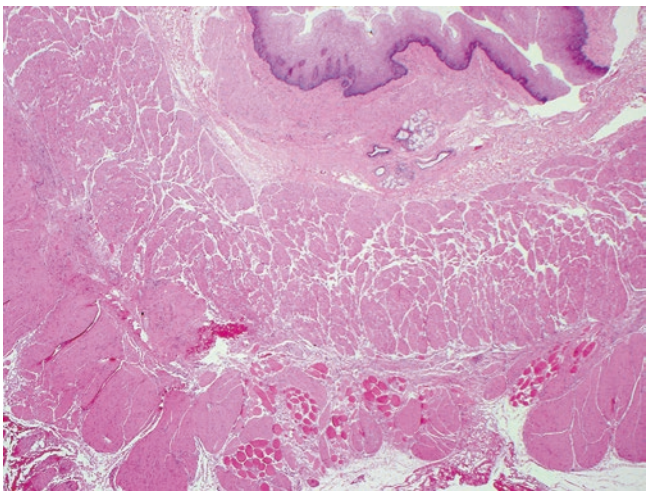

Fig. 1.1 Full-thickness section of esophagus showing four layers: mucosa, submucosa, muscularis propria, and adventitia

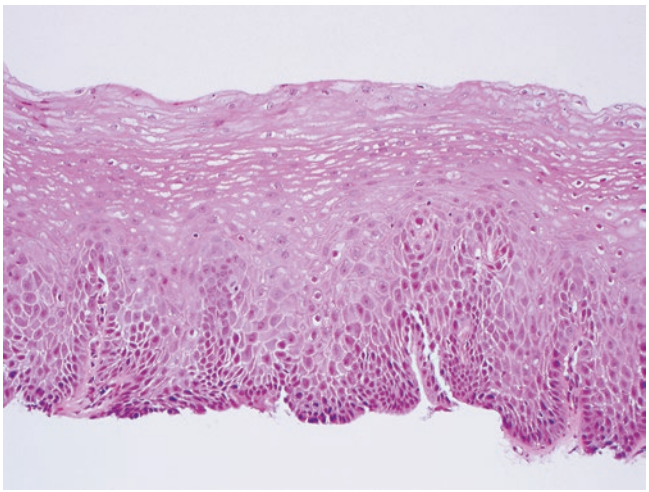

Fig. 1.3 Normal esophageal squamous epithelium, with basal, prickle, and superficial layers; and projections of the lamina propria extending into the overlying epithelium (< 2/3 of epithelial thickness) to form papillae

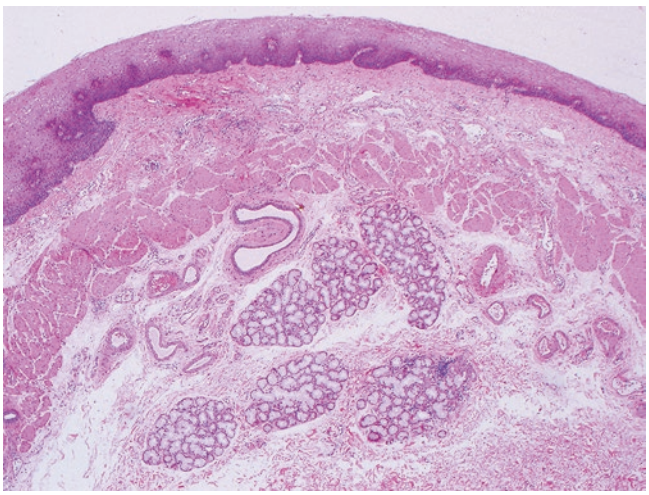

Fig. 1.2 Normal squamous mucosa, consisting of nonkeratinizing stratified squamous epithelium, lamina propria, and muscularis mucosae. The submucosa contains submucosal glands, ducts, and large caliber vessels, which are important anatomic land markers when evaluating submucosal invasion

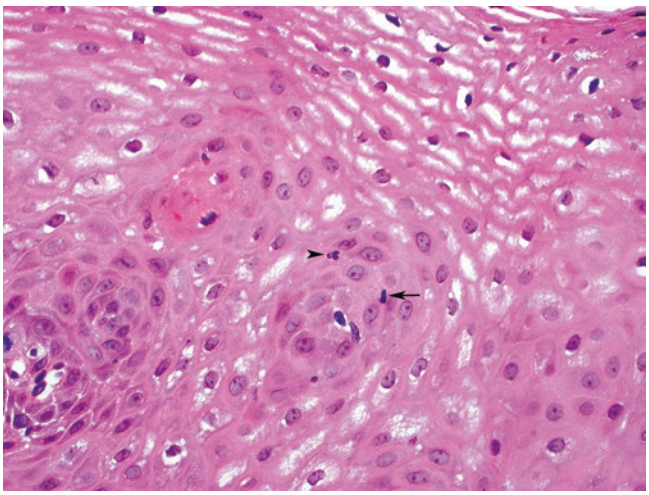

Fig. 1.4 Occasional intraepithelial lymphocytes (arrow) can be seen as a normal finding within the esophagus. Sometimes, the nuclei of the lymphocytes can become convoluted (arrowhead) and may cause confusion with the nuclei of neutrophil

The lamina propria lies beneath the epithelium and above the muscularis mucosae. It consists of connective tissue, vessels, scattered inflammatory cells such as lymphocytes as well as plasma cells, and mucous-secreting glands. Papillae are fingerlike projections of the lamina propria extending into the overlying epithelium, normally less than 2/3 of epithelial thickness (Fig. 1.3). The esophageal cardiac-type glands seen within the lamina propria are composed of cells secreting neutral mucins and resemble the gastric cardiac glands (Fig. 1.5). Their ducts are lined by simple mucus-producing cells. The muscularis mucosa is composed of longitudinally arranged smooth muscle fibers and may be traversed by the squamous epithelium-lined submucosal gland ducts. In cases of Barrett esophagus, the muscularis mucosae may become reduplicated (Fig. 1.6) [4].

The submucosa consists of loose connective tissue containing blood vessels, nerves, lymphatics and submucosal glands (Fig. 1.2). The submucosal glands consist of mucus cells and produce mucin which has a local protective effect (Fig. 1.7). The ducts lining these submucosal glands are proximally lined by a single layer of cuboidal epithelium which more distally becomes stratified squamous epithelium

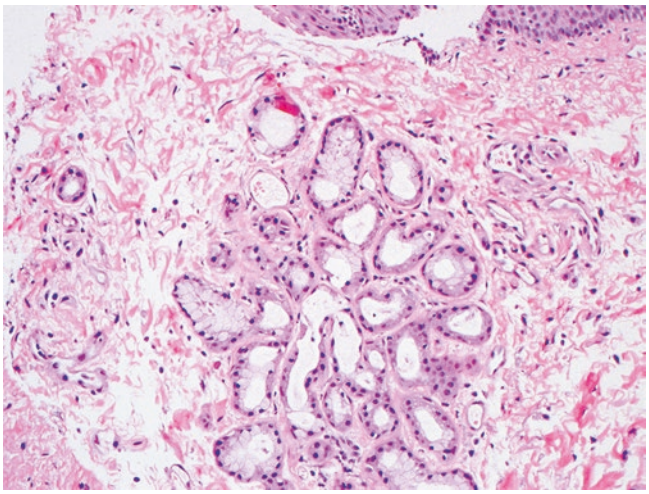

Fig. 1.5 Esophageal mucous-secreting glands in the lamina propria, similar to cardiac-type glands

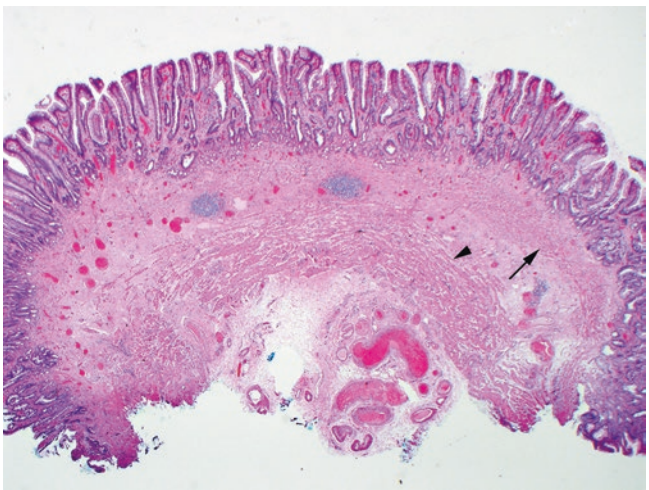

Fig. 1.6 Endoscopic mucosal resection showing duplication of the muscularis mucosae in a case of Barrett esophagus. The original muscularis mucosa is thicker and seen below (arrowhead). The duplicated, more delicate muscle layer is seen superficially (arrow). The fibroconnective tissue between these two layers should not be confused as submucosa

as it penetrates the muscularis mucosae and overlying epithelium to open into the esophageal lumen. Small periductal aggregates of lymphocytes and plasma cells can be seen adjacent to the ducts.

The muscularis propria of the esophagus has presence of both striated and smooth muscle. The Auerbach's plexus and its associated interstitial cells of Cajal are found between the two muscle layers. A short proximal segment of the muscularis propria (approximately 5%) is composed only of striated muscle [5]. Distal to the most proximal segment, there is a mixture of smooth and striated muscle fibers. Greater than 50% of the distal muscularis propria is composed only of smooth muscles.

The majority of the esophagus is surrounded by fascia. The serosa lines only short segments of the thoracic and intra-abdominal esophagus derived from the pleura and peritoneum, respectively.

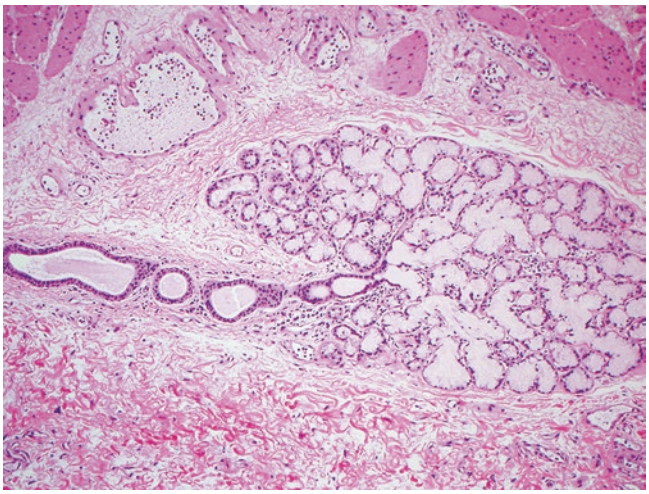

Fig. 1.7 Esophageal submucosal glands and ducts

Lymphatic Drainage

The esophagus has a rich supply of lymphatic vessels which form anastomosing networks within the submucosa and connecting longitudinal channels in the muscularis propria. The cervical esophagus primarily drains into the internal jugular and paratracheal lymph nodes, while the thoracic esophagus drains into the mediastinal and bronchial lymph nodes and the abdominal esophagus into the subdiaphragmatic lymph nodes. Esophageal carcinomas can show wide nodal metastasis due to their rich lymphatic network. Unlike the colon, the esophageal mucosa contains lymphatics, accounting for the small but definite risk of lymph node metastasis for intramucosal esophageal carcinomas [6, 7].

Innervation

Both parasympathetic and sympathetic nerves supply afferent and efferent fibers to the esophagus. The vagus nerve supplies both parasympathetic and sympathetic fibers to the esophagus. Cervical and paravertebral sympathetic fibers also end at the esophagus. The esophagus also has its own intrinsic innervation system composed of Meissner's plexus (ganglion

cells in the submucosa) and Auerbach's plexus (between the circular and longitudinal layers of the muscularis propria). The submucosal and muscle layers of the esophagus also contain widely distributed interstitial cells of Cajal.

Stomach

Anatomy

The stomach is an extremely distensible J-shaped organ located in the upper abdomen. At its upper end, it joins the esophagus, just left of the midline and below the diaphragm. Inferiorly, it connects to the duodenum, just right of the midline. Grossly, the stomach can be divided into four regions: cardia, fundus, body (corpus), and antrum [8]. The inferolateral margin of the stomach is known as the greater curvature, while the superomedial margin is known as the lesser curvature. The point where the tubular esophagus becomes the stomach is known as the GEJ. Generally, the GEJ is at the same level where the squamous esophageal mucosa transitions to the gastric mucosal folds. The gastric cardia is a small and ill-defined area found just distal to the lower end of the esophagus, extending approximately 1–3 cm from the GEJ. The gastric fundus is the portion of the stomach that lies above the GEJ, but just below the hemidiaphragm. The gastric antrum constitutes the distal 1/3 of the stomach, extending distal to the incisura and proximal from the pyloric sphincter. The remainder of the stomach is referred to as the gastric body (corpus). Of note, some do not distinguish between the corpus and the fundus and designate both parts of the stomach as fundus since they have the same type of mucosa. The term rugae applies to the thickened folds of the gastric mucosa. The incisura angularis is the angle along the lesser curvature which marks the approximate point at which the stomach narrows before joining the duodenum.

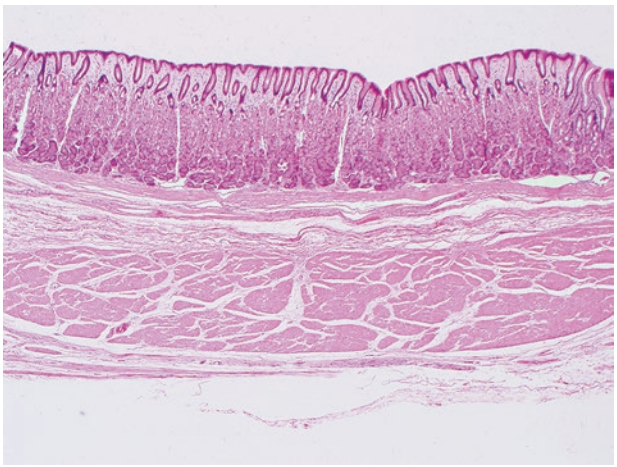

Fig. 1.8 Full-thickness section of stomach showing four layers: mucosa, submucosa, muscularis propria, and serosa

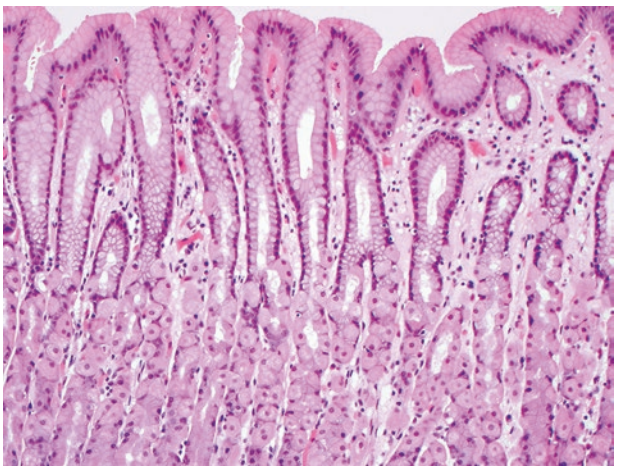

Fig. 1.9 Gastric foveolae. The mucosal surface epithelium and gastric pits are composed of tall, columnar, and mucous-secreting cells with basally situated nuclei and mucus-filled cytoplasm

Normal Histology

The gastric wall consists of four layers: mucosa, submucosa, muscularis propria, and serosa (Fig. 1.8). The gastric mucosa has two main epithelial components: the superficial foveolar component and the deeper glandular component (Figs. 1.9, 1.10, and 1.11). Throughout the entire stomach, the foveolar component is relatively uniform comprising tall, columnar, and mucous-secreting cells with basally situated nuclei and mucus-filled cytoplasm. These foveolar cells line the entire mucosal surface and gastric pits (foveolae) (Fig. 1.9). The deeper layer consists of coiled glands that empty into the base of these foveolae. However, the glandular layer of the stomach differs in structure and function depending on the individual gastric zone.

Within the gastric cardia, the foveolae occupy about half of the mucosal thickness (Fig. 1.10). It contains mucus-secreting

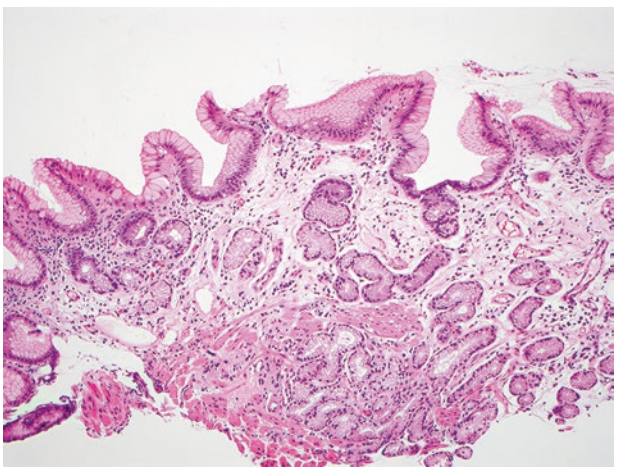

Fig. 1.10 Gastric cardiac mucosa. The foveolae are overlying mucus-secreting glands and occupying about half of the mucosal thickness. Inflammatory cells are typically present in the lamina propria

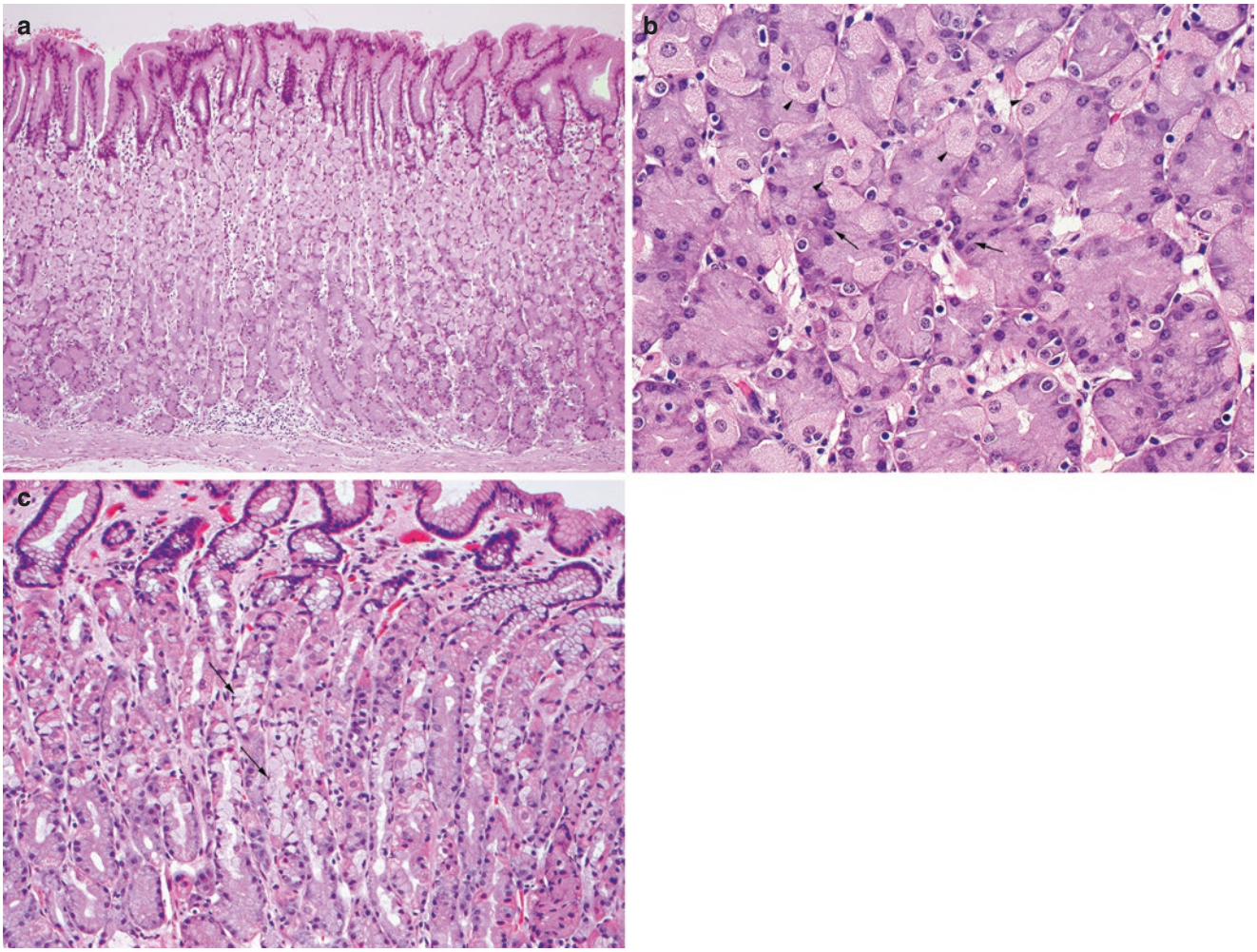

Fig. 1.11 Gastric fundic mucosa. (**a**) The oxyntic glands beneath the foveolae consist of tightly packed straight glands and are divided into three portions: base, neck, and isthmus. (**b**) Chief cells (black arrow) characterized by cuboidal shape with basophilic cytoplasm and basally situated nuclei; parietal cells (arrowhead) have a characteristic "fried-egg" appearance with acidophilic cytoplasm and centrally placed nuclei; endocrine cells (white arrow), sitting between the chief cells with a round shape, distinct cell border, and clear cytoplasm. (**c**) Mucous neck cells (arrows) intermixed with chief cells and parietal cells in the junctional region of the gastric pits and glands, characterized by clear or vacuolated cytoplasm with basal nuclei

glands that are loosely packed with abundant intervening lamina propria. The mucus cells have ill-defined borders and a bubbly cytoplasm. They secrete mucus and pepsinogen II. Single or small clusters of oxyntic cells may also be seen especially near the junctional zone with the fundus.

The fundic (oxyntic gland) mucosa found in the fundus and body shows tightly packed straight glands with little intervening lamina propria. They can be divided into three parts: base, neck, and isthmus (Fig. 1.11a). The chief/zymogenic cells (pepsinogen I and II secreting) are the major component of the basal portion. These cells are cuboidal with basophilic cytoplasm (due to the presence of a rough endoplasmic reticulum rich in ribosomal ribonucleic acid), basally situated nucleus with small nucleoli (Fig. 1.11b). The parietal cells (acid and intrinsic factor secreting) predominate in the isthmic portion of the glands [9]. These cells are triangular in shape with the base parallel to the basement membrane. They have a deep pink-colored (acidophilic) cytoplasm (due to abundant microcanaliculi composed of protein) with a centrally placed nucleus (Fig. 1.11b). They can be highlighted by the use of human milk fat globulin antibody [10]. The neck portion contains a mixture of zymogenic and parietal cells with admixed mucous neck cells. These mucous neck cells resemble the mucus cells in the pyloric region but can be difficult to appreciate on the H&E stain and can be highlighted on the PAS stain (Fig. 1.11c).

The antral and pyloric glands are identical with the foveolae occupying about half of the mucosal thickness (Fig. 1.12a). Both regions contain mucus-secreting glands that are loosely packed with abundant intervening lamina propria. Single or small clusters of oxyntic cells may also be seen especially near the junction with the gastric body (Fig. 1.12b).

The stomach also contains a variety of endocrine (hormone producing) cells. In the gastric antrum, the gastrin-producing G cells comprise approximately 50% of the entire

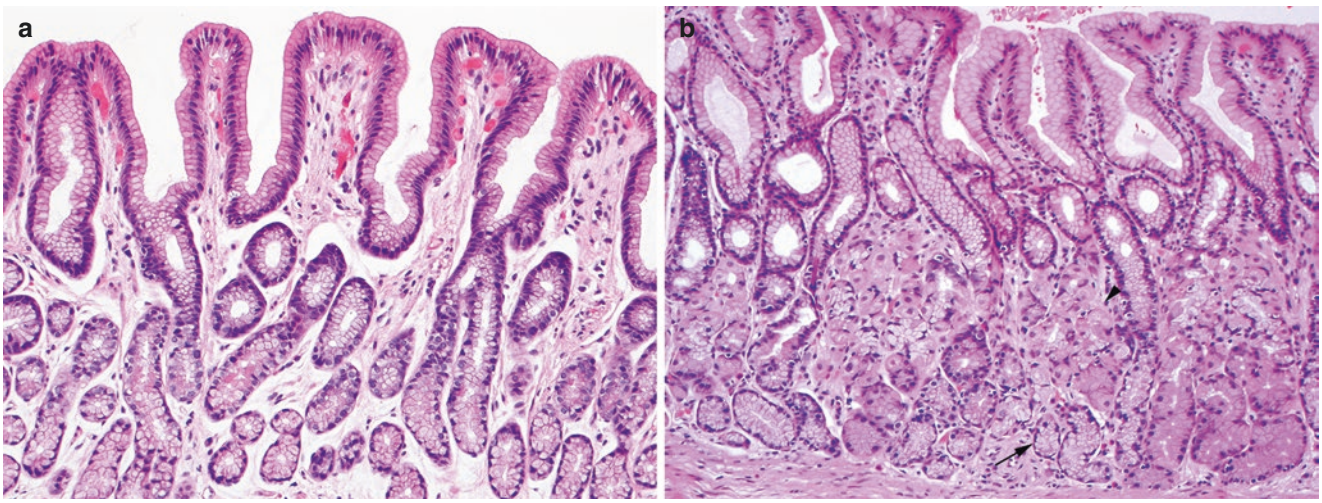

Fig. 1.12 (**a**) Gastric antral mucosa composed of foveolae and pyloric glands, with each occupying about half of the mucosal thickness. (**b**) Antral fundic transitional zone mucosa, containing both pyloric glands (arrow) and oxyntic glands (arrowhead)

endocrine cell population, approximately 30% are serotonin-producing enterochromaffin (EC) cells, and about 15% are somatostatin-producing D cells. In the fundic mucosa, the histamine-secreting enterochromaffin-like (ECL) cells predominate, with smaller numbers of EC cells and X cells (producing unknown secretion). These endocrine cells are usually inconspicuous and difficult to appreciate on H&E stain. However, on closer inspection, they are round in shape, with clear cytoplasm and small nuclei (Fig. 1.11b). In the fundic mucosa, the endocrine cells are mostly located toward the base of the glands and are range in 10–20 cells per crypt. However, in the antral mucosa, these endocrine cells are more numerous ranging between 20 and 50 cells per crypt, located in the neck region. Immunostains such as chromogranin and synaptophysin can be used to highlight these endocrine cells [11]. Individual hormones such as gastrin can also be demonstrated by specific antibodies.

The lamina propria consists of a fine meshwork of reticulin, collagen, and elastic fibers beneath the basement membrane, providing structural support to the overlying epithelium. A mixture of few lymphocytes, plasma cells, macrophages, and fibroblasts can be seen within the lamina propria. Occasional neutrophils and mast cells may also be present. The lamina propria also contains nerve fibers, capillaries, vessels, and lymphatics. Occasional small lymphoid aggregates composed of small lymphocytes (primary lymphoid follicles) can also be seen within the lamina propria in a normal stomach [12]. The muscularis mucosae consist of two layers: the inner circular and outer longitudinal.

The submucosa lies between the muscularis mucosae and muscularis propria. It is composed of loose connective tissues containing elastic fibers. A network of veins, arteries, and lymphatics as well as the Meissner's nerve plexus is found in the submucosa.

The muscularis propria is composed of three layers: outer longitudinal, inner circular, and the innermost oblique. The oblique layer is incomplete in nature and is present anterior to the circular layer and is most obvious in the cardiac region. At the pylorus, the inner circular layer forms the pyloric sphincter.

Lymphatic Drainage

The lymphatic drainage of the stomach has been identified into four main areas. The left gastric lymph nodes comprise the largest group, draining the lower end of the esophagus and most of the lesser curvature. The right gastric and hepatic nodes drain the pyloric region and the lesser curvature. The pancreaticosplenic nodes drain the proximal portion of the greater curvature, while the distal portion of the greater curvature drains into the right gastroepiploic and pyloric lymph nodes.

The gastric lamina propria immediately superficial to the muscularis mucosae has a network of lymphatics which penetrate the muscularis mucosae and communicate with the lymphatic channels present in the submucosa. Hence, intramucosal gastric adenocarcinomas that are even entirely superficial to the muscularis mucosae have a potential for lymph node metastasis.

Innervation

The celiac plexus supplies the sympathetic nerves to the stomach. The left and right phrenic nerves also innervate the stomach. The vagus nerve provides the parasympathetic supply to the stomach. Of note, either side of the subserosal layer of the stomach is devoid of true nerve plexus.

Small Bowel

Anatomy

The small bowel extends from the gastric pylorus to the cecum and measures approximately 6–7 m in adults [13]. It is divided into three parts: duodenum, jejunum, and ileum. The duodenum measures approximately 12 inches in length and is the most proximal portion of the small bowel, extending from the gastric pylorus into the duodeno-jejunal flexure. The duodenum itself is subdivided into four parts: The first portion known as the duodenal cap or bulb, the second or descending portion (into which the common bile duct and pancreatic ducts open), the third or horizontal portion; and the fourth or ascending portion which connects to the jejunum. The ligament of Treitz which consists of a strip of fibromuscular tissue marks the origin of the jejunum. Distal to the ligament of Treitz, the rest of the small bowel is subjectively subdivided into the jejunum (the proximal two-fifths) and the ileum (the distal three-fifths).

The duodenum is retroperitoneal, while the jejunum lies in the peritoneal cavity. The remainder of the small bowel is intraperitoneal until it ends at the ileocecal valve.

Normal Histology

The wall of the small bowel is divided into four basic layers: mucosa, submucosa, muscularis propria, and serosa (Fig. 1.13). The mucosal lining of the small bowel is designed to provide maximal surface area for the basic function of food absorption [14, 15]. The mucosa is composed of an epithelial layer, lamina propria, and muscularis mucosae. The entire luminal surface of the small bowel is composed of microscopic finger-like projections known as villi (Fig. 1.14). Each villous surface is lined by a single layer of epithelium composed of various cell types, beneath which lies the lamina propria containing a rich network of arteriovenous capillaries and lymphatic channels. The crypts of Lieberkuhn (pit-like crypts or depressions of the surface epithelium) lie beneath the villi in between the intervening regions. The normal villus-to-crypt ratio ranges between 3:1 and 5:1 [14].

Four main cell types are identified within the surface epithelium of the small bowel: absorptive cells, goblet cells, endocrine cells, and Paneth cells. The absorptive cells are the most common type seen within the surface epithelium. They are tall and columnar and have an eosinophilic cytoplasm and basally located round nucleus. A brush border composed of microvilli and glycocalyx is seen on their luminal surface. The microvilli are best seen on ultrastructural examination, and the brush border can also be highlighted on the PAS stain or CD10 immunostain (see Fig. 9.23). The goblet cells are scattered among the absorptive cells. They are characterized by presence of apical mucin droplet with an attenuated and basally situated nucleus. The numbers of goblet cells increase from the duodenum toward the ileum. Endocrine cells are more abundant within the crypts, but they can also be scattered within the villous epithelium. The cytoplasm of these endocrine cells contains abundant fine eosinophilic granules which contain secretory products. The main portion of the endocrine cell is located at the base of the epithelium. They have a small nucleus which is present on the luminal side of the cytoplasmic granules. The Paneth cells have bright coarse eosinophilic granules which are api-

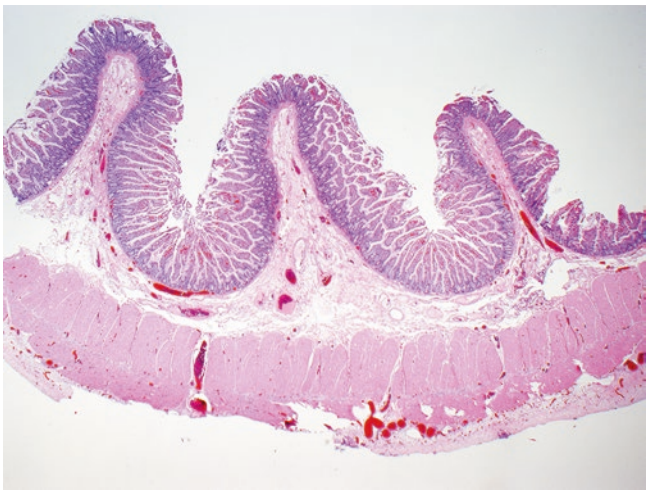

Fig. 1.13 Full-thickness section of small bowel showing four layers: mucosa, submucosa, muscularis propria, and serosa. Note the villi sitting on the mucosal circular folds (plicae circulares)

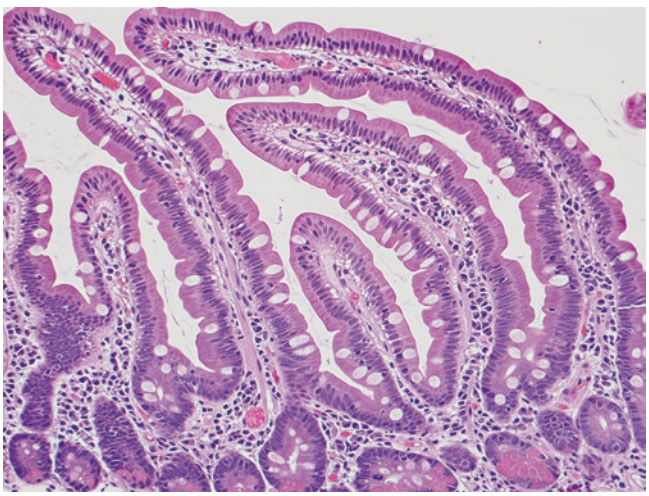

Fig. 1.14 Normal small bowel villi. Finger-like projections lined by a single layer of absorptive epithelium interspersed with goblet cells lying on lamina propria containing some inflammatory cells, a rich network of arteriovenous capillaries and lymphatics. Note the Paneth cells at the base of the crypts

cally oriented. The Paneth cells secrete growth factors and antimicrobial proteins which play a role in immunity against bacterial infections. The size as well as color of the eosinophilic cytoplasmic granules and the position of the nucleus help in the histologic distinction between endocrine cells and Paneth cells. The Paneth cell granules are larger, coarser, brightly eosinophilic, and apical relative to the basally located cell nucleus. In contrast, the endocrine cell granules are smaller, finer, deeply eosinophilic, and basally oriented relative to the apically displaced nucleus. Of note, it may be difficult to appreciate the Paneth cells on H&E-stained sections if the tissue is fixed in fixatives containing picric acid (like Hollande's or Bouin's) as they mask the eosinophilic staining of the granules [16].

There are two specific structures in the second portion of the duodenum: major and minor duodenal papilla. The major duodenal papilla is the landmark separating foregut and midgut, where common bile duct and pancreatic duct open into the duodenum, and the minor duodenal papilla is the opening of the accessory pancreatic duct which is typically located 2 cm proximal to the major papilla. The histology of the major papilla is different from the adjacent duodenal mucosa. It is surrounded by thin smooth muscle bundles, the sphincter of Oddi, and contains ampulla of Vater where the pancreatic duct and the distal common bile duct unite (Fig. 1.15). The epithelium at the major papilla tends to be flat and often has focal gastric mucinous metaplasia. There is no muscularis mucosae and submucosal tissue in the papilla. The ampulla of Vater is lined by cuboidal to low columnar pancreaticobiliary-type epithelium with occasional goblet cells, but no absorptive-type cells. The epithelium may form papillary structures. There are peribiliary glands and pancreatic acini in the vicinity. Understanding the local anatomy and normal histology is important when evaluating carcinoma arising around the papilla, ampulla, distal common bile duct, or pancreatic head.

Small nodules of lymphoid tissue can be seen within the mucosa of the small bowel. Few scattered intraepithelial lymphocytes (one lymphocyte for every four to five epithelial cells) can also be seen within the normal small bowel [17–19]. These intraepithelial lymphocytes are CD3 positive, and majority of them also express CD8 [20, 21]. The intraepithelial lymphocytes usually decrease in number from the base toward the tip within the normal small bowel (Fig. 1.16; also see Fig. 9.2).

The framework of the lamina propria is composed of interweaving collagen bundles and other connective tissue fibers. A network of blood capillaries, lymphatics, and nerve fibers courses through the lamina propria. The lamina propria of the small bowel also contains numerous lymphocytes, plasma cells, and eosinophils. A few histiocytes, dendritic cells, and mast cells may also be present. The lamina propria rests upon a thin fibromuscular layer known as the muscularis mucosae, which separates the mucosa from the underlying submucosa.

The submucosa which lies between the muscularis mucosae and muscularis propria is composed of a mixture of collagenous and elastic fibers with fibroblasts. Few scattered inflammatory cells such as histiocytes, lymphocytes, and plasma cells can be seen within the submucosa along with adipose tissue. The submucosa also contains a rich network of large arterials, venules, and lymphatics. Neural structures are also present in the submucosa, including the Meissner's plexus.

The submucosa of the duodenum contains the Brunner's glands. They are most concentrated in the gastroduodenal

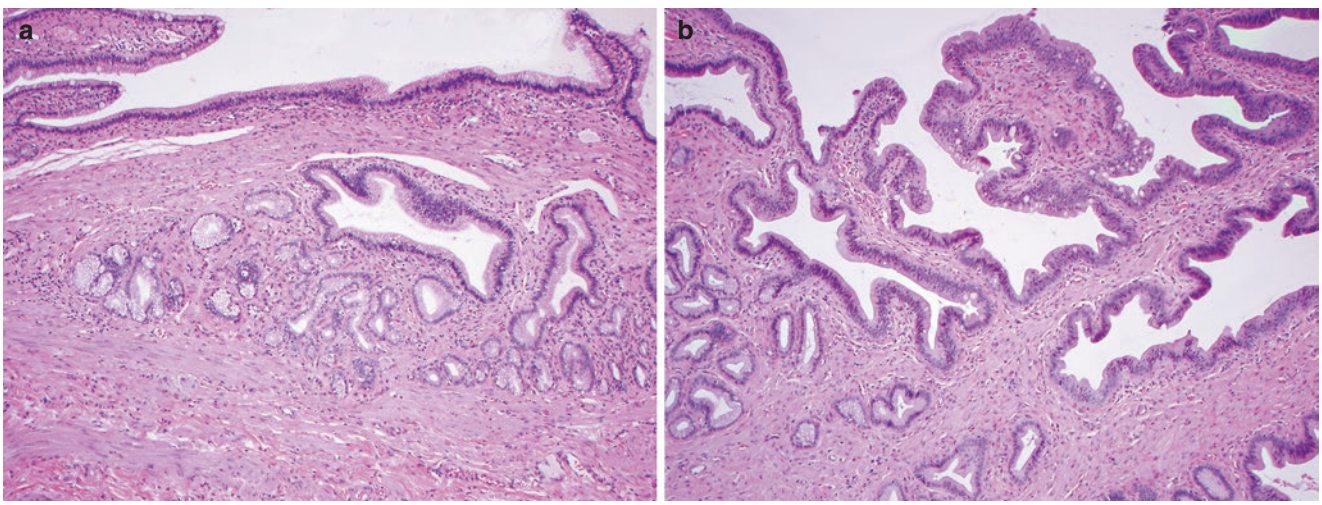

Fig. 1.15 Major papilla and ampulla of Vater. (**a**) The major papilla is lined by flat epithelium showing gastric mucinous metaplasia and surrounded by thin smooth muscle bundles of sphincter of Oddi. (**b**) The ampulla of Vater is lined by cuboidal to low columnar pancreaticobiliary-type epithelium with occasional goblet cells, with a papillary appearance and scattered peribiliary glands

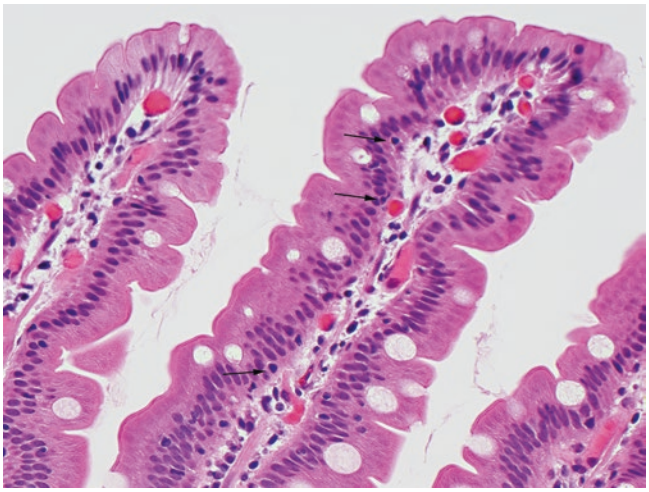

Fig. 1.16 Scattered intraepithelial lymphocytes (arrows) within the normal small bowel mucosa (one lymphocyte for every four to five epithelial cells)

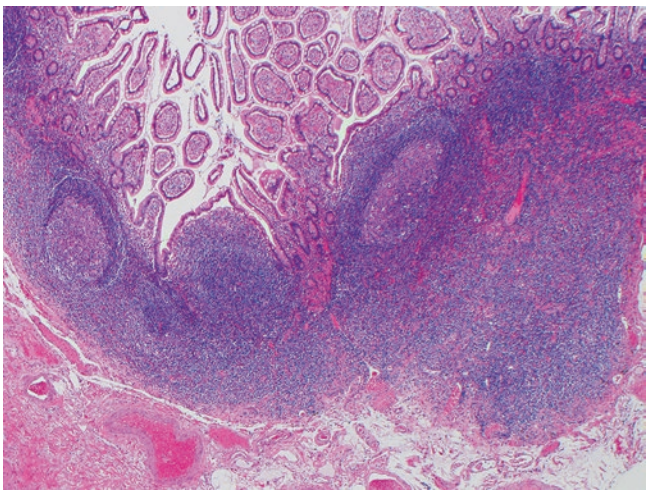

Fig. 1.18 Peyer's patches in terminal ileum containing prominent reactive lymphoid aggregates/follicles in mucosa and submucosa

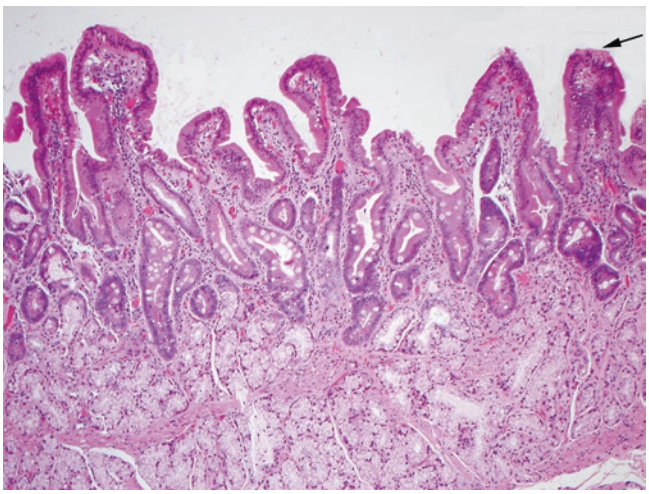

Fig. 1.17 Duodenal bulb mucosa containing abundant Brunner's glands. Note the focal gastric foveolar metaplasia (arrow)

junction and gradually decrease in quantity along the length of duodenum. They serve as microscopic landmark for duodenum. Brunner's glands are lobular collections of glands lined by cuboidal to columnar cells with uniform pale appearing cytoplasm with an oval basally located nucleus (Fig. 1.17). They contain neutral mucin which is PAS positive and diastase resistant. Their ducts are lined by similar epithelium.

The ileum shows prominent well-defined lymphoid tissue including Peyer's patches and isolated lymphoid follicles (Fig. 1.18). Peyer's patches can be seen within the submucosa and also within the mucosa. The follicles within Peyer's patches are composed predominantly of B lymphocytes with admixed follicular dendritic cells and macrophages. Most follicles also contain a germinal center composed of CD10-positive and bcl-2-negative B cells. The germinal center is surrounded by a mantle zone of small IgD-positive and IgM-positive B cells.

The muscularis propria is the outer smooth muscle layer surrounding the submucosa. It consists of an outer longitudinal layer and inner circular area. Blood vessels, lymphatics, and nodes traverse through the muscularis propria. The myenteric plexus of Auerbach lies between the outer longitudinal and inner circular muscle layers. Interstitial cells of Cajal form a network around the Auerbach's plexus and within the circular muscle layer.

The serosa envelopes the outermost surface of the small bowel. It consists of a single layer of cuboidal mesothelial cells, beneath which lies a thin layer of loose connective tissue.

Lymphatic Drainage

The lymphatic drainage of the duodenum occurs to the peripancreaticoduodenual lymph nodes consisting of the retropancreatic, hepatic artery, inferior pancreaticoduodenal, and superior mesenteric lymph nodes. The rest of the small bowel drains along the mesentery to the cecal, ileocolic, superior mesenteric, and mesenteric lymph nodes.

Innervation

The celiac and superior mesenteric plexuses provide the sympathetic nerves to the small bowel. The parasympathetic nerve supply to the small bowel is provided by the vagus nerve.

Appendix

Anatomy

Appendix is a slender tubular structure that protrudes from the posteriomedial aspect of the cecum, originating within about 2 cm below the insertion of the ileum into the cecum. The length of the appendix is quite variable, but on average measures 7–10 cm [22]. It measures approximately 0.3–0.5 cm in diameter. The appendix is covered by the peritoneum along almost its entire external surface.

The exact role of the appendix in the human body is uncertain. Some believe it to be a functionless vestigial structure. However, others have suggested that the lymphocytes derived from the appendix migrate to other sites within the GI tract and help in immunity [23].

Normal Histology

Histologically the appendix is similar to the colon, consisting of four layers, namely, mucosa, submucosa, muscularis propria, and serosa. However, the most prominent feature is the abundance of organized lymphoid tissue which is circumferentially arranged within both the lamina propria and submucosa (Fig. 1.19).

The surface epithelium of the appendix consists of absorptive cells which are tall and columnar with eosinophilic cytoplasm and round basally situated nucleus. These absorptive cells are admixed with goblet cells, neuroendocrine cells, and scattered Paneth cells. The crypts of the appendix are more irregular in shape, length, and distribution when compared to the colon. The crypts may even be absent in areas where the lymphoid tissue is prominent or abundant. Few intraepithelial lymphocytes may be present within the crypt epithelium, but neutrophils and plasma cells are normally absent.

The lamina propria surrounds the crypts and forms a connective tissue framework around them. Plasma cells, lymphocytes, macrophages, eosinophils, and mast cells are normally present within the lamina propria. A varying number of well-defined lymphoid aggregates may be present within the lamina propria, and they may even extend beneath the muscularis mucosae into the underlying submucosa. However, the amount of lymphoid tissue within the appendix varies with age. Of note, in newborns, there may be scant or no lymphoid tissue present. The amount of lymphoid tissue within the appendix increases with age, peaking at around 10 years. Then, it steadily diminishes in quantity throughout the rest of the life. The lamina propria also contains a rich network of blood capillaries, lymphatics, and nerve fibers.

The muscularis mucosae lie beneath the lamina propria, and in the appendix, it may be attenuated, poorly developed, or even focally absent in the areas of prominent lymphoid aggregates.

The submucosa lies between the mucosa and muscularis propria. It consists of a meshwork of elastic and collagenous fibers with admixed fibroblasts. A few lymphocytes, plasma cells, macrophages, and mast cells may be present within the submucosa. Prominent vessels including arterioles, venules, and lymphatics along with the Meissner's plexus are also present within the submucosa.

The muscularis propria of the appendix consists of an inner circular layer and an outer longitudinal layer. The Auerbach's (myenteric) plexus lies between these two muscle layers. The subserosa lies external to the outer longitudinal layer of the muscularis propria. It consists of loose

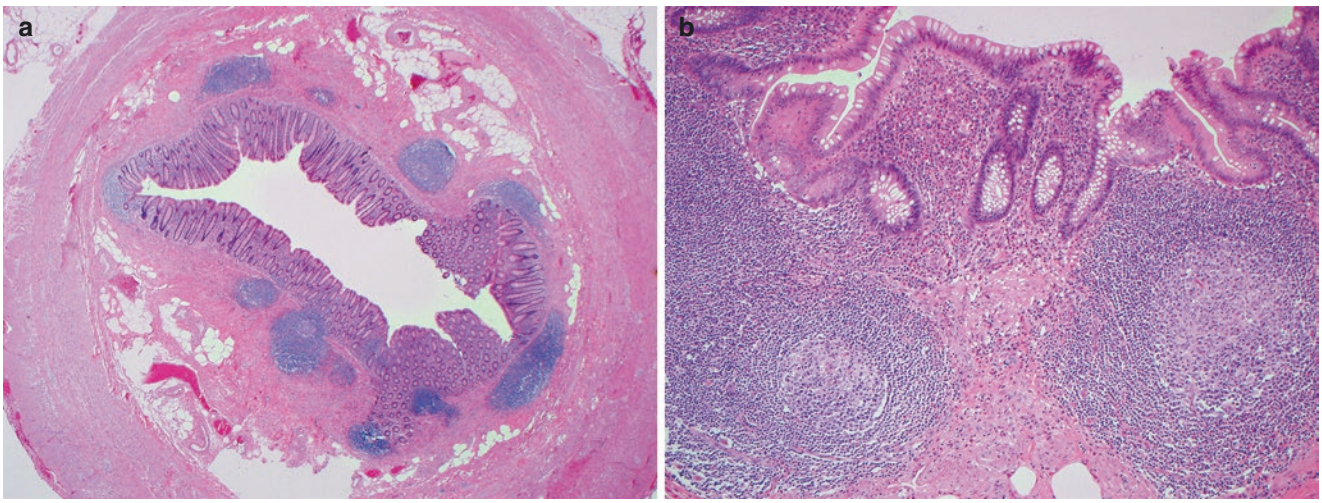

Fig. 1.19 Normal appendix. (**a**) Four layers of appendix: mucosa, submucosa, muscularis propria, and serosa. Scattered lymphoid aggregates circumferentially arranged within both the lamina propria and submucosa. (**b**) Appendiceal mucosa, similar to colonic mucosa, but with irregular crypts and prominent lymphoid aggregates and follicles

connective tissue with intermixed blood vessels, lymphatics, and nerve fibers. The serosa is the outermost layer composed of cuboidal mesothelial cells. Of note, the attachment of the fibrofatty mesoappendix lacks the serosa.

Lymphatic Drainage

The appendix drains into the ileocolic chain of lymph nodes.

Innervation

The parasympathetic nerves to the appendix are derived from the vagus nerve, while the sympathetic nerves come from the superior mesenteric plexus.

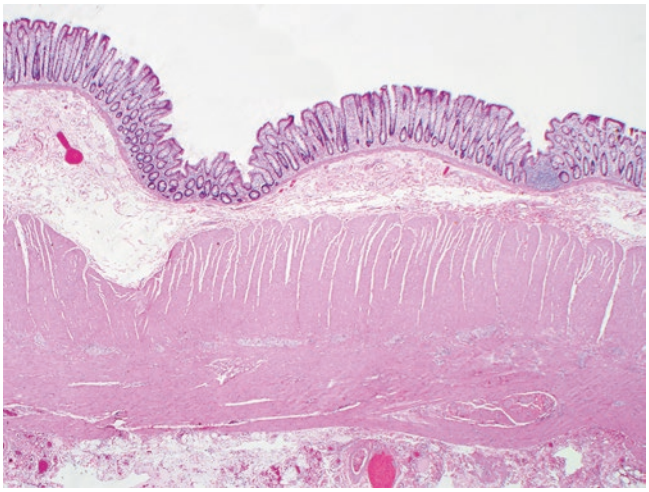

Fig. 1.20 Full-thickness section of colon showing four layers: mucosa, submucosa, muscularis propria, and serosa

Colon

Anatomy

The colon connects the terminal ileum to the anal canal and measures about 1.0–1.5 m in an adult [24, 25]. The major regions of the colon consist of cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum. The cecum is bulbous and along with the ascending colon constitutes the colon on the right side of the abdomen. The ventral surfaces of the cecum and ascending colon are covered by the peritoneum, while their dorsal aspect lies directly on the posterior abdominal wall. The transverse colon extends between the hepatic flexure and splenic flexure and is suspended by the lesser omentum. The descending colon is attached to the left posterior abdominal wall. The sigmoid colon starts around the pelvic rim and is suspended entirely by the mesentery, leading to its increased susceptibility for volvulus. The sigmoid colon connects to the rectum which passes between the peroneal muscles to exit the abdominal cavity.

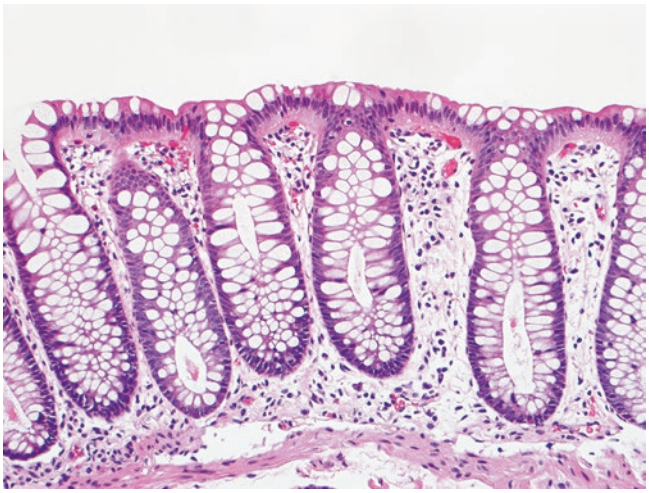

Fig. 1.21 Normal colonic mucosa. Regularly and parallelly arranged crypts perpendicular to the muscularis mucosae consisting of absorptive cells, goblet cells, and endocrine cells. Paneth cells are normally present in proximal colon. The lamina propria contains a variable number of inflammatory cells and a rich network of capillaries, venules, and lymphatics

Normal Histology

Histologically, the colon consists of four distinct compartments: mucosa, submucosa, muscularis propria, and serosa (Fig. 1.20).

The mucosa consists of columnar epithelium lining the colonic crypts that extend deep into the lamina propria up to the muscularis mucosae (Fig. 1.21). These crypts are arranged perpendicular to the muscularis mucosae running parallel to each other and imparting a "rack of test tubes" appearance. The epithelial cells identified within the mucosa consist of absorptive cells, goblet cells, endocrine cells, and Paneth cells. The basement membrane provides support to the overlying epithelial cells. Normally, it is 3–5 μm in thickness with a regular outline. Basement membrane irregularity, with entrapment of the capillaries within the superficial lamina propria and thickness greater than 10 μm, is considered pathological [26, 27].

The absorptive cells compose majority of the surface epithelium. They are columnar in shape with lightly eosinophilic cytoplasm and basally placed oval nucleus. The luminal surface shows tightly packed apical microvilli. The goblet cells can be seen both within the surface epithelium and crypts. They are oval to round in shape with relatively

clear cytoplasm on the H&E-stained section. They have a dense, irregular, and hyperchromatic nucleus. The endocrine cells are mainly located in the crypts. They contain small, deeply eosinophilic granules that are basally oriented [28]. They have a small nucleus that is pushed toward the lumen. The Paneth cells are pyramidal in shape with apical densely eosinophilic granules and basally located oval nucleus and can be present in proximal colon but normally absent in distal colon and rectum [29]. They are usually seen at the base of the crypts (Fig. 1.22). Of note, the Paneth cell granules are autofluorescent on H&E-stained sections [30].

Few intraepithelial lymphocytes can be seen within normal colon and range from one to five lymphocytes per 100 epithelial cells. However, 20 or more lymphocytes per 100 epithelial cells are considered pathological. Increased intraepithelial lymphocytes can be seen within the epithelium overlying lymphoid aggregates, and this should not be misinterpreted as pathological in nature. Rare intraepithelial eosinophils may also be occasionally seen within the normal colon [31].

The lamina propria extends between the basement membrane and muscularis mucosae. It has of a mixture of inflammatory and mesenchymal cells organized within an extracellular matrix. The entire length of the colonic lamina propria contains thousands of well-defined lymphoid aggregates, especially prominent within the cecum. In addition to these lymphoid aggregates, the lamina propria also contains a mixture of lymphocytes, plasma cells, eosinophils, mast cells, and macrophages. The density of the inflammatory cells within the lamina propria varies within different segments of the colon. The cecum and right colon are more cellular than the other segments of the colon. There is usually a progressive decrease in the cellularity of the lamina propria from the right to the left colon. Muciphages are macrophages with ingested mucin. They are normal constituents of the lamina propria and commonly seen within the left colon and rectum (Fig. 1.23). The lamina propria also contains a rich network of capillaries, venules, and lymphatics. The muscularis mucosae is formed by a thin layer of smooth muscle, forming the deep boundary of the lamina propria. It also contains vascular channels and nerve twiglets.

The submucosa consists of loosely arranged smooth muscle and fibroadipose tissue with a rich network of angiolymphatic and neural tissue. Scattered inflammatory cells and few lymphoid aggregates may also be seen within the submucosa. The amount of adipose tissue within the submucosa varies significantly among individuals and also between the right and left colon. The ileocecal valve and cecal regions show abundance of mature adipose tissue within the submucosa, often times even resembling a lipoma. The submucosa contains two neural plexuses, namely, the plexus of Meissner which is located immediately beneath the muscularis mucosae and the deeper Henle's plexus. These neural plexuses consist of neurons, glial cells, ganglion cells, and stromal components (Fig. 1.24). The interstitial cells of Cajal are also present within the submucosa and play an important role in the gut motor activity [32–34].

The muscularis propria of the colon consists of an inner circular layer and outer longitudinal layer. Blood vessels and lymphatics are seen within the muscularis propria. The interstitial cells of Cajal are also present between the muscle layers and around the nerve plexuses. The subserosal fibroadipose tissue lies beyond the muscularis propria, which is limited by the serosa consisting of a mesothelial lining and adjacent fibroelastic tissue.

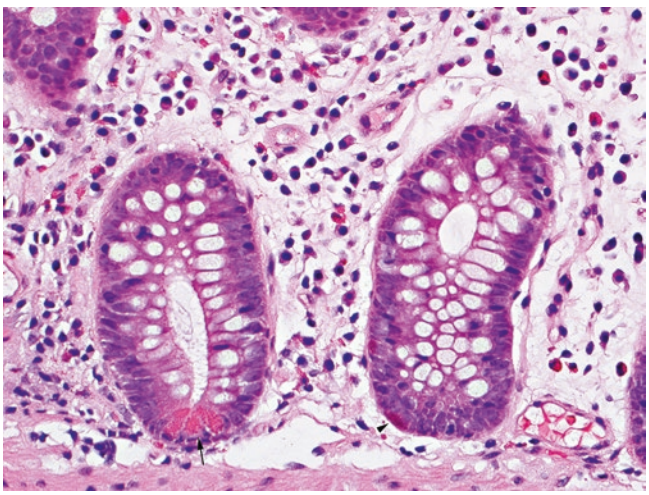

Fig. 1.22 Paneth cells (arrow) versus endocrine cells (arrowhead) in colonic mucosa

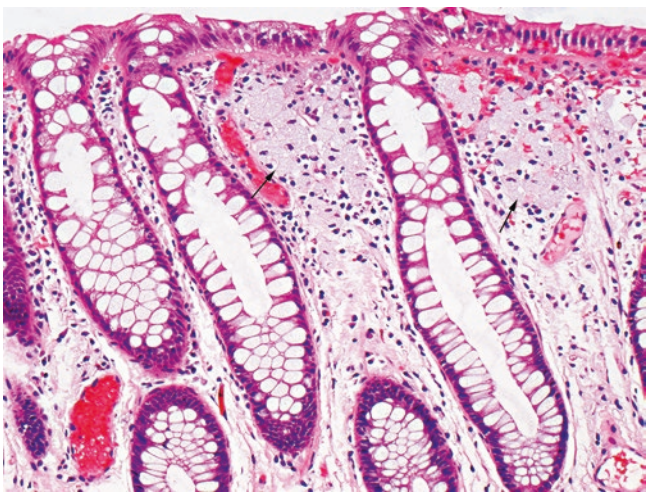

Fig. 1.23 Muciphages (arrows) in lamina propria are a common finding within the left colon and rectum

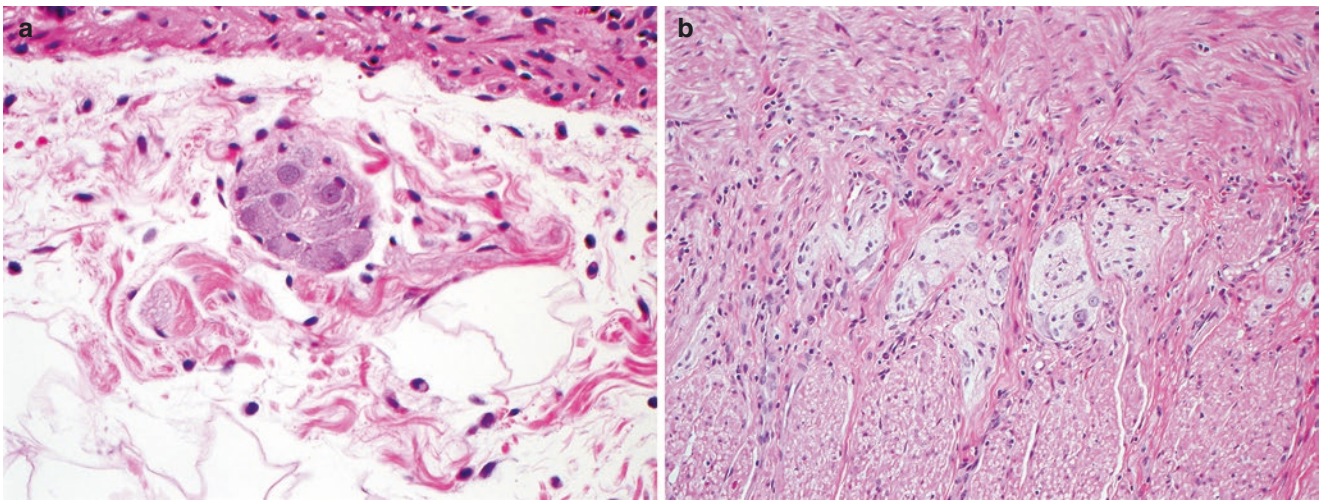

Fig. 1.24 Colonic neural plexuses. (**a**) The submucosal plexus of Meissner, consisting of neurons, glial cells, ganglion cells, and stromal components. (**b**) The myenteric plexus (or Auerbach's plexus) located between the longitudinal and circular layers of muscularis propria

Lymphatic Drainage

The cecum, ascending colon, and hepatic flexure drain into the pericolic, ileocolic, and right colic lymph nodes. The transverse colon and splenic flexure drain into the pericolic, middle colic, and left colic lymph nodes. The descending and sigmoid colon drain into the pericolic, left colic, sigmoid, and inferior mesenteric lymph nodes.

Innervation

The ascending colon and proximal two-thirds of the transverse colon receive their sympathetic, parasympathetic, and sensory supply via nerves from the superior mesenteric plexus. The distal one-third of the transverse colon, descending colon, and sigmoid colon receive their sympathetic, parasympathetic, and sensory supply via nerves from the inferior mesenteric plexus, composed of parasympathetic innervation via the pelvic splanchnic nerves and sympathetic innervation via the lumbar splanchnic nerves.

Anal Canal

Anatomy

The anal canal is the most terminal part of the large intestine connecting the rectum to the anus. It extends from the level of the pelvic floor (anorectal ring) to the anal opening (anus). In an adult, the anal canal measures around 3–4 cm in length [35, 36]. The sequence of epithelial zones from the rectum to the perianal skin is divided into four different areas: (1) zone covered by colorectal type of mucosa; (2) anal transitional zone; (3) zone covered by squamous epithelium; and (4) perianal skin lined by keratinized squamous epithelium, skin appendages, and hair follicles. The muscles of the anal canal (from inside out) consist of musculus submucosae ani, internal anal sphincter, anal longitudinal muscle, and external anal sphincter.

Normal Histology

The colorectal zone of the anal canal is a continuation of the rectal mucosa [37]. The anal transitional zone is lined by small basal cells whose nuclei are arranged perpendicular to the basement membrane (Fig. 1.25). The superficial cells can be flattened to columnar in shape. The anal transitional zone may also show small areas of mature squamous epithelium and simple columnar epithelium. The squamous epithelium just distal to the anal transitional zone is nonkeratinized. Toward the distal end of the anal canal, keratinization becomes apparent as it blends with the perianal skin containing hair and skin appendages.

The anal glands open into the anal transitional zone. They are present within the submucosa and extend into the internal sphincter with some even penetrating the external sphincter [38]. The lining epithelium of these anal glands is similar to the epithelium lining the anal transitional zone (Fig. 1.26a, b). Intraepithelial microcysts and goblet cells may also be seen within the anal glands. The anal glands are surrounded by myoepithelial cells and may also show few lymphocytes around them. Within the perianal skin, an additional type of glands known as the anogential mammary-like glands is also seen. They are lined by a simple columnar

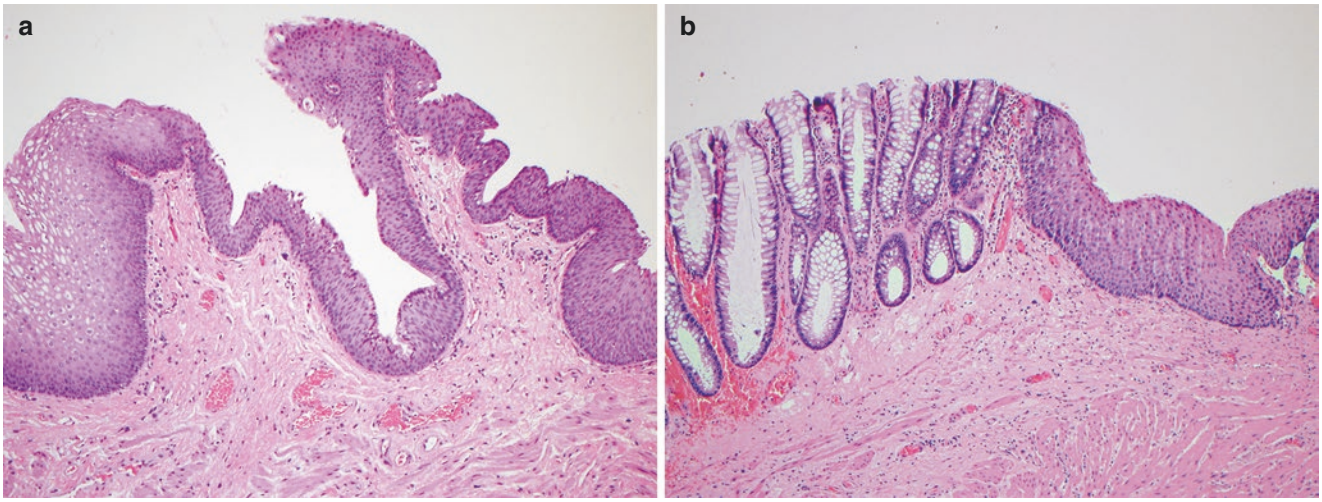

Fig. 1.25 (**a**) The anal transitional zone mucosa (right), lined by multilayered small basal cells, in comparison to the anal squamous epithelium (left). (**b**) Transition from the columnar colonic epithelium to anal transitional zone mucosa

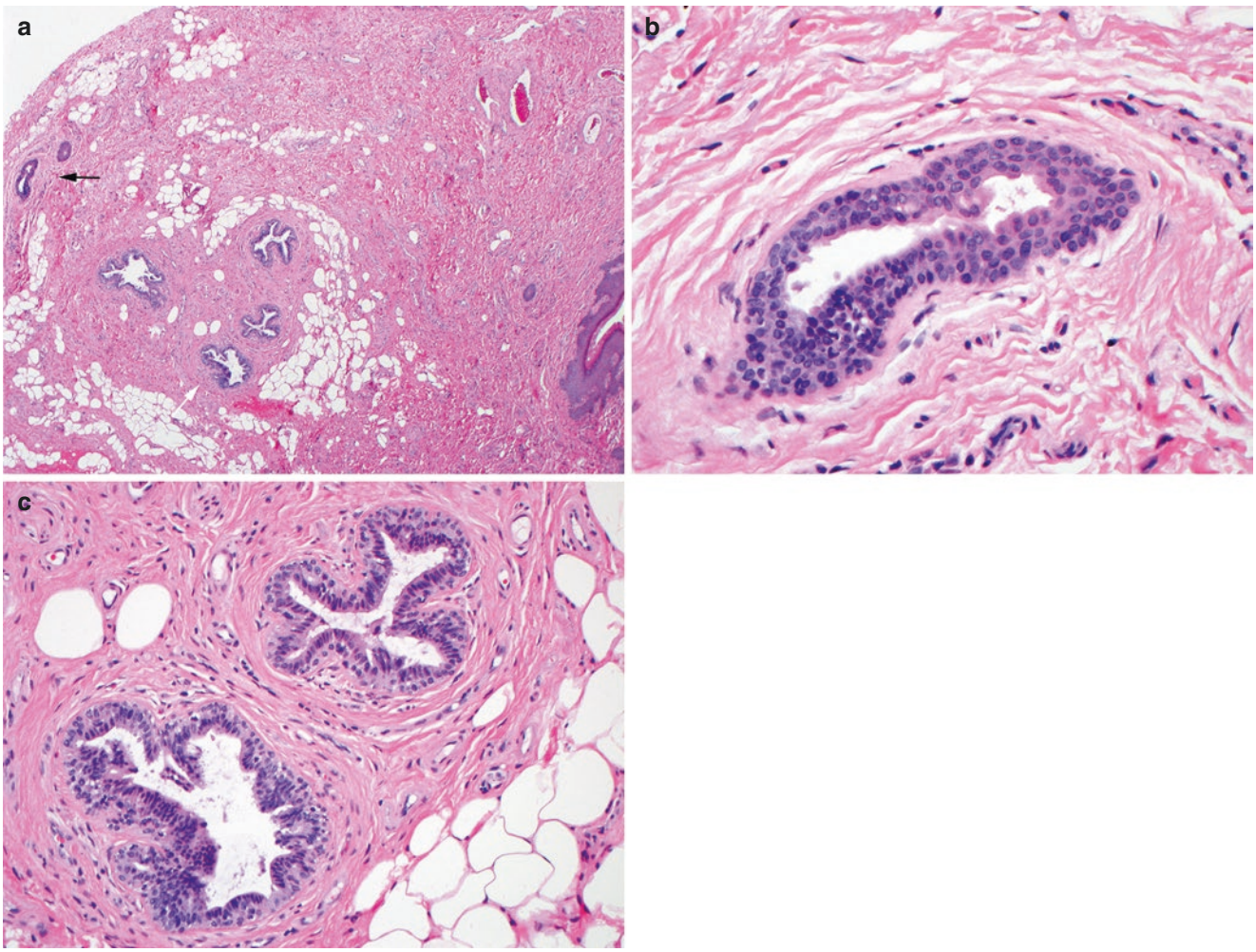

Fig. 1.26 Anal glands and anogenital mammary-like glands. (**a**) Two distinct structures in this section: anal gland ducts (black arrow) and anogenital mammary-like glands (white arrow). (**b**) An anal gland duct lined by transitional zone epithelium. (**c**) Transverse section of anogenital mammary-like glands lined by one layer of low columnar epithelial cells surrounded by myoepithelial cells and loose connective tissue, with small acini formation (arrow)

epithelium with cytoplasmic projections protruding into the glandular lumen and surrounded by an outer myoepithelial layer (Fig. 1.26a, c).

The lamina propria consists of loose connective tissue containing a variable number of mast cells and lymphocytes. The muscularis mucosae of the rectum continue into the proximal anal canal and can also be found in the proximal anal transitional zone. Few interstitial cells of Cajal may be seen in the internal anal sphincter but not in the external sphincter [39].

Lymphatic Drainage

The upper part of the anal canal drains to the hypogastric, obturator, and internal iliac lymph nodes. The lower part of the anal canal and perianal skin drain into the superficial inguinal nodes.

Innervation

Sympathetic fibers from the superior rectal and hypogastric plexuses innervate the internal anal sphincter. The pudendal and fourth sacral nerves provide the innervation to the external anal sphincter.

References

1. Abid S, Mumtaz K, Jafri W, Hamid S, Abbas Z, Shah HA, et al. Pill-induced esophageal injury: endoscopic features and clinical outcomes. Endoscopy. 2005;37(8):740–4. https://doi.org/10.1055/s-2005–870129.
2. McCullough RW, Afzal ZA, Saifuddin TN, Alba LM, Khan AH. Pill-induced esophagitis complicated by multiple esophageal septa. Gastrointest Endosc. 2004;59(1):150–2.
3. McClave SA, Boyce HW Jr, Gottfried MR. Early diagnosis of columnar-lined esophagus: a new endoscopic diagnostic criterion. Gastrointest Endosc. 1987;33(6):413–6.
4. Abraham SC, Krasinskas AM, Correa AM, Hofstetter WL, Ajani JA, Swisher SG, et al. Duplication of the muscularis mucosae in Barrett esophagus: an underrecognized feature and its implication for staging of adenocarcinoma. Am J Surg Pathol. 2007;31(11):1719–25. https://doi.org/10.1097/PAS.0b013e318093e3bf.
5. Meyer GW, Austin RM, Brady CE 3rd, Castell DO. Muscle anatomy of the human esophagus. J Clin Gastroenterol. 1986;8(2):131–4.
6. Shimada H, Nabeya Y, Matsubara H, Okazumi S, Shiratori T, Shimizu T, et al. Prediction of lymph node status in patients with superficial esophageal carcinoma: analysis of 160 surgically resected cancers. Am J Surg. 2006;191(2):250–4. https://doi.org/10.1016/j.amjsurg.2005.07.035.
7. Eguchi T, Nakanishi Y, Shimoda T, Iwasaki M, Igaki H, Tachimori Y, et al. Histopathological criteria for additional treatment after endoscopic mucosal resection for esophageal cancer: analysis of 464 surgically resected cases. Mod Pathol. 2006;19(3):475–80. https://doi.org/10.1038/modpathol.3800557.
8. Lewin KJ, Riddell RH, Weinstein WM. Normal structure of the stomach. In: Lewin KJ, Riddell RH, Weinstein WM, editors. Gastrointestinal pathology and its clinical implications. New York: Igaku-Shoin; 1992. p. 496–505.
9. Rubin W, Ross LL, Sleisenger MH, Jefries GH. The normal human gastric epithelia. A fine structural study. Lab Invest. 1968;19(6):598–626.
10. Walker MM, Smolka A, Waller JM, Evans DJ. Identification of parietal cells in gastric body mucosa with HMFG-2 monoclonal antibody. J Clin Pathol. 1995;48(9):832–4.
11. Rindi G, Buffa R, Sessa F, Tortora O, Solcia E. Chromogranin A, B and C immunoreactivities of mammalian endocrine cells. Distribution, distinction from costored hormones/prohormones and relationship with the argyrophil component of secretory granules. Histochemistry. 1986;85(1):19–28.
12. Genta RM, Hamner HW, Graham DY. Gastric lymphoid follicles in Helicobacter pylori infection: frequency, distribution, and response to triple therapy. Hum Pathol. 1993;24(6):577–83.
13. Ahrens EH Jr, Blankenhorn DH, Hirsch J. Measurement of the human intestinal length in vivo and some causes of variation. Gastroenterology. 1956;31(3):274–84.
14. Rubin W. The epithelial "membrane" of the small intestine. Am J Clin Nutr. 1971;24(1):45–64. https://doi.org/10.1093/ajcn/24.1.45.
15. Holmes R, Hourihane DO, Booth CC. The mucosa of the small intestine. Postgrad Med J. 1961;37:717–24.
16. Goldman H, Antonioli DA. Mucosal biopsy of the esophagus, stomach, and proximal duodenum. Hum Pathol. 1982;13(5):423–48.
17. Dobbins WO 3rd. Human intestinal intraepithelial lymphocytes. Gut. 1986;27(8):972–85.
18. Ferguson A, Murray D. Quantitation of intraepithelial lymphocytes in human jejunum. Gut. 1971;12(12):988–94.
19. Hayat M, Cairns A, Dixon MF, O'Mahony S. Quantitation of intraepithelial lymphocytes in human duodenum: what is normal? J Clin Pathol. 2002;55(5):393–4.
20. Selby WS, Janossy G, Bofill M, Jewell DP. Lymphocyte subpopulations in the human small intestine. The findings in normal mucosa and in the mucosa of patients with adult coeliac disease. Clin Exp Immunol. 1983;52(1):219–28.
21. Cerf-Bensussan N, Schneeberger EE, Bhan AK. Immunohistologic and immunoelectron microscopic characterization of the mucosal lymphocytes of human small intestine by the use of monoclonal antibodies. J Immunol. 1983;130(6):2615–22.
22. Buschard K, Kjaeldgaard A. Investigation and analysis of the position, fixation, length and embryology of the vermiform appendix. Acta Chir Scand. 1973;139(3):293–8.
23. Bjerke K, Brandtzaeg P, Rognum TO. Distribution of immunoglobulin producing cells is different in normal human appendix and colon mucosa. Gut. 1986;27(6):667–74.
24. Smith ME, Morton D. The colon. In: Smith ME, Morton D, editors. The digestive system. Edinburgh: Churchill Livingstone; 2001. p. 175–86.
25. Guyton A. The digestive and metabolic systems. In: Guyton A, editor. Anatomy and physiology. Philadelphia: WB Saunders; 1984. p. 643–700.
26. Gledhill A, Cole FM. Significance of basement membrane thickening in the human colon. Gut. 1984;25(10):1085–8.
27. Anagnostopoulos I, Schuppan D, Riecken EO, Gross UM, Stein H. Tenascin labelling in colorectal biopsies: a useful marker in the diagnosis of collagenous colitis. Histopathology. 1999;34(5):425–31.
28. Schonhoff SE, Giel-Moloney M, Leiter AB. Minireview: development and differentiation of gut endocrine cells. Endocrinology. 2004;145(6):2639–44. https://doi.org/10.1210/en.2004–0051.
29. Porter EM, Bevins CL, Ghosh D, Ganz T. The multifaceted Paneth cell. Cell Mol Life Sci. 2002;59(1):156–70.
30. Rubio CA, Nesi G. A simple method to demonstrate normal and metaplastic Paneth cells in tissue sections. In Vivo. 2003;17(1):67–71.

31. Rothenberg ME, Mishra A, Brandt EB, Hogan SP. Gastrointestinal eosinophils. Immunol Rev. 2001;179:139–55.
32. Rumessen JJ, Peters S, Thuneberg L. Light- and electron microscopical studies of interstitial cells of Cajal and muscle cells at the submucosal border of human colon. Lab Invest. 1993;68(4):481–95.
33. Ward SM, Sanders KM. Interstitial cells of Cajal: primary targets of enteric motor innervation. Anat Rec. 2001;262(1):125–35.
34. Takayama I, Horiguchi K, Daigo Y, Mine T, Fujino MA, Ohno S. The interstitial cells of Cajal and a gastroenteric pacemaker system. Arch Histol Cytol. 2002;65(1):1–26.
35. Fenger C. The anal transitional zone. Location and extent. Acta Pathol Microbiol Scand A. 1979;87A(5):379–86.
36. Nivatvongs S, Stern HS, Fryd DS. The length of the anal canal. Dis Colon Rectum. 1981;24(8):600–1.
37. Wendell-Smith CP. Anorectal nomenclature: fundamental terminology. Dis Colon Rectum. 2000;43(10):1349–58.
38. Seow-Choen F, Ho JM. Histoanatomy of anal glands. Dis Colon Rectum. 1994;37(12):1215–8.
39. Hagger R, Gharaie S, Finlayson C, Kumar D. Distribution of the interstitial cells of Cajal in the human anorectum. J Auton Nerv Syst. 1998;73(2–3):75–9.