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REVIEW AND PERSPECTIVES

The differential diagnosis of *Helicobacter pylori* negative gastritis

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Abstract

Gastric biopsies are often submitted with as clinical question *Helicobacter pylori* (*HP*) infection. Regularly, the morphology suggests a *HP* infection but the organism is not detected in special stains. This review presents a practical approach to deal with such biopsies. The first step is to exclude a false negative result of the search for *HP*, by ensuring that both antral and oxyntic mucosa are present, by the use of sensitive stains, identification of marked reactive changes, such as intestinal, pseudo-pyloric, pancreatic metaplasia that may suggest a diagnosis of (*HP* associated or autoimmune) atrophic gastritis, and finally identification of signs of the use of proton pump inhibitors (PPI) as in such biopsies, *HP* may sometimes be found only within parietal cells. The differential diagnosis should include lymphocytic gastritis, other diseases affecting the stomach, such as inflammatory bowel disease (IBD), vasculitis, granulomatous disease, viral infection, such as cytomegalovirus (CMV) or more rarely Epstein-Barr virus (EBV) infection, or other bacterial infections, such as *Enterococcus* and *Treponema pallidum*. Clinical input may be required to ensure the patient is not taking medication that may cause gastritis, such as antibiotics used for *HP* eradication or common medications that cause a form of gastropathy. When these have been excluded, a known cause has not been found and in such a case, the term idiopathic focal/diffuse gastritis can be used.

Keywords H. pylori negative · Gastric atrophy · Infections · Autoimmune · Drugs · Medication · Gastropathy · Lymphocytic gastritis

Introduction

With the decline of the prevalence of *Helicobacter pylori* (*HP*) infection in some populations [1–3], pathologists are more likely to face gastric inflammation in the absence of identifiable bacteria or of a non-infectious cause. If *HP* is not identified, the first consideration is whether both antral and oxyntic mucosa have been sampled. This is of particular importance for patients treated with proton pump inhibitors (PPI), in which case the organisms may be found in parietal cells (PCAs). When the biopsy shows extensive antral intestinal metaplasia, organisms might have moved into the more proximal gastric mucosa because of the presence of gastric acid, which they require to buffer the ammonium cations their urease activity generates. A second consideration is a pathologist failing to recognize organisms that are present, either because only a hematoxylin-eosin (HE) stain was performed or *HP* present only in PCA were not detected in the modified Giemsa stain. The latter is not rare as both the organism and the background are blue, which can make *HP* very difficult to detect. In addition, *HP* may not have been considered and a special stain not ordered due to a low number of neutrophils in the inflammatory infiltrate. Finally, other causes of *HP* negative gastritis, such as bacterial or viral infections, and iatrogenic causes need to be considered. The causes of *HP* negative gastritis are listed in Table 1.

Failure to detect *HP*

Failure to detect HP is not rare. Although *HP* is commonly diagnosed by histological examination [4], its reliability depends on the stain used, the biopsy sites, and the number of biopsies taken [4, 5].

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Table 1 *H. pylori* negative gastritis

Group	
A. Failure to detect *H. pylori* ("false negative")	1. Non-use of special stains 2. Insufficient biopsy sampling 3. Biopsy post-treatment
B. *H. pylori* negative gastritis	1. Lymphocytic gastritis 2. Collagenous gastritis 3. Atrophic gastritis • Autoimmune gastritis • *H. pylori*-associated atrophic gastritis 4. Non-*H. pylori* infectious gastritis •Viral (EBV, CMV) •Bacterial (non-*H. pylori*, *Helicobacter*, *Syphilis*, *Enterococcus*, etc.) 5. IBD-associated gastritis 6. Sarcoidosis 7. Eosinophilic gastritis 8. Graft-versus-host disease 9. Diffuse reactive ("chemical") gastropathy •Reflux associated •Medication associated
C. "Idiopathic" chronic gastritis	1. Chronic gastritis, *H. pylori* not identified

Special stains

Evaluating sections stained only with HE can be sufficient in heavily infected tissue but may be inadequate when few bacteria are present or the amount of inflammation is less than that usually encountered [6]. *HP* is easiest to detect with silver stains [7, 8] or by immunohistochemistry, because of the high contrast between organism and background [5, 6]. This is particularly important in patients treated with PPI when the organism may be within PCA or post-treatment when fewer bacteria are present. Furthermore, *HP* may be present even when there is little inflammation, while pathologists often use the presence of an inflammatory infiltrate as hallmark of the potential presence of *HP* [9], (Figs. 1 and 2).

Sampling

Taking biopsies from only one site is a major reason for failing to detect the bacteria. The false negative rate is about 10% when only antral mucosa is biopsied and about 15% if only oxyntic mucosa is biopsied. Initially, *HP* gastritis predominates in the antrum and spares the corpus, and antrum biopsies only can be adequate. When the disease progresses and/or with PPI use or antibacterial treatment (with antibiotics or bismuth salts) 2 to 4 weeks prior to biopsy, corpus mucosa is also infected and *HP* might no longer be found in antrum biopsies [7, 9]. Atrophy and intestinal metaplasia usually start at the incisura angularis and distal corpus and then extend to the mid antrum [8]. Biopsies from this region are adequate in patients without intestinal metaplasia, as *HP* cannot flourish in areas with intestinal metaplasia, but might not be adequate when intestinal metaplasia is present [8]. These considerations emphasize the need to obtain multiple biopsies from both antrum and corpus, for initial diagnosis but especially when biopsies are taken to evaluate the success of therapy [10]. A

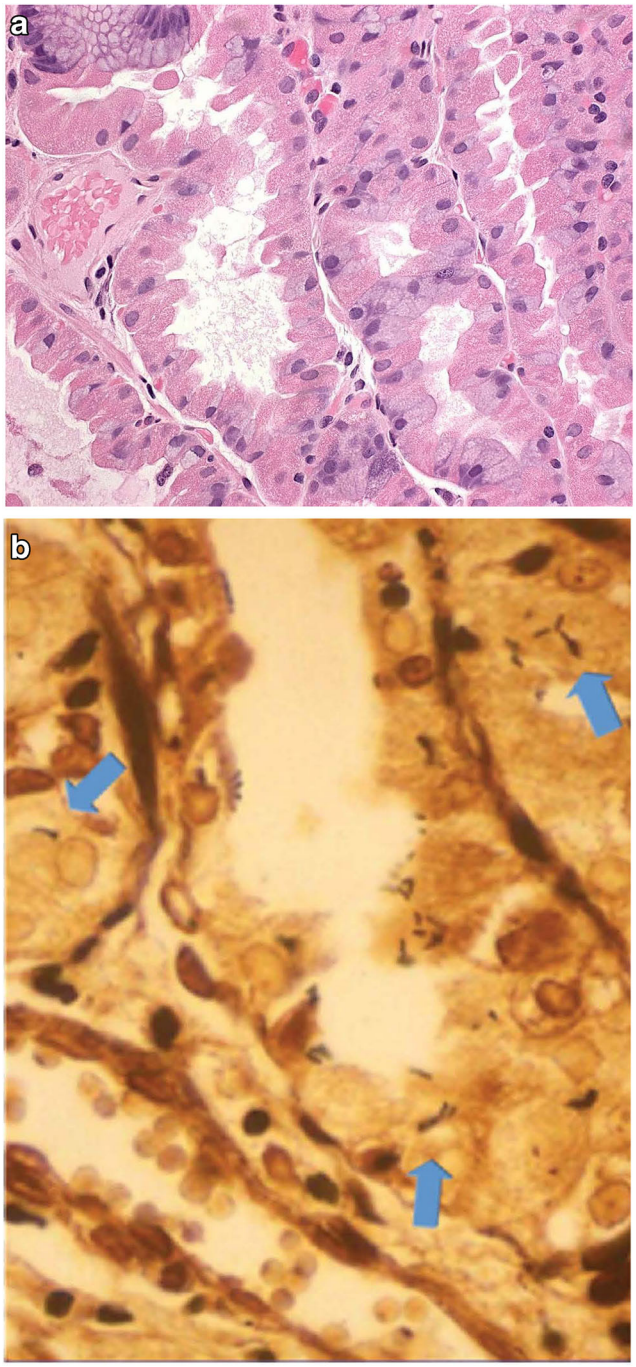

Fig. 1 **a** Oxyntic mucosa with parietal cell hypertrophy secondary to hypergastrinemia commonly seen with PPI use. No bacteria are seen with an H&E stain. **b** *HP* are easily seen deep in the crypts with a Warthin-Starry stain

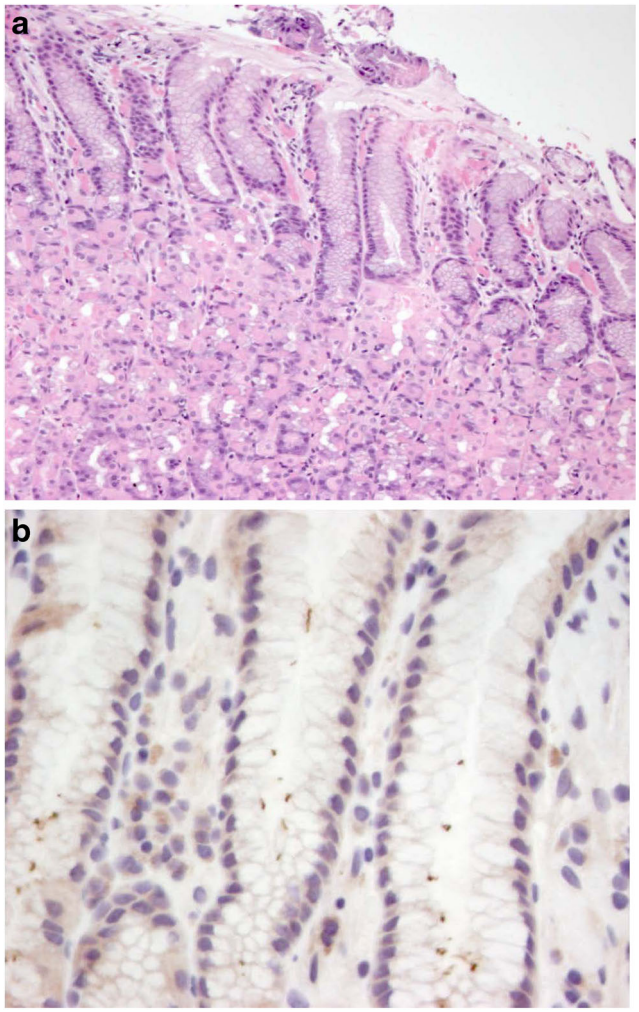

Fig. 2 **a** Oxyntic mucosa post-treatment with mild to no inflammation. No bacteria are seen with an H&E stain. **b** Bacteria are easily seen deep in the crypts by immunohistochemistry

minimum of four biopsies (two from the antrum and two from the greater curvature of the corpus, with maybe an additional biopsy from the angulus as a bonus) are recommended [10].

HP negative gastritis

Not uncommonly, *HP* are not identified even though biopsies from the antrum and body have been obtained and a silver or immunohistochemical stain have been carried out. For such biopsies, one should consider the possibility of lymphocytic gastritis, collagenous gastritis, atrophic gastritis including autoimmune gastritis (AIG), non/*HP* infectious gastritis, recent treatment by antibiotics or PPI, and inflammatory bowel disease (IBD).

Lymphocytic gastritis

Lymphocytic gastritis is uncommon and characterized by an increased number of intraepithelial lymphocytes (IELs) in surface and foveolar epithelium. Lymphocytic gastritis is diagnosed when the number of intraepithelial lymphocytes (IELs) is > 20 [11] or > 25/100 epithelial cells [12, 13]. An increased number of IEL may be focal. Most pathologists as a rule do not count lymphocytes but depend on a global visual impression. Counting is useful when in doubt.

Lymphocytic gastritis has been associated with *HP* infection, celiac disease, Crohn's disease (CD), HIV infection, lymphoma, and occasionally, a clear cause is lacking and then the term "idiopathic" is used [12]. The most common associations are celiac disease, in particular in Western countries [14, 15], and *HP* infection, especially in patients from countries with a high infection rate [16].

Differences exist between lymphocytic gastritis associated with celiac disease and that associated with *HP* infection. Lymphocytic gastritis associated with celiac disease is more intense in the antrum than in the body, and the inflammatory infiltrate in the lamina propria may have few or no plasma cells (although rarely they are numerous). In *HP*, gastritis plasma cells are usually very prominent, while this is rare in celiac disease-associated lymphocytic gastritis. Celiac disease can be confirmed by positive tissue transglutaminase serology, or by intraepithelial lymphocytosis with or without villous blunting in an accompanying duodenal biopsy [12, 15]. Endoscopically, *HP* gastritis is usually overt and can be varioliform. Histologically, the lamina propria has a mononuclear inflammatory infiltrate, often admixed with neutrophils, that usually but not always involves oxyntic mucosa; the inflammation predominates in the antrum in about 20% of cases [12]. Intraepithelial lymphocytosis in lymphocytic gastritis associated with *HP* infection usually affects antrum and corpus equally, but may be more severe in the antrum [12]. In most cases, *HP* are rare or even absent (Fig. 3) even with adequate antral and oxyntic mucosal sampling, although in odd cases they can be numerous. When *HP* are not found in the presence of intraepithelial lymphocytosis of equal severity in the antrum and corpus, serologic testing for an *HP* infection should be undertaken. Characteristically, duodenal pathology is absent or, when present, IEL tend to be located at the lateral sides rather than the tips of duodenal villi [17]. Lymphocytic colitis may also be present [12]. When this is found medication associated damage, especially with Olmesartan and immune-checkpoint inhibitors, or systemic pathology (autoimmune gastroenteritis) need to be considered. Of note, healing of lymphocytic gastritis following *HP* eradication [18, 19] has been described even in *HP* negative patients [18], and some investigators have suggested that other infectious agents, such as *Propionibacterium acnes* may play a role [20]. Corpus predominant lymphocytic gastritis is usually infectious (most commonly *HP*) [12, 17], but other causes may also need to be considered [20].

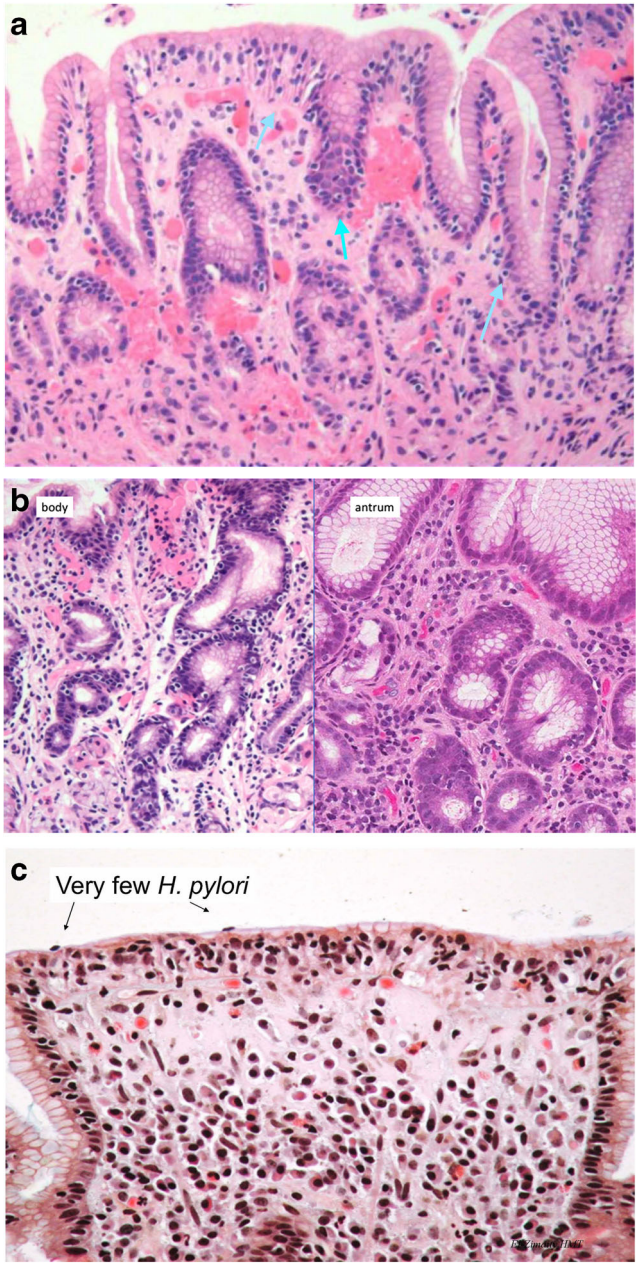

Fig. 3 **a** Lymphocytic gastritis in celiac disease is relatively mild and frequently antral predominant. **b** *HP*-associated lymphocytic gastritis tends to involve both the antrum and body and is associated with marked lamina propria inflammation. **c** Few (black arrow) or no bacteria are seen in *HP*-associated lymphocytic gastritis

Collagenous gastritis

Collagenous gastritis is rare and histologically distinct from *HP* negative chronic gastritis. Histologically, it is characterized by a more than 10-μm (up to 30–70 μm) thick subepithelial collagen band, often with entrapment of capillaries. The lamina propria contains a prominent lymphoplasmacytic inflammatory infiltrate, frequently attenuated at the epithelial surface with detachment of the epithelium [21, 22] (Fig. 4). An eosinophil-rich pattern (> 30 eosinophils/high-power field) [21] as well as a lymphocytic gastritis-like pattern have also been reported [21, 23–25], features that overlap with AIG. Occasionally, the infiltrate obscures the thickened subepithelial collagen plate, which can result in an erroneous diagnosis of chronic gastritis [26]. The inflammation is usually associated with mucosal atrophy [21], leading to a depressed mucosal pattern on endoscopy, whereas when the changes are less severe the mucosal lesions are nodular, leading to a cobblestone appearance on endoscopy [27]. The etiology is not known, but association with autoimmune diseases [28], IgA deficiency [29], common variable immunodeficiency [30], and systemic lupus erythematosus [31] have been reported.

Adult and pediatric forms of collagenous gastritis have been described [28]. In children, the condition tends to be

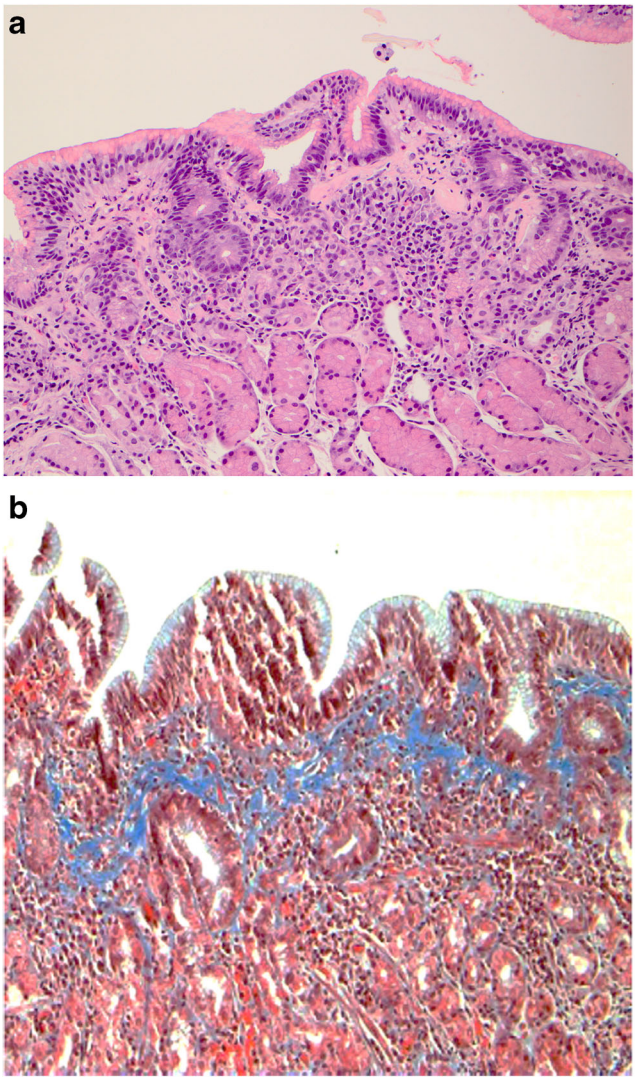

Fig. 4 **a** Collagenous gastritis with subepithelial deposition of collagen bands in the superficial lamina propria. **b** Trichrome stain highlights the collagen band

limited to the stomach (collagenous gastritis) and patients present with severe anemia and a nodular gastric mucosa. In adults, diffuse involvement of the gastrointestinal tract (collagenous gastro-enterocolitis) is characteristic and patients present with collagenous sprue and/or chronic watery diarrhea [22, 25]. The subepithelial collagen band has been found more prominent in the corpus/fundus in children but more prominent in the antrum in adults [21]. However, collagenous sprue and collagenous colitis have been described in children under 18 years old and collagenous gastritis without diffuse involvement of the gastrointestinal tract has been described in adults, which suggests a substantial overlap between these two age categories [21, 32, 33].

Although collagenous gastritis is considered a chronic benign disorder, spontaneous gastric perforation in a 15-year boy has been reported [34], and long-term follow-up has shown progressive glandular atrophy, intestinal metaplasia, and linear neuroendocrine hyperplasia as well as epithelial changes interpreted as indefinite for dysplasia. These are features of AIG but in the presence of a collagen band [35]. There is no standard therapy for this condition [22]. Successful treatment of collagenous gastritis with a gluten free diet has been reported [36].

Atrophic gastritis

Atrophic gastritis is characterized by progressive loss of oxyntic and/or antral mucosa. It can be a late result of *HP* infection or of AIG in which sensitized T cells and autoantibodies progressively destroy the gastric mucosa. The term gastric atrophy is sometimes used for end stage atrophic gastritis, irrespective of the nature of the underlying disease. *HP* infection and AIG are not mutually exclusive and *HP* may accelerate AIG in individuals with a genetic predisposition to AIG (Table 2).

In *HP*-associated atrophic gastritis, the inflammation extends like a sleeve from the incisura angularis in proximal direction, resulting in an advancing front of corpus mucosal atrophy which can be associated with intestinal metaplasia [42] (Fig. 5). As the lesser curve is shorter than the greater curve, atrophy can be identified in cardia mucosa on the lesser curve side, while the upper corpus and fundus mucosa may still be relatively intact and this is where residual *HP* may be found (Fig. 5). Many regard this as synonymous with multifocal atrophic gastritis, although this issue has not been resolved. Unlike in AIG, serum gastrin levels are only mildly elevated in *HP* associated atrophic gastritis, and usually there is no ECL hyperplasia [38, 43]. This may be because antrum mucosa affected by atrophy or intestinal metaplasia contains few gastrin producing G cells. The development of ECL cell hyperplasia secondary to hypergastrinemia requires an intact antrum to produce the G cell hyperplasia typically seen in AIG [38]. Nonetheless, ECL hyperplasia has been described secondary to chronic *HP* gastritis with and without PPI use [44, 45] (Table 2), but this requires a functionally intact antrum.

Classical AIG is a non-infectious immune-mediated gastritis that progressively destroys the oxyntic mucosa, resulting in reduced production of gastric acid and intrinsic factor (IF) necessary for vitamin B12 absorption but in younger patients also in iron deficiency. The presence of antibodies usually defines AIG as approximately 90% of patients with AIG have antibodies to PCAs and 50–70% to IF [46, 47]. The target antigens are the α and β subunits of H+/K+ adenosine triphosphatase, the protein of the secretory canaliculi of PCA responsible for the secretion of hydrogen ions in exchange for potassium ions (proton pump). These patients may also have multisystem autoimmune disorders affecting endocrine organs, such as thyroid, adrenal, and pancreas [48–50]. Young patients may have a genetic disposition, but the prevalence increases with age. Antibodies to PCA increase with the duration of *HP* [51] infection, especially those with CagA pathogenicity islands. *HP* will not be found in atrophic mucosa, but may still be detectable in biopsies from the fundus or upper greater curve. AIG has been described in association with and/or following *HP* infection, which may potentiate and even initiate AIG [45, 52, 53]. It has been suggested [38] that when AIG develops more than 10 years after *HP* induced atrophic gastritis, it is more likely to go along with anti-IF antibodies, higher gastrin levels reflecting more extensive atrophy, and less likely with anti-*HP* antibodies (which have been reported in 26% of atrophic gastritis cases). This is conceivable assuming that *HP* has been eradicated and over time antibody titers dropped to become negative.

The characteristics of *HP* associated and autoimmune atrophic gastritis are summarized in Table 2. Atrophic gastritis has two major forms: one with hypergastrinemia and antral G cell hyperplasia and ECL hyperplasia and the second with marginal hypergastrinemia and lacking ECL cell hyperplasia. The first form, which is more common, is associated with anti-PCA and anti-IF auto-antibodies, marked hypergastrinemia and low serum vitamin B12 and low iron [39]. Occasionally no antibodies are found, in which case longstanding *HP* infection sparing the antrum may be considered. The second variant also shows atrophy and pseudopyloric and intestinal metaplasia with loss of specialized oxyntic glands, but has marginal hypergastrinemia in the absence of ECL hyperplasia, despite the loss of oxyntic mucosa. This is likely the result of antral inflammation with atrophy and intestinal metaplasia, which destroys G cells precluding hypergastrinemia. However, anti-PCA antibodies are found in many patients with a *HP* infection, indicating that they are not specific for AIG [38] and that their presence does not define AIG. Conversely, the presence of anti-PCA and anti-IF antibodies is required for a diagnosis of AIG.

Table 2 Differences between AIG and *HP* associated atrophic gastritis

	HP associated	Autoimmune	References
Other autoimmune disease	1%	56%	[37]
Anti-parietal cell antibodies	Low titer when present	High titer (occasionally absent)	[38, 39]
Anti-intrinsic factor antibodies	Low titer when present	High titer (occasionally absent)	[38, 39]
Anti-*HP* antibodies			[37, 38, 40, 41]
Anti-*HP* IgG	72–100%	0–18%	
Anti-CagA IgG	86–93%	NA	
Hypergastrinemia	Mild	Marked	[38]
Corpus mucosa	Atrophic with intestinal metaplasia, pseudo-pyloric metaplasia, and occasionally pancreatic metaplasia	Atrophic with intestinal metaplasia, pseudo-pyloric metaplasia, and occasionally pancreatic metaplasia	[37]
	HP uncommon, can be found in proximal biopsies	Absent	
	ECL hyperplasia infrequent (10%)	ECL hyperplasia present	
	Absence of neuroendocrine tumors	Occasional neuroendocrine tumors (22%)	
Antrum mucosa	Atrophic with intestinal metaplasia	Reactive gastropathy; occasionally with intestinal metaplasia	[37, 39]
	Normal G cell population	Marked G cell hyperplasia	

It therefore needs gastric biopsy histopathology, presence of absence of *HP*, serum gastrin levels, and auto-antibody titers to distinguish between these entities with any degree of certainty. Biopsies should be taken from oxyntic and antral mucosa; from upper and lower greater and lesser curve preferably in separate containers. The AIG associated histological changes do not necessarily involve the entire gastric mucosa diffusely. When they are found, notably in association with ECL hyperplasia, auto-antibody titers, serum gastrin and vitamin B12 levels, and iron status need to be established to confirm or refute the diagnosis.

Morphologically, oxyntic mucosa in AIG shows loss of specialized mucosa with failure of glands to reach the muscularis mucosae, accompanied by architectural distortion. The muscularis mucosae may be thickened, a feature difficult to assess as it is rarely fully sampled, or duplicated. The latter reflects prior ulceration analogous to that seen in IBD and Barrett's esophagus. Ulceration does occur in *HP* gastritis but not in case of AIG only [54]. Pseudopyloric metaplasia is invariably present, metaplastic cells showing granular or eosinophilic cytoplasm rather than the clear cytoplasm of normal pyloric glands. Intestinal metaplasia is often present, as well as hypertrophy of residual islands of PCAs. Pancreatic metaplasia may be found, and when not in or around the cardia, a diagnosis of AIG needs to be considered. Hyperplasia of enterochromaffin-like (ECL) cells is typically seen around pseudopyloric gland bases as a second (outer) layer of nuclei surrounded by clear cytoplasm. Immunostaining for chromogranin and/or synaptophysin shows characteristic linear hyperplasia, which may extend into the mid-zone of the gastric mucosa. Endocrine micronests may also be visible in the lamina propria between glands and occasionally within the muscularis mucosae and even submucosa, but these do not represent a neoplastic proliferation unless identified macroscopically or endoscopically as a nodule or small polyp, and even then are invariably harmless. We prefer the term "micronests" rather than micro-NETs (neuroendocrine tumors) to avoid any misinterpretation of these microscopic foci.

The lamina propria contains a lymphoplasmacytic inflammatory infiltrate of variable density, notably in the basal part

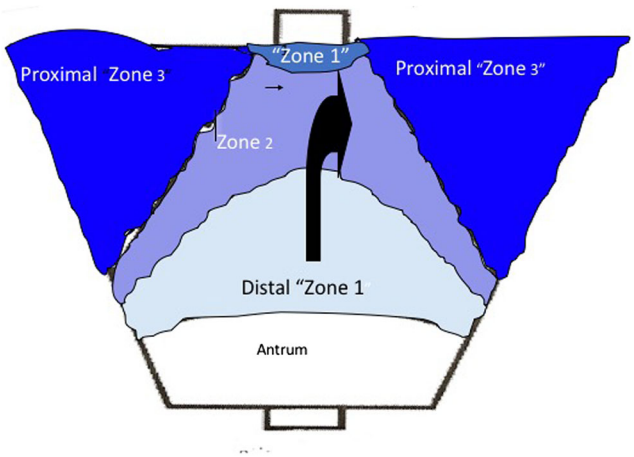

Fig. 5 An atrophic front is seen at two locations. **a** Distally, corpus atrophy begins at the border line (antrum-corpus border, zone 1) and extends proximally diffusely. Proportionately atrophy extends more rapidly up the lesser curve than the greater curvature such that locations high on the greater curvature (zone 3) are among the last to show atrophy. **b** Proximally, atrophy in the gastric cardia extends distally mostly on the lesser curve

of the mucosa, and IELs may be present. Neutrophils are variable and may be intraluminal. Eosinophils may be present, and when basal and marked, a diagnosis of AIG needs to be considered.

At endoscopy or in a resection specimen, the gastric mucosa often shows small polyps. These tend to represent small neuro-endocrine tumors. Larger polyps can also be found, including hyperplastic polyps, which may become dysplastic, intestinal-type adenomas (which may progress to carcinoma), fundic gland polyps, residual islands of relatively unaffected oxyntic mucosa (which have been called oxyntic mucosa pseudopolyps), and pyloric gland adenomas [44, 55].

In AIG, antral mucosa often shows mild chronic inflammation as in reactive gastropathy but almost never intestinal metaplasia or atrophy. The inflammation may be related to medication or duodeno-gastric reflux or even a sequel of an *HP* infection in the past. Alternatively, this may be due to auto-immunity to the regularly found PCAs in the antrum, although pseudo-hypertrophy is not seen in antral PCAs. A characteristic feature is G cell hyperplasia, the source of hypergastrinemia, due to loss of acid secretion in combination with a functionally intact antral mucosa. G cell hyperplasia is seen as rings of G cells around the mid-part of the glands [56–58] (Fig. 6), extending down into the lower third, reminiscent of the linear ECL cell hyperplasia seen in corpus mucosa. The lack of mid-zone G cells should immediately raise the question of whether one is dealing with atrophic oxyntic mucosa and prompt a search for a double layer of nuclei at the bases of the glands indicative of ECL hyperplasia and even micronests of endocrine cells in oxyntic mucosa. Of note, the most common cause of G cell hyperplasia is long-term acid suppression with PPI, but second most common is AIG/atrophic gastritis. Loss of G cells, such as with extensive atrophy or intestinal metaplasia, may preclude this. G cell hyperplasia is usually easy recognized in the mid zone of the mucosa and may extend downwards, whereas ECL hyperplasia in oxyntic mucosa is maximal in the pit bases and extend upwards. In case of doubt, gastrin stains are of value in establishing the origin of the biopsy as antral but as the distribution of G cells is different from that of ECL cells, stains for chromogranin A or synaptophysin (or both) allow identification of the origin of the biopsy.

Non-HP infectious gastritis

Although the most common cause of infectious gastritis is *HP*, various other infectious microorganisms can affect the gastric mucosa. These are listed in Table 3, along with differential diagnoses of infectious gastritis. Non-*HP* infectious gastritis tends to be more frequent in immunosuppressed patients.

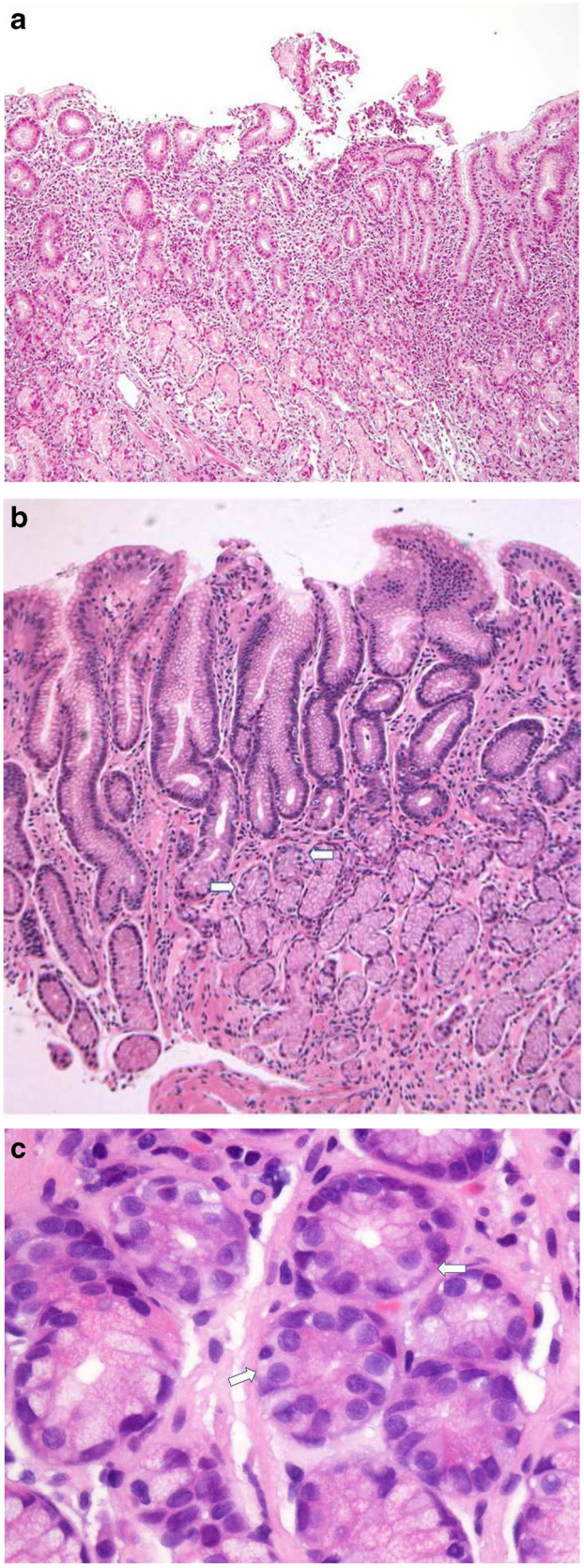

Fig. 6 **a** Oxyntic pseudopyloric metaplasia resembles antral mucous glands except for the absence of endocrine gastrin producing (G) cells. **b** Antrum with G cells (arrow). **c** Antrum with G cell hyperplasia>

Table 3 Differential diagnoses of infectious gastritis

Category	Subcategory	Differential Diagnoses
Prominent lamina propria inflammation	Lymphoplasmacytic	*H. pylori* gastritis
		Syphilitic gastritis
	Lymphocytic	Epstein-Barr virus-associated gastritis lymphomatoid (natural Killer cell) gastroenteropathy
	Neutrophilic	Phlegmonous gastritis (bacterial)
	Granulomatous and histiocytic	*Infectious*:
		Mycobacterium (tuberculosis, avis, atypical)
		Tropheryma whippelii
		Fungi
		Parasites
		Non-infectious:
		Crohn's disease
		Sarcoidosis
		Foreign body granuloma
		Other etiologies:
		Xanthogranulomatous gastritis
		Congenital immune disorders
		Vasculitis
		Idiopathic
Limited lamina propria inflammation	Viral inclusions	CMV gastritis
		HSV gastritis
		Adenovirus

Cytomegalovirus (CMV)-associated gastritis

Immunocompromised patients (including patients using steroids) are at risk. The symptoms are usually nonspecific, unless complications such as perforation occur. Two forms of gastric CMV infection have been described [59]. In the first form, patients are asymptomatic and at endoscopy, no lesions are found. In biopsies, viral inclusions are typically found in glandular epithelium with little associated tissue reaction. In the second form, CMV inclusions are found in swollen endothelial and stromal cells, especially in areas of ulceration. These patients typically present with mucosal erosion, ulceration, hemorrhage, necrosis, perforation, and/or fistula formation [59–61]. Noteworthy is the Ménétrier disease-like presentation reported in pediatric patients with CMV-associated gastritis, secondary to profuse foveolar hyperplasia [62].

Infected epithelial, endothelial, or stromal cells display characteristic amphophilic intranuclear and/or basophilic granular intracytoplasmic inclusions [63] (Fig. 7). CMV inclusions are usually found on HE stains, but if the biopsy is small with equivocal virally induced cytopathogenic changes, immunohistochemistry for CMV immediate early antigen or PCR testing for viral DNA can be helpful to confirm the diagnosis.

Herpes simplex virus (HSV)-associated gastritis

HSV-associated gastritis is very rare and has been almost exclusively reported in immunocompromised patients [64–66]. The endoscopic findings are variable but in one report the gastric mucosa had an aspect similar to that in Ménétrier disease with superficial erosions in a congested and edematous

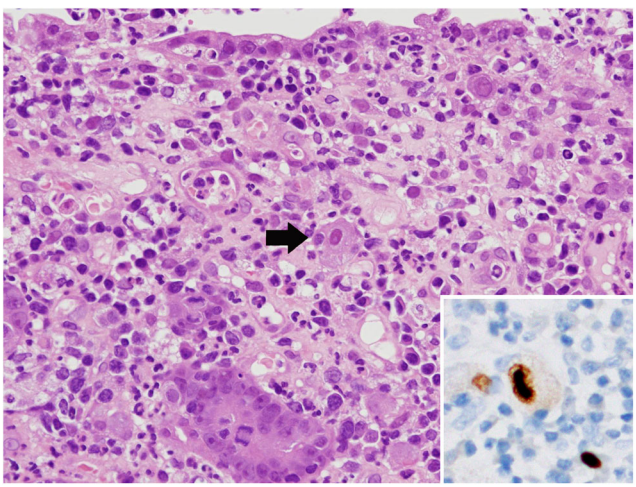

Fig. 7 CMV gastritis. The infected cells can show either characteristic owl's-eye intranuclear inclusions or granular basophilic cytoplasmic inclusions

mucosa. Infected cells in the esophagus showed ground-glass nuclei or eosinophilic intranuclear inclusions surrounded by a halo, but in gastric mucosa, inclusions were not found. Immunohistochemical staining for HSV was not found helpful [67].

Epstein-Barr virus (EBV)-associated gastritis

EBV-associated gastritis can be found in immunocompetent individuals in the setting of infectious mononucleosis [68]. Striking endoscopic findings are diffuse wall thickening, erosions, and even necrosis [68, 69]. Microscopically, EBV-associated gastritis is characterized by a dense polymorphic lymphocytic infiltrate with lymphoepithelial lesions [68]. The diagnosis is confirmed through detection of EBV-encoded small RNAs (EBER) by in situ hybridization in infected lymphocytes in the lamina propria [68].

Non-*HP* bacterial gastritis

Helicobacter species, other than *HP*, can be implicated in the pathogenesis of gastritis, gastric ulcers, gastric cancer, and MALT lymphoma. Although originally referred to as *H. heilmannii*, non-*HP* helicobacters (NHPH) include at least five different *Helicobacter* species including *H. heilmanii*, *H. suis*, *H. felis*, *H. bizzozeronii*, and *H. salmonis*. All are known to colonize the stomach of animals such as dogs, cats, cattle, and pig [70]. Presumably, infection is acquired by human contact with farm animals and household pets. Although the associated gastritis is usually milder than *HP*-associated gastritis, MALT lymphoma seems more frequent [71, 72]. Compared to *HP*, NHPH are longer with 6 to 8 coils. It is easy to miss these bacteria as typically, they are present in small groups within mucus covering the gastric mucosa and in gastric pits or sometimes only in the canaliculi of PCAs [73]. These may stain non-specifically with a *HP* immunostain, which emphasizes the importance of morphology for making the diagnosis.

The incidence of intestinal syphilitic manifestations is increasing. Endoscopic findings are non-diagnostic and include diffuse mucosal erythema and edema, erosions, and thickened rugal folds that can simulate a diffusely invasive carcinoma or lymphoma. Some patients present with peptic ulcers resistant to standard therapy [74]. Microscopically, syphilitic gastritis is characterized by a dense lymphoplasmacytic infiltrate with gland destruction. Plasma cells are prominent in the infiltrate, and this important diagnostic feature should alert the pathologist to consider this diagnosis. Proliferative endarteritis and ill-formed granulomas also occur [63, 74] (Fig. 8). *Treponema pallidum* can be visualized using the Warthin-Starry silver stain, by immunofluorescence or by immunoperoxidase staining. Triple or quadruple *Helicobacter* therapy also eradicates *T. pallidum*.

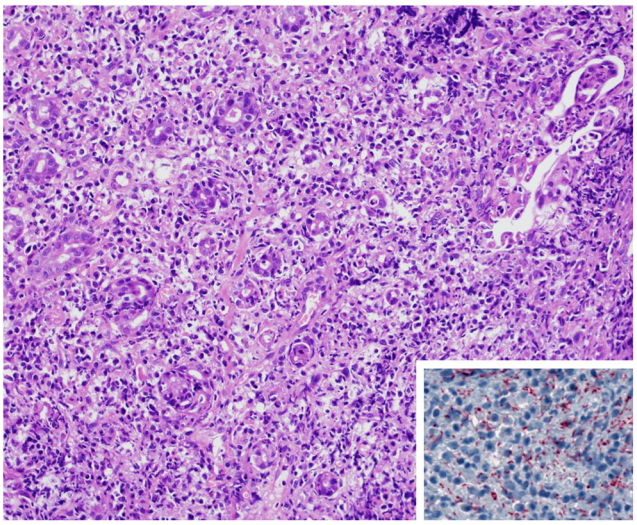

Fig. 8 Gastric syphilis. The gastric mucosa is infiltrated by a dense lymphoplasmacytic infiltrate. A lymphoma is a commonly considered in the differential diagnosis

Phlegmonous gastritis is a rare acute condition caused by localized or disseminated bacterial infection and associated with a high mortality rate. Immunosuppressed patients are at risk, but cases have been reported in patients without any risk factors following endoscopic resection of the gastric mucosa [75]. Frequently associated species include *Streptococcus* spp., *Staphylococcus* spp., *Haemophilus influenza*, *Klebsiella pneumoniae*, *Enterococcus* spp., and *Clostridium* spp. [76]. Diffuse mucosal damage, sometimes with necrosis, mucosal and submucosal neutrophilic infiltrate, and abscess formation are characteristic [63]. *Enterococcus* can attach to the surface epithelium where it is readily mistaken for coccal forms of *HP* (which are not viable), or co-exist with *HP*.

Emphysematous gastritis is a form of severe gastritis associated with a high mortality rate and characterized by intramural gas formation, in addition to the features of phlegmonous gastritis [77, 78]. Risk factors include among others ingestion of corrosive substances, diabetes mellitus, immunosuppressive therapy, and recent abdominal surgery [79]. *Clostridium* spp., *Escherichia coli*, *Streptococcus* spp., *Klebsiella* spp., *Enterococcus* spp., *Staphylococcus* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, *Candida* spp., and *Mucor* spp. have been implicated [77]. While abdominal CT scan detects intramural gas, upper endoscopy usually reveals mucosal erythema, erosions, and nodularity [77]. Biopsies show a diffuse neutrophil infiltrate with ulcers, hemorrhage and/or necrosis, cystically dilated glands, and admixed bacterial organisms.

Gastric tuberculosis is recognized with increasing frequency, in part in migrants from endemic areas. It can occur in immunocompromised patients, often without concomitant pulmonary disease [63, 80]. Morphologically, the presence of necrotizing granulomas is essentially diagnostic, particularly when they are confluent and large (400 μm in diameter) and

surrounded by a cuff of lymphocytes [81]. An acid-fast bacillus stain, bacterial culture, and/or PCR will confirm the diagnosis.

A granulomatous reaction can also be initiated by fungal and parasitic infections, including *Cryptococcus*, anisakis, and taenia [63, 82], while poorly formed granulomas can be seen in Whipple's disease. Cryptococcal infection, which can be detected on a mucicarmine stain, can present as either a disseminated disease or an isolated finding [82]. Anisakis can also cause granulomatous inflammation characterized by marked eosinophilia surrounding a central abscess or granulation tissue and has been reported to result in an inflammatory mass lesion [63]. Whether or not *HP* infection can generate a granulomatous reaction is still under discussion.

Gastritis in inflammatory bowel disease

Depending on the population, involvement of the stomach is found in 5 to 70% of all IBD patients, particularly CD. Although isolated gastric CD was once thought to be uncommon, recent data suggest that 30–80% of CD patients have either endoscopic or histologic changes, although particularly in children it is unclear if these are unequivocal evidence of the disease [80, 83] or a more general sign of an activated immune system. Endoscopic findings include nodularity, antral fold thickening, mucosal friability, loss of vascular pattern, and aphthous or linear ulceration [80, 83]. Microscopic features include mild diffuse chronic gastritis, aphthous erosions, focally enhanced gastritis, focal chronic active *HP* negative gastritis [84], and granulomas [85, 86]. Whether or not the presence of *HP* negative diffuse chronic gastritis is clinically significant, or a more general sign of an activated immune system is unclear. Focally enhanced gastritis appears as a lympho-histiocytic inflammatory infiltrate involving a few foveolae/glands [77, 78] and is more specific if neutrophils are present [84] (Fig. 9). It is not a specific diagnostic marker of CD, as it can be seen over 20% of children with ulcerative colitis [85, 87]. Although the presence of granulomas has been considered to represent gastric involvement with CD [86], they have been described in ulcerative colitis [85]. In the stomach, granulomas when present are more common in the antrum and tend to be superficial and loose. In a small proportion of CD cases, initial presentation is gastric and it may take years for other manifestations to occur. It is unclear whether, in the absence of symptoms, it is worth investigating the more distal bowel. Granulomatous gastritis has many other causes that should be excluded before suggesting IBD [88, 89] (Table 3).

Ulcerative colitis is more commonly associated with diffuse duodenitis and its intensity tends to mirror colonic involvement, diminishing as the large bowel disease is brought under control. A diagnosis of involvement of the stomach with IBD should only be made in patients in whom the diagnosis of ulcerative colitis has been clinically and histopathologically confirmed. If a history or prior biopsies from the lower GI-

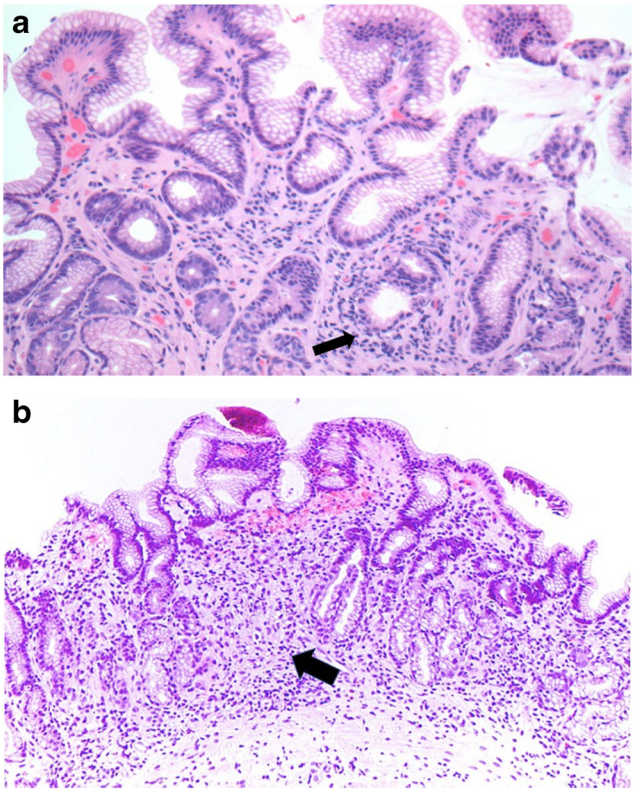

Fig. 9 Crohn's disease. Focal enhanced gastritis (**a**) with ill formed granuloma (**b**)

tract are not available, a descriptive diagnosis with a differential is more appropriate. Consensus guideline for what qualifies as significant involvement is still lacking. The North American IBD Genetics Consortium (arbitrarily) allows up to 10 minor lesions in a given location before significant disease can be concluded [90].

Sarcoidosis

Gastric sarcoidosis accounts for up to 20% of granulomatous gastritis. It can be detected as an isolated finding or a manifestation of multisystem disease [80]. Endoscopy may demonstrate nodularity, erosions, and/or rigidity of the wall of the stomach [91]. The presence of compact, non-necrotic granulomas in an otherwise normal mucosa and detection of extragastric granulomatous disease are highly suggestive. However, confirmation requires correlation with pulmonary disease and with clinical findings and exclusion of other granulomatous conditions. In practice, CD, tuberculosis, and sarcoidosis are the most prevalent.

Eosinophilic gastritis

Eosinophilic gastritis is defined as increased eosinophils within the lamina propria (≥ 30 eosinophils in at least five separate high-power fields (×400)) in the absence of other causes of

mucosal eosinophilia [92, 93]. Most cases represent a manifestation of eosinophilic gastroenteritis, a group of diseases collectively referred to as "eosinophilic gastrointestinal disorders" that include eosinophilic gastritis, esophagitis, enteritis, and colitis [94]. The differential diagnosis of mucosal eosinophilia includes food and drug allergy, parasitic infection, systemic connective tissue disorder, collagen vascular disease, CD, *HP* infection, AIG [54], and even gastric cancer and lymphoma [94–98]. Thus, it is important to exclude these other causes of mucosal eosinophilia prior to establishing a diagnosis of eosinophilic gastritis. Morphologically, clusters of eosinophils, intraepithelial or intraluminal, may be found. Extension of eosinophils into the muscularis mucosae and submucosa is also observed [92, 93].

Graft-versus-host disease

Graft-versus-host disease (GVHD) can develop as early as 1–2 months following allogeneic bone marrow transplantation [63, 80, 99]. Symptoms include nausea, vomiting, dyspepsia, anorexia, and/or food intolerance. Histological findings include scattered necrotic epithelial cells in the neck region (the proliferation zone) of gastric glands but not in the surface epithelium. Typically, the lamina propria does not contain an inflammatory infiltrate. In severe cases, glands are often dilated and attenuated and contain granular eosinophilic debris, which has been referred to as apoptotic abscesses. Gland destruction, ulceration, and mucosal necrosis may also be seen, although such severe changes are rare, and iatrogenic damage, such as conditioning regimens utilizing radiation and/or chemotherapy during the peri-transplant period, or CMV infection ought to be ruled out first [63, 80, 100, 101]. For this reason, biopsies should be obtained at least 20 days after transplantation.

The 2015 NIH consensus guidelines simplified the diagnosis of GVHD by reducing the number of categories from 4 to 3, which inevitably is more reproducible [102]. Biopsies are reported as "no GVHD," "possible GVHD," or "likely GVHD," the latter being a combination of the previous categories "consistent with GVHD" and "definite GVHD." In the tubal gut, it is almost impossible to distinguish between acute and chronic injury. Minimal criteria for acute GVHD are defined as "variable apoptotic criteria ($\geq$ 1/piece) in crypts." Criteria for chronic GVHD include gland destruction, ulceration, or submucosal fibrosis, which are all considered to reflect severe or long-standing disease but are not specific for chronic GVHD [102]. The term "possible GVHD" is often used when there are other mitigating factors, such as CMV gastritis with inclusions near the apoptotic changes, so the possibility of both diseases needs to be considered. However, the threshold for making the diagnosis of GVHD remains a problem, as decreasing the minimum requirements for apoptotic bodies to be present in 1 or 2 pits per biopsy, rather than 5 or 6, increases sensitivity but decreases specificity.

Reactive ("chemical") gastropathy

Reactive gastropathy represents the most common diagnosis of "gastritis" made in general practice. It results from acute or prolonged irritation from various noxious agents including among others bile, drugs, such as NSAIDs, 5-aminosalycilic acid, bisphosphonates, platelet aggregation inhibitors and selective serotonin reuptake inhibitors, iron, tetracyclines (doxycycline), and alcohol (86, 87). Reactive gastropathy can involve the oxyntic mucosa as well as the antral mucosa but is more commonly seen in the antrum [103]. Reactive gastropathy associated with duodeno-gastric reflux (bile) is noxious, as it contains activated pancreatic enzymes and solubilizes gastric mucin and predominantly affects the distal stomach in contrast to drug-related changes that can be found more equally in the corpus. Of note, when duodeno-gastric reflux is potentiated by gastroenterostomy or partial gastrectomy, both inflammatory polyps and carcinoma post-gastrectomy occur primarily around the anastomosis site.

Microscopic features include those associated with long standing damage, including foveolar hyperplasia with a corkscrew appearance (71, 86, 88), hyperplasia of smooth muscle fibers (a difficult criterion as normal has not been well defined), and paucity of inflammatory cells [104] (Figs. 10 and 11). Mucosal congestion with edema is also a common finding, but it is again difficult to know where normal finishes and pathology begins [92, 93]. These changes can be induced rapidly. Changes due to longstanding repeated injury include surface epithelium exfoliation, foveolar epithelium mucin depletion, nuclear enlargement, and hyperchromasia [89, 90]. Scattered eosinophils or neutrophils are often seen in the lamina propria, although in the absence of erosions, neutrophils

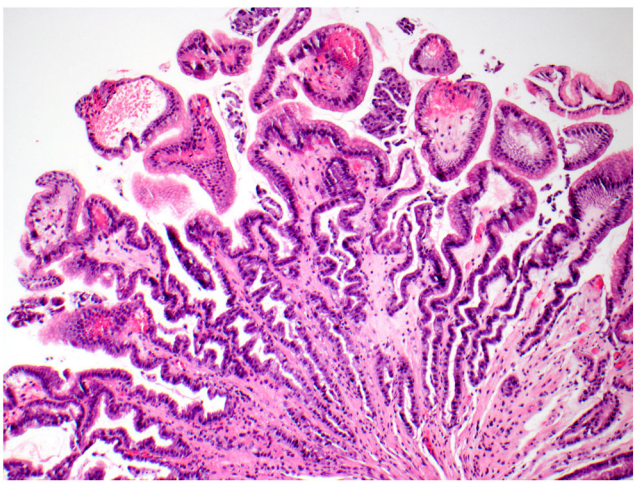

Fig. 10 Reactive gastropathy. Characteristic changes, such as foveolar hyperplasia, are present. Little inflammation is appreciated in the lamina propria

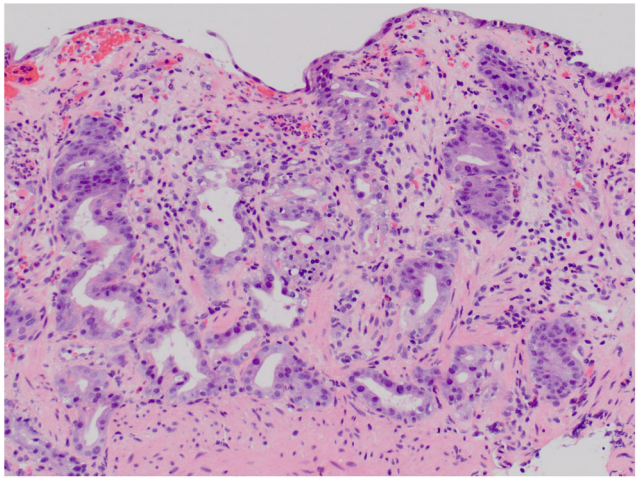

Fig. 11 Reactive gastropathy as seen with NSAIDs ingestion with typical features of reactive gastropathy with marked mucin depletion and lamina propria fibrosis

are usually lacking and sometimes even in their presence. It has been suggested that eosinophils are a hallmark of NSAID induced damage, but as this is likely the most common cause of gastropathy one would expect eosinophilia to be found more frequently, especially around mucosal erosions. Degenerative changes in gastric capillaries, with fibrinoid material around the vessel beneath the damage, are seen especially with doxycvcline treatment [105].

Drug-induced gastritis

The key to a correct diagnosis is appropriate review of medications received by the patients. Only a few examples of this ever-expanding category are presented, as detailed documentation is available in the literature [106].

Doxycycline-induced gastritis

Recent reports have refined the pathology of doxycycline-induced gastritis, a commonly prescribed antibiotic. Patients may develop odynophagia and epigastric/retrosternal pain and show multiple superficial esophago-gastric linear ulcerations. Biopsies typically demonstrate acute erosive gastritis with coagulative necrosis of the mucosa and capillary walls and neutrophilic inflammatory infiltrates [107, 108].

Caustic gastritis

Caustic gastritis results from accidental or suicidal ingestion of acid or alkali agents and causes severe gastric injury. The extent and severity of injury vary depending on the ingested agent [109]. The mucosa shows various degrees of edema, hemorrhage, coagulative necrosis, and ulceration. In surviving patients, significant scarring and stricture may develop [109, 110].

Colchicine and taxol-induced gastritis

Colchicine and taxol inhibit tubulin polymerization which induces mitotic arrest [111–113]. The same type of epithelial cell injury, notably an increased number of (arrested and/or abnormal ring like) mitotic figures, is seen with both medications. Apoptotic debris is also common in pits and glands, particularly in the antrum [111]. Ring mitotic figures are observed in association with high levels of colchicine, and when present, this reflects drug toxicity. As an inflammatory reaction is usually lacking, gastropathy would be a more appropriate term than gastritis.

Iron pill gastritis

Mucosal injury can be detected after taking iron tablets [114]. While patients may complain of epigastric discomfort, nausea, and/or vomiting, endoscopy may detect mucosal erythema, small hemorrhage, erosions, and/or ulcerations. Biopsies usually reveal features of reactive gastropathy associated with gold-brown pigment deposits in the superficial mucosa with various degrees of epithelial atypia which can, in some cases, closely mimic epithelial dysplasia. Iron pill gastritis should be differentiated from gastric siderosis due to systemic iron overload or hemochromatosis, which tends to show more prominent deposition in the basal glandular epithelium rather than the lamina propria [115]. Also, for this condition, the term gastropathy would be more appropriate.

Gastric mucosal calcinosis

Gastric mucosal calcinosis results from the accumulation of aluminum phosphate secondary to antacid use or sucralfate therapy in organ transplant or chronic renal failure patients [116]. In such cases, pink to purple refractile crystals within the lamina propria are seen subjacent to the surface epithelium [116]. The mucosal changes and deposits are not dissimilar from those recently reported as OsmoPrep-associated gastritis, which is associated with a tablet form of sodium phosphate [117].

Lanthanum carbonate

Lanthanum carbonate is a poorly absorbed phosphate binding agent used to treat hyperphosphatemia in dialysis patients [118, 119]. Gastric mucosal deposition is common (over 85% of dialysis patients) and presents as fine, granular, brown material located in histiocytes or multinucleated giant cells [118, 119] (Fig. 12).

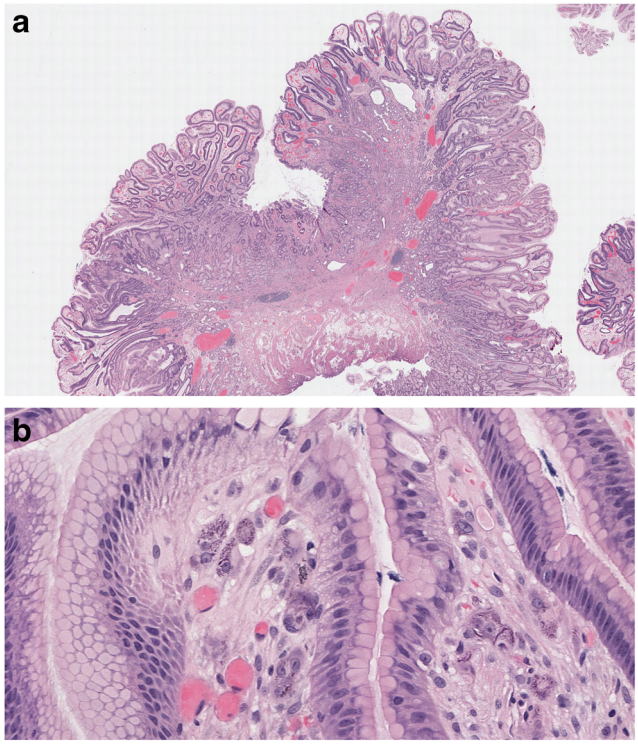

Fig. 12 Lanthanum Carbonate. **a** Overview is that of reactive gastropathy. **b** Detail showing black, coarse granular deposits corresponding to Lanthanum carbonate

Kayexalate in sorbitol

Kayexalate in sorbitol, used to treat hyperkalemia in patients with acute or chronic renal failure, can be associated with the occurrence of basophilic crystals [120]. The hyperosmolar sorbitol carrier is directly toxic to the mucosa and can cause ulcerations. The rhomboid or triangular crystals have a characteristic internal mosaic pattern mimicking fish scales. The crystals are red on periodic acid-Schiff (PAS)/Alcian blue and acid-fast stains and blue with a rapid Giemsa (Diff-Quik) stain [120].

Idiopathic chronic gastritis

When all listed causes have been excluded, about 15–25% of biopsies remain without a known cause for the chronic gastritis [121–123]. Gastritis tends to be mild, antral dominant, with lymphoid aggregates, but erosions and ulcers do occur [122, 124]. Such cases can be signed out as "chronic gastritis; *HP* not identified."

Conclusion

It is not infrequent to receive gastric biopsies with on the request form as question asked by the clinician "rule out *H. pylori*," with morphology suggestive of *HP*-associated gastritis, but without morphological evidence even in special stains for the presence of the organism. In this situation, the systematic approach to the differential diagnosis as elaborated above is recommended. This is summarized in Fig. 13.

The first step (A) is to exclude false negative search for *HP*. Assure that of both antral and oxyntic mucosa are present. If not, this might explain why *HP* are not found as 10–15% of *HP* positive patients have them in only one of these sites [9]. Then assure that appropriate special stains were ordered. If a Giemsa-based stain (such as modified Giemsa, Diff-Quick) was carried out, request a Warthin-Starry or immunostain. Finally verify if the patient has been treated with PPI or triple (anti-*HP*) therapy. PPI-induced PCA changes might not be immediately visible as it takes weeks for these changes to develop, so this requires accurate clinical information. The

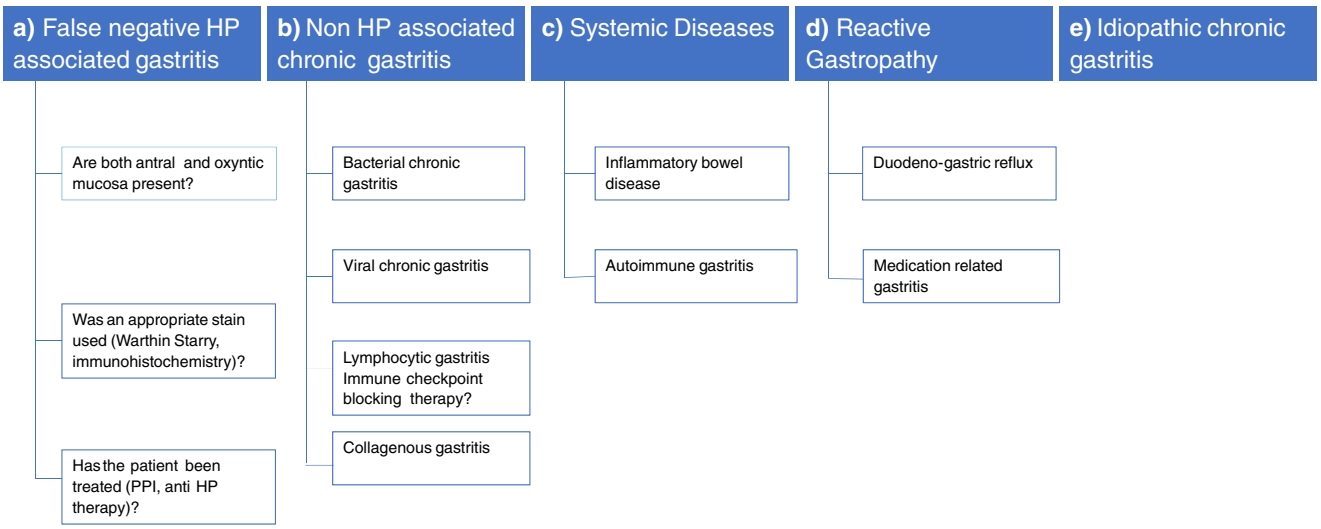

Fig. 13 Algorithm for dealing with *H. pylori* negative gastritis

second step (B) is to look for morphological characteristics suggesting a form of non-*HP* associated chronic gastritis. Consider other forms of infectious gastritis. In the presence of IELs (> 1 in 4 epithelial cells), consider lymphocytic gastritis or immune-checkpoint blocking therapy-associated gastritis. In the presence of a subepithelial collagen band, consider collagenous gastritis. In the presence of features of chronic atrophic gastritis, determine the status of antral mucosa gastritis (when G cells are present consider auto-immune gastritis, when absent, this may be atrophic oxyntic mucosa, or post-*HP* inflammation-induced absence of G-cells). In the third step (C), exclude systemic disease. Does the patient have a history of IBD or intestinal biopsies with IBD changes? Appropriate clinical input is required for this. In case of ECL hyperplasia (evident as a double layer of nuclei in the deep part of the pits) verify G cell hyperplasia and consider auto-immune gastritis. In the fourth step (D), features of reflux or medication injury have to be looked for and appropriate clinical information drawn. Organisms are often hard to find in the absence of mucin, so when there is diffuse reactive (chemical) gastropathy, *HP* are rarely found. In some conditions, such as post-gastric resection or gastro-enterostomy, duodeno-gastric reflux may result in diffuse gastropathy. When all the above have been excluded, consider as a final step (E) a diagnosis of idiopathic chronic gastritis.

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