Normal and Pathologic Mucosa

111

Marta C. Cohen

Normal Mucosa

The four regions of the stomach are the cardia, fundus, body, and antrum. Throughout the stomach, the wall is organized in four layers: mucosa, submucosa, muscularis propria, and serosa.

The gastric mucosa has a superficial layer of columnar mucus-secreting cells that contains foveolae (pits) where deep-seated coiled glands open (Fig. 111.1) [25]. The foveolae, also lined by the superficial columnar mucus-secreting cells, correspond to invaginations of the surface epithelium. They are wider in the antral mucosa (proximal to the pylorus) where at times adopt a slightly villous appearance (Fig. 111.2).

The columnar cells from the superficial mucosa depict basal located nuclei with an inconspicuous nucleoli and clear apical cytoplasm that contain neutral mucins which are positive with periodic acid-Schiff (PAS) stain [13, 14, 25]. The coiled glands are immersed in the loose connective tissue that constitutes the lamina propria, which extends between the muscularis mucosae and the more superficial foveolae.

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In the different areas of the stomach, the foveolae show subtle different features, and the deep glands diverge in function and histological appearance:

Cardia

This is the most proximal anatomic region of the stomach. It is situated immediately distal to the esophagus and is characterized by the presence of mucinous surface epithelium with underlying mucus-type or mixed mucus/oxyntic-type glands (Fig. 111.3) [19]. Traditionally, the cardia has been described as a 1–2-cm normal structure present at birth and with no definite anatomical limit with the gastric body [13]. However, it has recently been proposed that while the normal anatomic cardia may be comprised of pure oxyntic-type mucosa, the mucus-type glands develop as a metaplastic event and are an histologic manifestation of gastroesophageal reflux [4–7]. However, studies conducted in pediatric patients and our own experience show that cardia mucosa is frequently present in the proximal stomach with underlying loosely packed pure mucus-type or mixed mucus/oxyntic-type glands [11, 14, 19]. The mucus-type glands occupy approximately one half of the mucosal thickness and secrete predominately neutral mucin with a minimal quantity of sialomucins (Fig. 111.4) [13, 18, 25]. Although the cardia glands can

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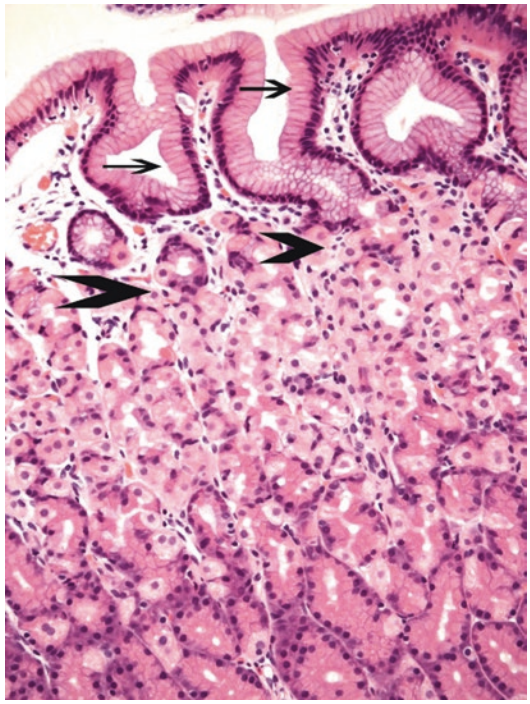

Fig. 111.1 Normal fundic-type gastric mucosa depicting a superficial layer of columnar mucus-secreting cells containing foveolae (*arrow*) where deep-seated glands open (*arrow head*) (H & E × 20)

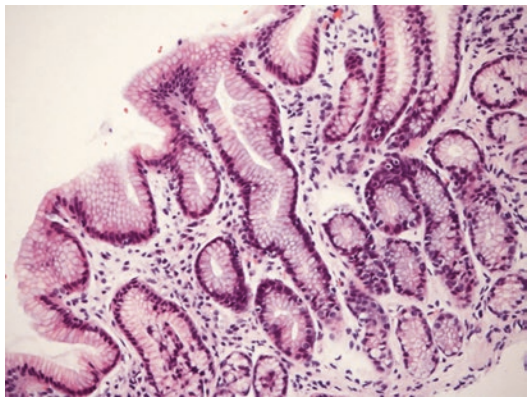

Fig. 111.2 The foveolae (pits) are wider in the antral mucosa (proximal to the pylorus) where at times adopts a slightly villous appearance (H & E × 10)

occasionally contain parietal cells, they do not usually include chief cells [14]. A rather unusual finding is the presence of ectopic intestinal mucosa or pancreatic acinar tissue in the cardia, described in a small percentage of infant postmortem examinations [14].

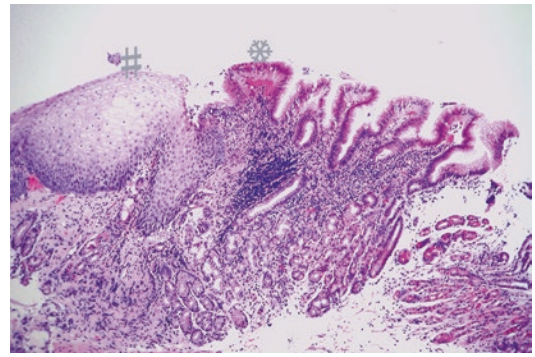

Fig. 111.3 The gastric cardia, situated immediately distal to the nonkeratinizing squamous mucosa of the esophagus (#), is characterized by the presence of mucinous surface epithelium with underlying mucus-type or mixed mucus/oxyntic-type glands (*) (H & E × 10)

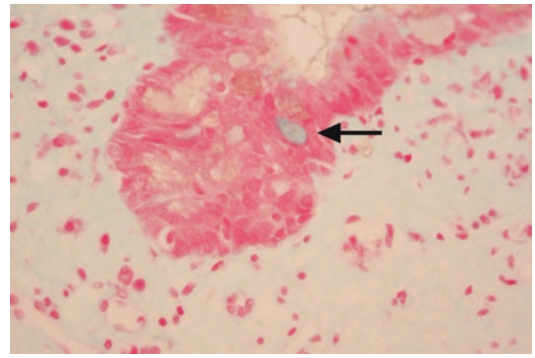

Fig. 111.4 The cardiac mucus glands secrete predominately neutral mucin with a minimal quantity of sialomucins (*arrow*) (Alcian blue pH 2.5 stain, × 40)

The different views expressed by adult and pediatric pathologists regarding the existence or not of the cardia-type mucosa could be explained by the inverse correlation between age and length of cardiac mucosa ($p = 0.005$) [11].

Fundus

The gastric fundus corresponds to that part of the body (corpus) that is adjacent to the cardia and bulges above it [14]. In comparison with the slightly villiform feature of the cardia and antral mucosa In comparison with the slightly villiform features of the cardia (Fig. 111.3 and 4) and antral mucosa (Fig. 111.2), the fundic foveolae (Fig. 111.1) appear, the fundic foveolae appear more flat,

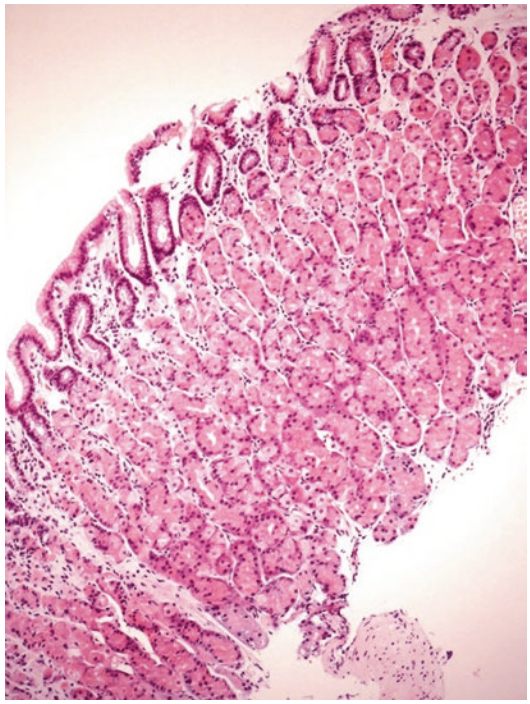

Fig. 111.5 Histology depicting rather flat fundic foveolae covering tightly packed acid-secreting glands (H & E × 10)

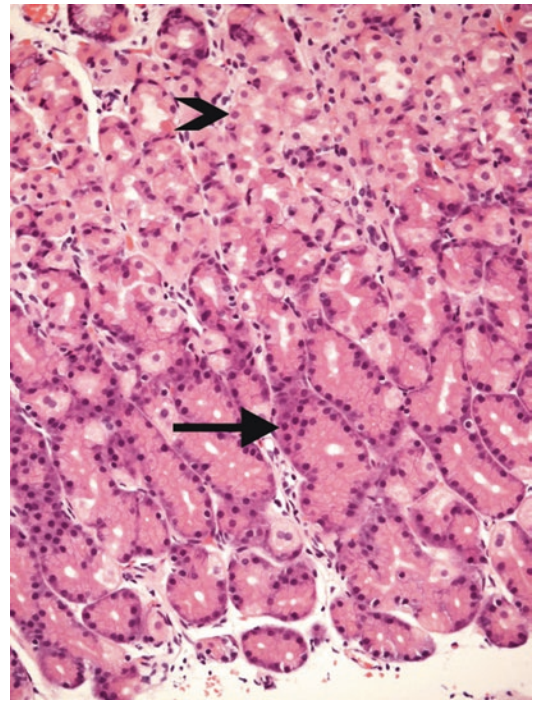

Fig. 111.6 Fundic glands are composed of bluish cuboidal chief cells (*arrow*), mucus cells, and pink parietal cells (*arrow head*) (H & E × 20)

making up less than 25% of the total mucosal thickness. The glands are tightly packed and straight rather than coiled (Fig. 111.5) [25]. They are composed of bluish cuboidal chief cells basally: chief, parietal, and mucus cells in the neck; and pink triangular parietal cells in the area corresponding to the isthmus of the gland (Fig. 111.6) [13]. The cellular products are inherent to each type of cell: chief cells secrete pepsinogen, parietal cells secrete acid, and mucus neck cells produce neutral and acidic mucin (in particular sialomucin) [25].

In addition to the above-described cell types, the fundic mucosa contains a variety of endocrine cells, mainly histamine-secreting enterochromaffin-like cells, although also serotonin enterochromaffin cells are also seen. The neuroendocrine cells are mostly located toward the base of the glands. Special stains (i.e., Grimelius) have now been replaced by immunohistochemical techniques (i.e., chromogranin, synaptophysin) to demonstrate the endocrine cells, not visible with routine hematoxylin and eosin stains. More sophisticated immunohistochemical techniques currently allow to identify specific hormones (i.e., gastrin or somatostatin) [25].

Body

The body or corpus makes up the majority of the stomach [13]. The mucosa of the body is identical to the mucosa of the fundus (see above).

Antrum

The antrum occupies the distal third of the stomach, extending between the incisura angularis and the pylorus. The foveolae (pits) occupy approximately half of the total mucosal thickness and may appear villiform (Fig. 111.2). The glands are mucus secreting, similar to the cardiac zone. Occasional parietal cells, but not chief cells, can be found at the junction with the adjacent body (fundic-type mucosa). As in the

fundus, the prepyloric antral mucosa contains endocrine cells that produce gastrin, enterochromaffin, somatostatin, and serotonin.

Lamina Propria

The collagenous tissue that provides support to the foveolae and glands constitutes the lamina propria. Elastic, reticulin, and occasional smooth muscle fibers as well as capillaries, arterioles, and nonmyelinated nerve fibers also contribute to the structure of the lamina propria [25]. During childhood, the lamina propria contains few lymphocytes, plasma cells, and rare eosinophils that do not expand the interglandular region (Fig. 111.7). B and T cell lymphocytes are scattered through the mucosa, and superficial aggregates are not usually seen. On the contrary, plasma cells (usually IgA-secreting type) often occur in small clusters [13]. Small lymphoid aggregates, devoid of germinal centers, can be rarely identified at the deepest part of the gastric mucosa.

Pathologic Mucosa

A detailed description of the histological characterization of various conditions presenting with an abnormal gastric mucosa is beyond the scope of this chapter.

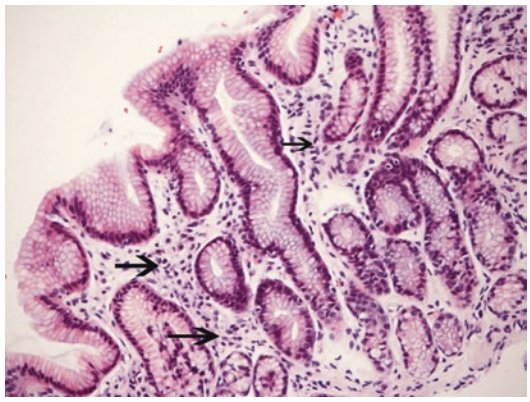

Fig. 111.7 Antral mucosa showing mucus glands immersed in the lamina propria; this contains few lymphocytes and plasma cells (*arrows*) (H & E × 10)

The term gastritis is used to denote inflammation-associated mucosal injury. However, epithelial cell injury and regeneration are not always accompanied by mucosal inflammation (i.e., chemical gastritis). Gastritis has a wide pathologic spectrum and anatomic distribution, as well as an evolving etiology. Different classification systems are in use. Key to the gastroenterologist and pathologist's collaborative work is a mutually understood and agreed classification [13, 14]. The Sydney pathologic classification of gastritis, published in 1990 and revised in 1994, is based on topography, morphology, and etiology of the inflammation [15]. The updated version of the Sydney System retained the general principles and grading of gastritis but provided with a useful visual analogue scale to help in the histological grading of gastritis. Although designed for gastritis in adults, the system has demonstrated that it applies to children as well [9].

According to the inflammatory cell infiltrates present in the gastric mucosa, the gastritis can be classified into acute or chronic forms. Chronic gastritis can further be subclassified as non-atrophic and atrophic and special types as chemical, radiation, lymphocytic, noninfectious, eosinophilic, reactive gastropathy (nonsteroidal anti-inflammatory drugs, bile reflux), etc. See Table 111.1.

The most usual entities encountered by the pediatric pathologist include, but are not limited to:

(a) *Helicobacter pylori* gastritis
(b) Lymphocytic gastritis
(c) Granulomatous gastritis and gastric Crohn's disease
(d) Eosinophilic gastritis
(e) Graft-versus-host disease
(f) Reactive gastropathy
(g) Nonspecific gastritis

Helicobacter pylori Gastritis

H. pylori infections have been associated with chronic gastritis, gastric and duodenal ulcer, and a higher risk of gastric carcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Diagnosis of *H. pylori* involves endoscopy with biopsy, culture, urease test, urea breath test, polymerase chain reaction (PCR),

and serologic detection of antibodies. However, the gold standard is the histologic detection of *H. pylori* in biopsy. *H. pylori* gastritis is infrequently biopsied in the acute phase of the infection. If performed, the histology shows mucosal injury with acute inflammatory cell infiltrates constituted by polymorphonuclear neutrophils. More commonly, the biopsy shows a chronic gastritis. *H. pylori* organisms present as coccoid and curved Gram-negative bacillus and are found particularly within the mucous lining of the surface epithelium. *H. pylori* are visible with hematoxylin and eosin (Fig. 111.8). The use of special stains such as silver stains (i.e., Warthin-Starry, Steiner), Giemsa or immunoperoxidase against

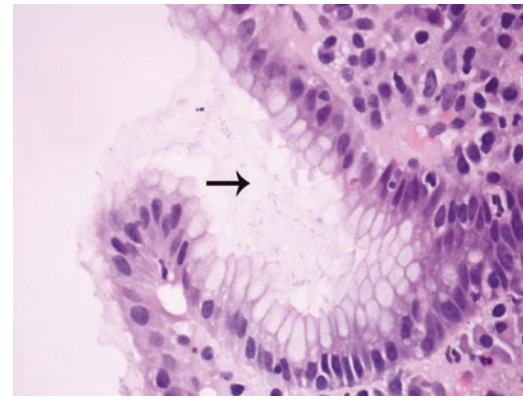

Fig. 111.8 Microphotography showing curved *H. pylori* organisms (*arrow*) of approximately 4 μ embedded within the mucus lining of the surface epithelium (H & E × 40)

Table 111.1 Etiologic-pathogenic classification of pediatric gastritis

Pattern of gastritis	Condition	
Infectious	Bacteria:	*Helicobacter pylori*
		Helicobacter heilmannii
		Streptococcus
		Staphylococcus
		Mycobacterium tuberculosis
		Treponema pallidum
	Fungi	*Candida albicans*
	Parasites	*Giardia lamblia*
	Virus	Cytomegalovirus
		Herpes
Noninfectious immune	Celiac disease	
	Graft-versus-host disease	
	Eosinophilic gastritis	
	Autoimmune gastritis	
	Henoch-Schönlein's disease	
	Polyarteritis nodosa	
Genetic/metabolic disorders	Cobalamin C disease	
	Chronic granulomatous disease	
Chemical/toxin injury	Nonsteroidal anti-inflammatory drugs (NSAIDs)	
	Other drugs	
	Bile reflux	
Physical agent injury	Tubes	
	Radiation	
Vascular	Congestion	
	Portal hypertension	
Unknown/uncertain	Crohn's disease	
	Ulcerative colitis	
	Ménétrier's disease (not associated with cytomegalovirus infection)	
	Non specific chronic gastritis	

From: Dimmick et al. [13, 14]

H. pylori is used when the organisms are difficult to identify with hematoxylin and eosin (Fig. 111.9). In children, *H. pylori* is a pangastritis, although the antrum and the cardia are usually more severely inflamed. Histologically, the lamina propria exhibits lymphoid and plasma cell inflammatory infiltrates which include a variable number of polymorphonuclear neutrophils (Fig. 111.10a) [1, 10, 15]. Usually, the pathologist encounters that the neutrophilic infiltrates involve the germinative area at the necks of the glands, constituting an "active" *H. pylori* chronic gastritis (Fig. 111.10b) [1]. Lymphoid follicles are fairly common at this stage. These are responsible for the nodularity of the gastric mucosa seen at endoscopy (Fig. 111.10c) [28]. Lymphoid hyperplasia and nodular gastritis appear to be more frequent in children than in adults and usually regress following *H. pylori* eradication [30].

Focal loss of glandular units, replaced by dense collagen bundles with scant inflammatory cells, has been described in treated long-standing *H. pylori* chronic gastritis [10]. The fibrous tissue is arranged in a "starry" shape, with a central area of scarring extending into the adjacent interglandular tissue. This feature could represent a very early stage of the atrophic gastritis described in some adult patients with *H. pylori*-associated chronic gastritis [2, 23]. In addition, the presence of isolated cells containing sulfated mucosubstances has been identified in gastric biopsies from pediatric patients with *H. pylori*-associated chronic gastritis.

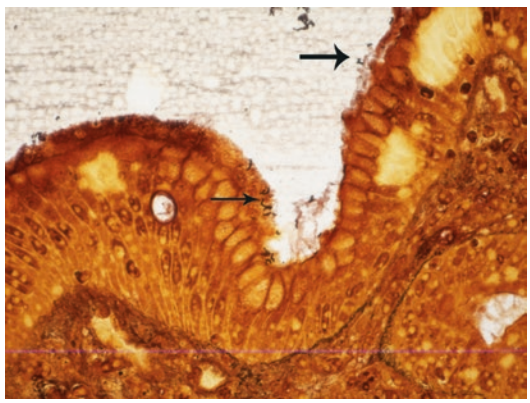

Fig. 111.9 *H. pylori* organisms positive with Warthin-Starry stain (*arrows*) (Warthin-Starry stain × 40

The presence of sulfated mucosubstances in patients with long-standing *H. pylori*-associated chronic gastritis, not present in the normal gastric mucosa, may represent a very early (perhaps reversible) stage of intestinal metaplasia [8].

Lymphocytic Gastritis

Lymphocytic gastritis is associated with *Helicobacter pylori* infection and with celiac disease. Initially described by Haot et al. [21], it is characterized by the presence of increased mucosal T cell lymphocytes both in the lamina propria as well as the surface and foveolar epithelium of the antrum and body with sparing of the deep glandular epithelium (Fig. 111.11a, b) [16, 21]. The number of intraepithelial lymphocytes in lymphocytic gastritis is 25 lymphocytes per 100 epithelial cells, although usually 30–65 lymphocytes per 100 epithelial cells are seen [34]. Children with lymphocytic gastritis and celiac disease had a mean of 40.64 lymphocytes per 100 epithelial cells [12]. There is no correlation between the histologic and clinical severity of lymphocytic gastritis in celiac disease, but the mucosa returns to normal with gluten withdrawal [14, 22]. In addition lymphocytic gastritis characterizes the endoscopic entity chronic varioliform gastritis. Of the patients with lymphocytic gastritis and celiac disease studied by DeGiacomo [12], only one had the endoscopic appearance of varioliform gastritis.

Granulomatous Gastritis and Gastric Crohn's Disease

Granulomatous gastritis may accompany systemic disease, infections, foreign body reaction, malignancy, or vasculitis but may also be an isolated finding [29]. In children, Crohn's disease is the most common type of granulomatous gastritis [13, 29]. Although histologic abnormalities are seen in up to 80 % of children with Crohn's disease, specific features such us giant cells are seen in approximately 30 % of cases [16]. Interestingly, histologic evidence of Crohn's disease may be found in absence of symptoms of inflammatory bowel disease or preceding them [16]. Histologic features of Crohn's disease include nonspecific chronic gastritis, chronic active gastritis, and the

more typical noncaseating giant cells granulomas (Fig. 111.12). A recent investigation conducted in children with inflammatory bowel disease indicated that although the presence of granulomas can support a diagnosis of Crohn's disease, severe inflammation and other abnormalities can occur in the proximal gastrointestinal tract either in Crohn's disease or ulcerative colitis [32].

In addition to the more convincing noncaseating giant cell granulomas, the presence of the so-called focally enhanced gastritis was initially considered to aid in establishing the diagnosis of Crohn's disease [24]. However, a retrospective case-controlled investigation conducted in children with inflammatory bowel disease, *Helicobacter pylori* and controls, showed that focally enhanced gastritis was present in 65.1 % of children with Crohn's disease, 20.8 % with ulcerative gastritis, 2.3 % controls, and 2.6 % children with *H. pylori* infection [31]. Focally enhanced gastritis characterizes by the presence of inflammatory cell

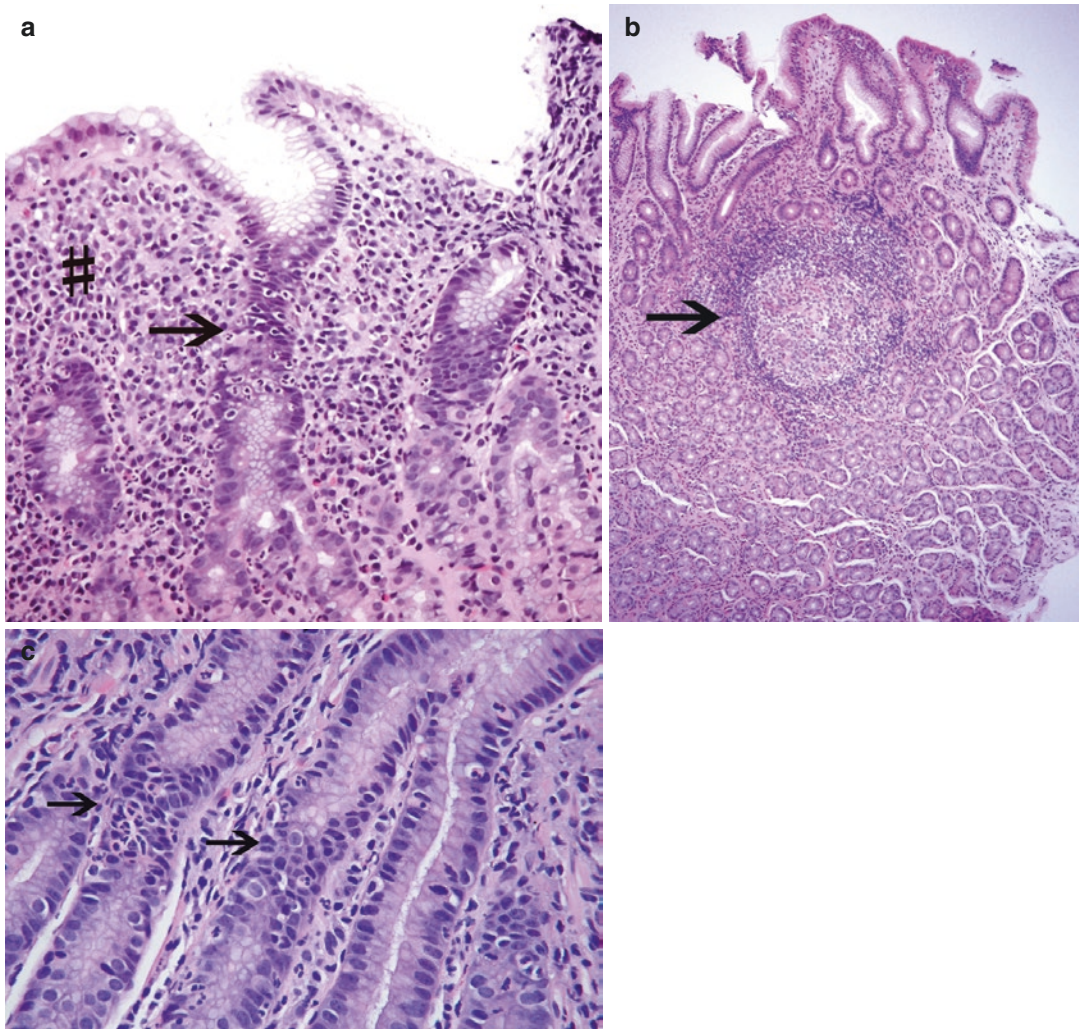

Fig. 111.10 (**a**) Antral mucosa depicting acute and chronic inflammatory cell infiltrates within the lamina propria (#) and invading the glandular necks (*arrow*) (H & E × 20); (**b**) higher magnification of glandular necks at the cardia showing neutrophilic infiltrates (*arrows*) which define an active gastritis (H & E × 40); (**c**) antral mucosa showing superficially located lymphoid follicles (*arrow*); these are responsible for the nodular appearance of the gastric mucosa at endoscopy (H & E × 20)

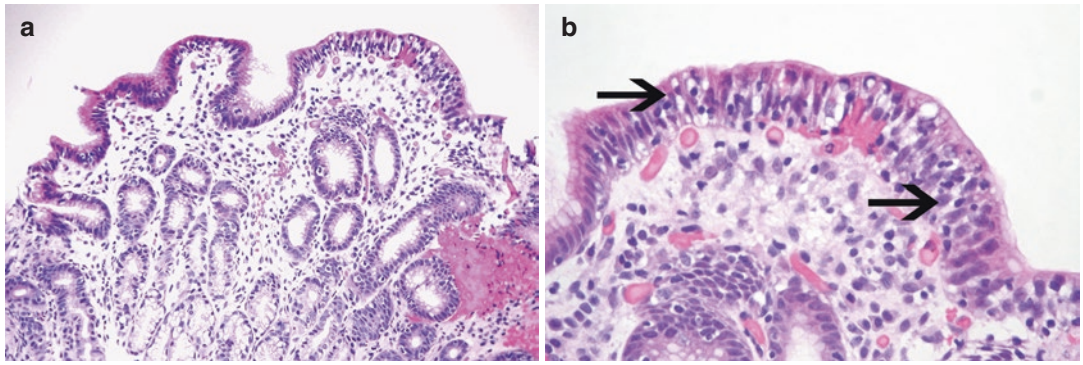

Fig. 111.11 (**a**) Patchy lymphocytic infiltration of superficial and foveolar epithelium which spares deep glands in a child with celiac disease (H & E × 20); (**b**) higher magnification of intraepithelial T cell lymphocytic infiltrates (*arrows*) (H & E × 40)

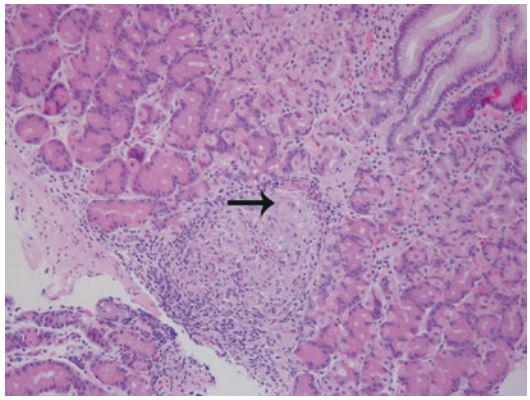

Fig. 111.12 Fundic-type gastric mucosa depicting non-caseating granulomas in a patient with Crohn's disease. The *arrow points* toward a giant cell (H & E × 20)

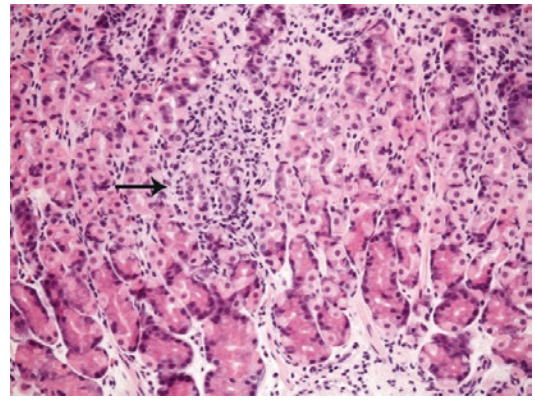

Fig. 111.13 Gastric biopsy in a child with Crohn's disease showing lymphoid inflammatory cell infiltrates surrounding fundic glands, constituting the so-called focally enhanced area of gastritis (*arrow*) (H & E × 20)

infiltrates (lymphocytes, mononuclear cells, and occasional neutrophils) surrounding a gastric foveola/gland or a small group of foveolae/glands (Fig. 111.13) [24].

With the exception of chronic granulomatous disease, other granulomatous gastritides are rare in children. These include sarcoidosis, Whipple disease, and vasculitis-associated and unclassifiable granulomas [13, 17]. Chronic granulomatous disease is an X-linked recessive immunodeficiency disorder occurring in boys, in which granulomatous gastric wall involvement is common [16]. The histological findings include presence of focal, chronic active inflammation in the antrum with granulomata, eosinophils, foci of necrosis, or giant cells. In my limited experience and that of other authors [14], pigmented histiocytes are not visualized.

Eosinophilic Gastritis

This is the gastric component of the eosinophilic gastroenteritis. The inflammatory cell infiltrate is mainly constituted by eosinophils involving the mucosa and submucosa, muscularis propria, and/or serosa of the stomach. Eosinophilic gastritis can be associated to food allergy, collagen vascular diseases, parasites, collagenous colitis, *H. pylori*, and idiopathic etiology [3, 14, 16].

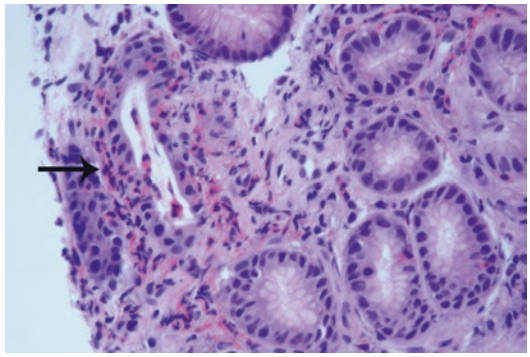

Fig. 111.14 Antral mucosa in a case of eosinophilic gastritis showing numerous eosinophils within the lamina propria and invading the adjacent glandular epithelium (*arrow*). (H & E × 40)

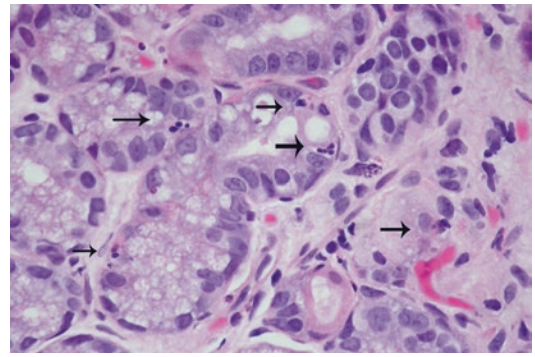

Fig. 111.15 Deep-seated glands in gastric antral mucosa depicting frequent apoptotic cells (*arrows*) in a case of graft-versus-host disease (H & E × 40)

Biopsies depict high number of eosinophils with fewer lymphocytes, plasma cells, and eosinophils within the lamina propria, with variable presence of mucosal necrosis and regenerative changes [14]. In allergic gastritis, the antrum is more commonly affected [20]. The histology depicts prominent infiltration of eosinophils within the lamina propria and invading the surface and foveolar epithelium (Fig. 111.14). Other inflammatory cell types included are lymphocytes, plasma cells, and neutrophils [13].

Graft-Versus-Host Disease

Graft-versus-host disease (GVHD), a common complication of hematopoietic stem cell transplantation, is a clinical syndrome that requires synthesis of clinical, laboratory, and histopathologic findings for diagnosis [33]. Histological features of early GVHD include crypt epithelial apoptosis and dropout and variable lymphocytic infiltrate within the superficial epithelium and lamina propria (Fig. 111.15). The features can be focal and subtle or more diffuse and severe, including crypt necrosis and denudation of areas of the superficial mucosa [27].

Reactive Gastropathy

The mucosal changes that characterize the chemical or reactive gastropathy are the presence of foveolar hyperplasia, reduced secretion of mucins, edema, vascular ectasia, and strands of smooth muscle in the lamina propria associated with minimal or absent inflammatory cells in the antral mucosa (Fig. 111.16) [14, 26]. The most frequent etiologies of reactive gastropathy in children are duodenal-gastric bile reflux and nonsteroidal anti-inflammatory drugs.

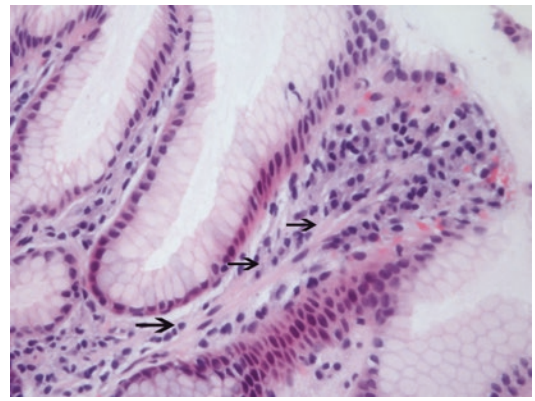

Fig. 111.16 Reactive gastropathy characterizes by foveolar hyperplasia, presence of strands of smooth muscle in the superficial lamina propria (*arrows*), and absence or minimal inflammation in the antral mucosa (H & E × 20)

Nonspecific Gastritis

A significant number of children present with chronic gastritis, usually of mild or moderate severity, for which no cause is identified. The inflammation is chronic with lymphocytes and plasma cells, usually patchy and more superficial than deep [13, 16]

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