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REVIEW

Pathology of non-infective gastritis

A Srivastava & G Y Lauwers[1]

Department of Pathology, Dartmouth Hitchcock Medical Center and Dartmouth Medical School, Lebanon, NH and [1]*Gastrointestinal Pathology Service, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*

Srivastava A & Lauwers G Y
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The discovery of *Helicobacter pylori* and its intimate role in the development of the most common form of chronic gastritis has elicited a much-needed interest in non-neoplastic gastric pathology. This has been paralleled by an increase in upper endoscopic examinations, which allow recognition of novel patterns and distribution of mucosal injury. Numerous attempts at classification have been made, most based on the acuteness or chronicity of gastric mucosal injury. In this review, we will not offer a new classification but present a detailed description of the major clinicopathological entities, based either on the salient morphological features or the underlying aetiologies, i.e. iatrogenic, autoimmune, vascular or idiopathic.

Keywords: classification, diagnostic features, gastritis, non-infective, stomach

Abbreviations: AIG, autoimmune gastritis; BMT, bone marrow transplant; ECL, enterochromaffin-like; EG, eosinophilic gastritis; FEG, focally enhanced gastritis; GAVE, gastric antral vascular ectasia; GVHD, graft-versus-host disease; IELs, intraepithelial lymphocytes; IGG, isolated granulomatous gastritis; LG, lymphocytic gastritis; MALT, mucosa-associated lymphoid tissue; NSAIDs, non-steroidal anti-inflammatory drugs; PHG, portal hypertensive gastropathy

Acute gastritis

Acute gastritis, usually a diffuse and intense mucosal alteration, is characterized by a sudden onset of symptoms and rapid resolution after the underlying aetiological mechanisms or agents (either chemical or physical) have been corrected. The patients can present with an acute gastroenteritis-like illness, or the symptomatology may be overshadowed by their general physical condition. Broadly speaking, acute gastritis arises when there is an acute imbalance between mucosal injury and repair mechanisms and can be organized in three groups based on the aetiologies: (i) infectious gastritis (not discussed here); (ii) secondary to caustic injury; and (iii) ulcero-haemorrhagic.

Address for correspondence: Gregory Y Lauwers MD, Gastrointestinal Pathology Service, Department of Pathology, Massachusetts General Hospital, 55 Fruit Street, WRN 2, Boston, MA 02114-2696 USA.
e-mail: glauwers@partners.org

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CAUSTIC GASTRITIS

Caustic gastritis will be mentioned briefly since it represents more of a therapeutic challenge than a diagnostic one. Most changes are antral and the severity of mucosal alterations varies with the substance ingested.[1–3] Commonly, the mucosa is oedematous and haemorrhagic and, in severe cases, coagulative necrosis associated with deep ulcerations and even perforation may be seen. Late complications may include fibrosis and stricture.[1–3]

ULCERO-HAEMORRHAGIC GASTRITIS

This pattern of gastritis is typically diagnosed in severely debilitated patients in a critical condition. It can be life-threatening due to uncontrollable haemorrhage and require emergency gastrectomy.[4] The epithelial damage is believed to be directly related to ischaemia related either to shock/hypotension or to

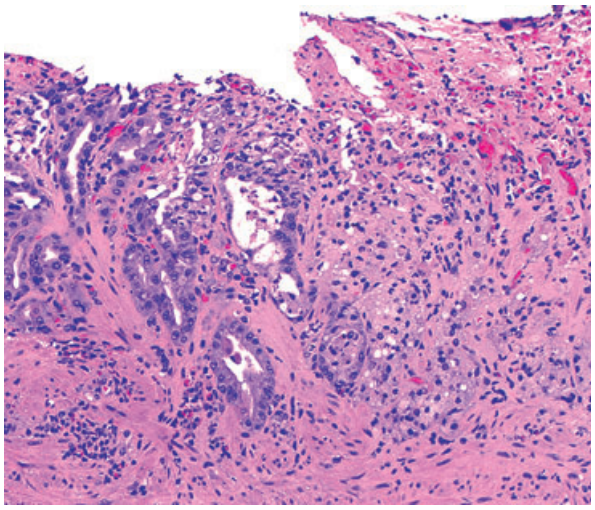

Figure 1. Acute gastritis. Erosion and complete effacement of the epithelium is observed. The residual glands, on the left, display regenerative changes with basophilic epithelium.

the release of vasoconstrictive substances.[4] In many cases, the aetiology remains unknown.

The endoscopic appearance of the gastric mucosa is characterized by multiple petechiae, predominantly in the body/fundus, or a diffusely haemorrhagic pattern. Similar lesions have been seen with massive ingestion of gastrotoxic drugs [non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, steroids] and after an alcoholic binge, but the pattern of distribution is usually different in these latter cases, the mucosal damage being centred predominantly in the antrum rather than the body of the stomach. Microscopically, the mucosa is characterized by an eroded surface epithelium with oedema and haemorrhage of the lamina propria and typically little inflammation.[5] In severe cases, the luminal surface is covered by a fibrinopurulent exudate and the lamina propria is replaced by eosinophilic hyaline material (Figure 1).[6] Concomitantly, the residual basal glands display marked regenerative changes, i.e. basophilic epithelial cells with numerous mitoses.[7] Transmural necrosis and deep ulcerations are rarely observed.

Reactive gastropathy

Reactive gastropathy represents the second most common diagnosis made on gastric biopsies, after *Helicobacter pylori* gastritis.[8] Originally reported after partial gastrectomy and believed to be specific for bile reflux gastritis, this distinctive histological picture is now considered to represent a non-specific response to a variety of other gastric irritants as well (hence the various synonyms).

Alkaline gastritis refers to mucosal injury caused by reflux of duodenal contents into the stomach, after a partial gastrectomy (Billroth I or II) or pyloroplasty.[9] It is also seen after cholecystectomy or ampullary sphincteroplasty, presumably due to a continuous flow of bile.[10] However, chronic NSAIDs use, which elicit gastric mucosal changes in 30–40% of patients, and various other chemical agents are now emerging as the dominant aetiology, and thus the term chemical gastropathy is being used interchangeably with reactive gastropathy.[5,11–14] Alcohol has also been implicated in this form of mucosal injury (alcoholic gastropathy).[15] Regardless of the mechanisms involved, either increased gastric pH and bacterial contamination by faecal-type microflora from bile reflux, or alcohol, and NSAID-induced injury, the characteristic foveolar hyperplasia is thought to represent a response to excessive cell exfoliation from the surface epithelium, and is associated with specific mucin and cytoskeletal alterations.[16,17]

Microscopically, reactive gastropathy is characterized by a constellation of changes including: (i) foveolar hyperplasia, with ensuing tortuosity of gastric pits and a corkscrew appearance; (ii) mucin paucity of the surface and foveolar epithelial cells, which appear cuboidal, with nuclear enlargement and hyperchromasia; (iii) superficial mucosal oedema with dilated capillaries; and (iv) 'tongues' of smooth muscle fibres extending from the muscularis mucosae upward into the lamina propria (Figure 2).[9,18] Interestingly, little inflammation is present and any sign to the contrary, even in the presence of foveolar tortuosity, necessitates to exclude *H. pylori* infection.[19]

An additional finding that may be seen in operated stomachs is the subnuclear vacuolization of foveolar cells.[20] In operated stomachs, chronic inflammation

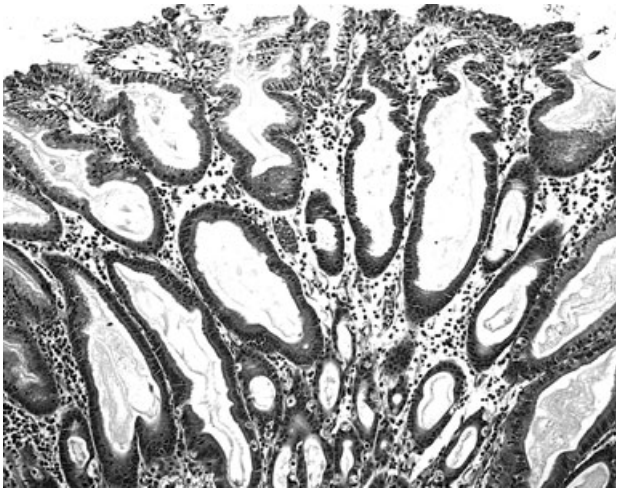

Figure 2. Reactive gastropathy. Characteristic changes such as foveolar hyperplasia and tortuosity of the gastric crypts (corkscrew appearance) are present. Little inflammation is appreciated in the lamina propria.

with intestinal metaplasia develops within 1–3 years after surgery[21] and is ultimately identified in 50–72% of patients, usually in the proximal remnant of the peristomal region, and is accompanied by mucosal atrophy in 20–45% of patients.[22,23]

Iatrogenic gastritis

DRUG-RELATED GASTRITIS/GASTROPATHY

Numerous drugs, acting through various mechanisms, have been associated with gastric mucosal damage. We will only highlight some common aetiologies.

Iron

Complaints of epigastric discomfort, nausea and vomiting are common after receiving iron therapy.[24] If an upper endoscopy is performed, it may show mucosal erythema and small subepithelial haemorrhages. Erosions and ulcers can also be seen.[24]

Microscopically, erosions, foveolar hyperplasia, or even hyperplastic-type polyps can be detected.[24] Because of the locally corrosive effect of iron, drug overdose has been associated with almost infarct-like necrosis.[24] Usually, the golden brown pigments are easily visible and can be highlighted by an iron stain.[24] The iron crystals may be embedded in granulation tissue, encrust the top of damaged epithelium, may be entrapped in the lamina propria, or may be present in either stromal cells, macrophages or even in vessel walls (Figure 3).[24,25] In most cases, the deposits disappear over 2–4 years. These changes should be differentiated from glandular siderosis, which may be associated with systemic iron overload or haemochromatosis.[25]

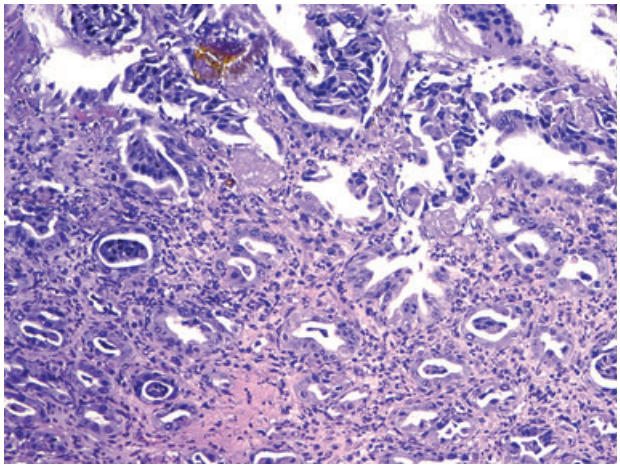

Figure 3. Iron-pill gastritis. Mucosal erosion is accompanied by acute and chronic inflammation and marked regenerative epithelial changes. Golden-brown pigments are identified on the luminal surface.

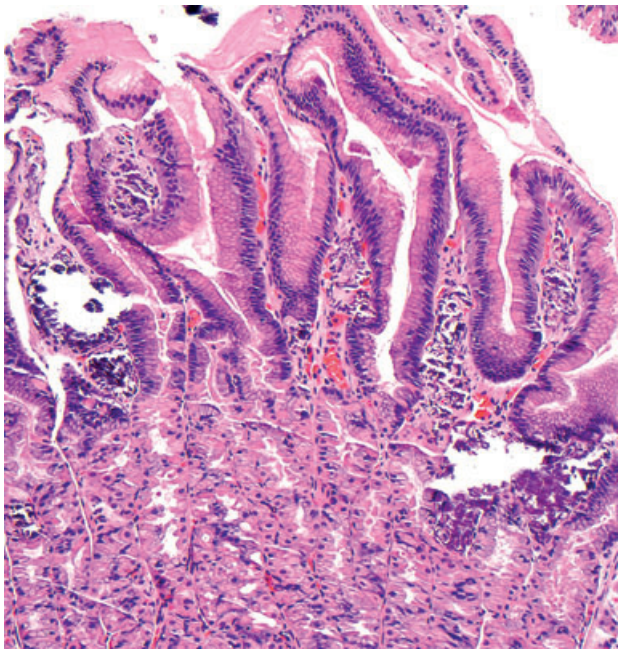

Figure 4. Gastric mucosal calcinosis. Pink refractile crystals are embedded in the lamina propria just underneath the surface epithelium. Note the presence of foveolar hyperplasia.

Iron-related mucosal damage can be seen in patients with gastric dysmotility as well as in healthy patients. The mechanism of injury is unclear, but it is possible that the physiological transport channels of iron are overrun and oxygen metabolites secondary to ferrous and ferric ion metabolism mediate the mucosal damage.[24]

Gastric mucosal calcinosis

Gastric mucosal calcinosis refers to the presence of small, deeply pink and partially calcified refractile crystals, found typically beneath the surface epithelium of the antrum. Usually, some degree of foveolar hyperplasia and mucosal oedema is present (Figure 4).[26–28] Gastric mucosal calcinosis seems more frequent in either orthotopic transplant patients (varied organs) or chronic renal failure patients, who have been prescribed either aluminium-containing antacids or sucralfate. In the elemental analysis of one such case, Greenson *et al.* have demonstrated that the crystals contained aluminium, phosphorus, calcium and chlorine.[26]

Colchicine

Mucosal changes are observed only when this alkaloid reaches toxic levels in patients with failing renal or hepatic function. The histological changes reflect, in part, the inhibition of tubulin polymerization. The gastric epithelium frequently shows nuclear pseudostratification and loss of polarity with numerous mitotic

figures arrested in metaphase, with the chromosomes often arranged as 'ring' mitoses.[29] Apoptoses can also be prominent and are typically located either in the proliferative region of the gastric crypt or the gland neck.

Kayexalate in sorbitol

Kayexalate in sorbitol, primarily used to manage hyperkalaemia in patients with renal failure, can lead to upper gastrointestinal tract injury in addition to the well-described ischaemic colonic necrosis.[30] The mucosa displays non-specific damage, with crystals either adherent to intact mucosa or admixed with exudates in ulcers or erosions. Unlike the patients with colonic injury, these patients do not require surgical intervention.

Miscellaneous

As expected, various chemotherapeutic agents have been associated with gastric mucosal changes. These include mitomycin C, 5-fluoro-2-deoxyuridine, and floxuridine.[31–33] It can be challenging to differentiate an adenocarcinoma from these changes, which may include ulceration and bizarre epithelial atypia accentuated at the base of the glands. The latter may show prominent eosinophilia, vacuolization and pleomorphic nuclei. Mitoses are usually limited. Similar changes can be seen in endothelial cells and fibroblasts.[31–33]

RADIATION GASTRITIS

Gastric mucosal injury may be seen following radiation therapy for upper abdominal neoplasia or in bone marrow transplant (BMT) recipients. However, it is diagnosed less commonly than radiation enteritis. Early changes (8–10 days after irradiation) consist of nuclear karyorrhexis and cytoplasmic eosinophilia of the gastric pit epithelium. During the next few days, mucosal oedema and congestion ensue and are accompanied by submucosal collagen bundle swelling, fibrin deposition and telangiectasia. Inflammation is usually insignificant.[34,35] Glandular necrosis with characteristic radiation-induced nuclear atypia follows. If extensive, there may be ulceration and haemorrhage, with possible late radiation effects such as endothelial proliferation and fibrinoid necrosis of the vessel walls. Recovery usually begins during the third week and is complete within 2–3 months.[34,35]

Autoimmune and other immunologically mediated gastritides

Presented in this section are those inflammatory disorders that are a manifestation of an autoimmune or other immunologically mediated forms of gastric mucosal injury.

TYPE A AUTOIMMUNE GASTRITIS

The classic (Type A) chronic autoimmune gastritis (AIG) is characterized by hypochlorhydria or achlorhydria resulting from parietal cell destruction secondary to circulating antibodies directed against H+/K+ ATPase located in the secretory canaliculi of oxyntic glands.[36] Intrinsic factor autoantibodies are also present in up to 60% of patients, leading to B12 deficiency and pernicious anaemia in some of these patients.[37] Other abnormalities include a low serum pepsinogen and a compensatory high serum gastrin concentration.[36] When diffuse atrophy is present, the body/fundic mucosa appears markedly thinned at endoscopy, with loss of mucosal folds and pebble-like elevations suggestive of intestinal metaplasia.[36] However, in earlier stages of the disease, multiple small polypoid nodules representing residual islands of oxyntic mucosa can be seen.[38]

Microscopically, the lamina propria reveals an intense mononuclear infiltrate predominantly composed of CD4+ T lymphocytes with an admixed population of plasma cells and B lymphocytes.[36] Notably, the infiltrate is deeply centred around the glands, in contrast to the superficial inflammation of *H. pylori* gastritis. Subsequently, pseudohypertrophy of individual residual parietal cells can be appreciated.[39] Lymphoid follicles may also be seen, as well as scattered polymorphonuclear elements. In contrast, the antral mucosa is devoid of significant inflammation but shows variable hyperplasia of G cells stimulated by the reduction in acid production.

As the inflammation persists, the oxyntic glands disappear and are replaced by neutral (periodic acid–Schiff positive) mucin-producing glands, 'pseudopyloric metaplasia'. If in doubt, the metaplastic origin of these glands is easily identified by the absence of G cells by immunohistochemistry. Eventually, the inflammation recedes and atrophy with metaplastic changes ranging from complete intestinal metaplasia (with goblet cells, Paneth cells, and absorptive cells) to pancreatic metaplasia, supervenes (Figure 5).[36,39]

Early in the disease, over 80% of patients with AIG show proliferation of enterochromaffin-like (ECL)-type endocrine cells secondary to hypergastrinaemia that parallels the degree of mucosal atrophy.[39] ECL hyperplasia takes the form of linear chains, small nodules, ribbons and tubules deep in the body/fundic mucosa; these are composed of small clear cells with round nuclei and finely dispersed chromatin. Eventually, between 1% and 5%[40,41] of these patients will develop

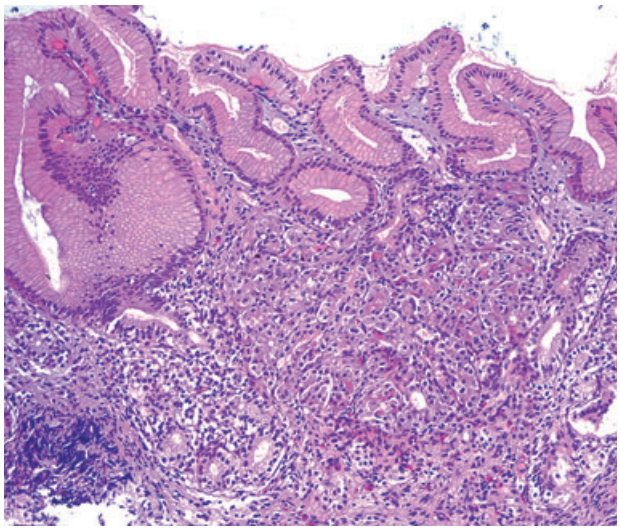

Figure 5. Autoimmune gastritis. This biopsy of the body fundic mucosa is characterized by a total atrophy of acidopeptic glands. Minimal inflammation remains. Pyloric and pancreatic/acinar metaplasia are observed.

multicentric low-grade gastric neuroendocrine (carcinoid) tumours, exclusively located in the fundus and most measuring < 10 mm.[42] Glandular epithelial dysplasia may also be observed in up to 40% of cases of AIG.[43]

GRAFT-VERSUS-HOST DISEASE

Gastric graft-versus-host disease (GVHD) occurs in up to 22% of patients following allogeneic BMT and much less commonly following blood transfusion.[44] In 18% of cases, GVHD of the upper gastrointestinal tract is seen without concomitant colonic disease.[45] The patients often complain of nausea, vomiting and dyspepsia rather than diarrhoea.[45] Endoscopically, the mucosa may appear normal in some and erythematous or eroded in others.[46]

The lesions arise as a result of the immunocompetent donor T cells targeting antigens on the recipient's epithelium and may be seen as early as 1–2 months post transplant (acute GVHD). After 2–3 months, chronic GVHD may follow and occurs more frequently in older patients. The foveolar surface epithelium is usually unaffected while the mucous neck region is more severely damaged with apoptosis, sometimes rare, and epithelial injury. The lamina propria characteristically shows only a sparse lymphocytic infiltrate. Crypt dilation with intraluminal granular eosinophilic debris may also be seen, but crypt destruction is uncommon.[47,48] Rarely, total gland destruction with fibrosis and eventual complete obliteration of mucosa can be observed. In this clinical setting, the differential diagnosis includes mucosal changes associated with cytoreductive regimens (radiation and chemotherapy injury) and cytomegalovirus infection.[47,49] However, the changes related to cytoreductive regimens typically resolve by the end of the third week post induction. Therefore, biopsies obtained for the evaluation of GVHD post BMT should be taken after 20 days.[50]

OTHER FORMS OF AUTOIMMUNE AND IMMUNOLOGICAL GASTRITIS

Examples of an atrophic pangastritis in *H. pylori*-negative patients, frequently associated with other autoimmune disorders, have been recognized. Anti-parietal cell and/or anti-intrinsic factor antibodies have been reported, but this type of gastritis is usually seen in the setting of autoimmune enteropathy and is suggestive of a generalized autoimmune disorder of the gastrointestinal tract, or other immunodeficiency disorders (congenital or acquired).[51–54]

The endoscopy of these rare lesions ranges from normal to diffusely abnormal with multiple ulcers. Unlike typical AIG, the gastric mucosa displays a diffuse inflammatory process extending throughout the entire stomach and is not confined merely to the body/fundus region.[54] The inflammatory infiltrate is composed of polyclonal plasma cells and numerous CD3+ T lymphocytes, with variable numbers of CD4+ and CD8+ T cells.[54] Interestingly, there is no associated neuroendocrine cell hyperplasia, suggesting that all the gastric cellular phenotypes are equally susceptible to inflammatory destruction.[54] Epithelial dysplasia may, however, develop in rare instances.

Similar morphological changes, i.e. apoptosis, increased intraepithelial lymphocytes and variably dense inflammatory infiltrate of the lamina propria, have been reported in patients with chronic variable immunodeficiency and HIV infection.[47,55]

Gastric manifestations of inflammatory bowel disease

The long-held belief that inflammatory lesions of the upper gastrointestinal tract in the setting of inflammatory bowel disease were diagnostic of Crohn's disease is now an obsolete dogma. The recently recognized focally enhancing gastritis, although more commonly seen in Crohn's disease, is also present in a significant number of patients with ulcerative colitis.

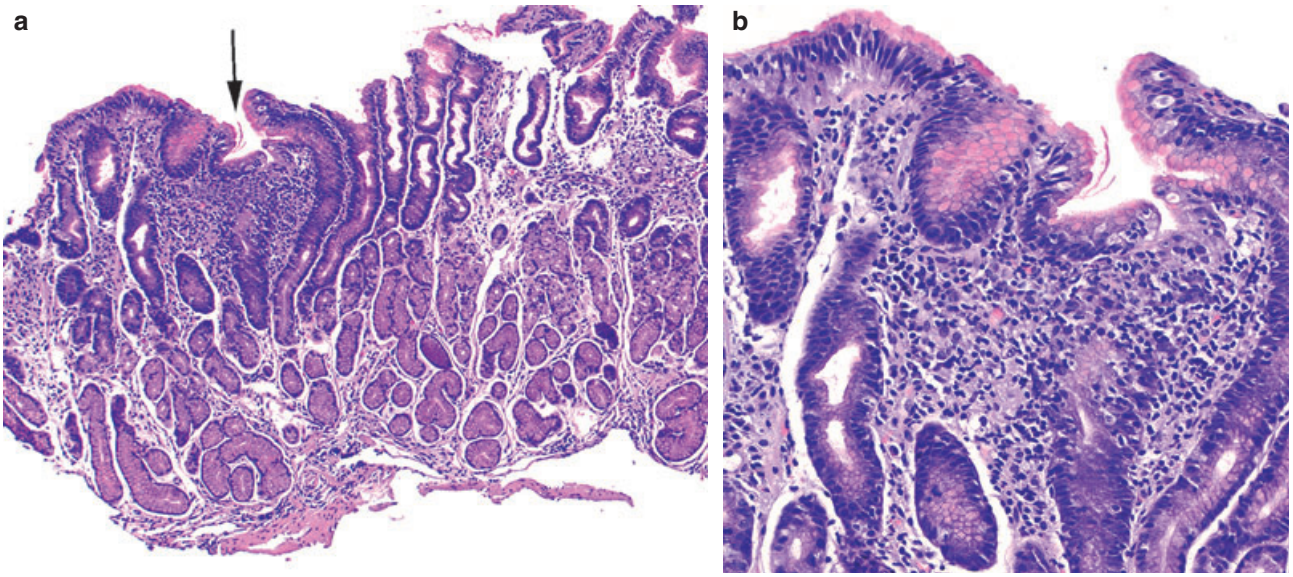

Figure 6. **a**, Low-power view of antral mucosa with focally enhanced gastritis. **b**, The distinctly focal inflammatory lesion is composed of a mixed infiltrate involving a single foveola.

CROHN'S DISEASE

Although clinically apparent gastric involvement is seen in only about 2–7% of patients with Crohn's disease, endoscopic and microscopic evidence of disease can be seen in 34–83% of patients.[56] In most cases, only focal acute and chronic inflammation, and granulomas are seen, while diffuse involvement with multifocal superficial erosions, mural rigidity and fistulas is uncommon.[57]

The endoscopic appearance is variable, ranging from normal, to nodular or thickened folds, to aphthous or linear ulcerations. Microscopically, the appearance is that of shallow ulcers, focal inflammation including lymphoid aggregates and plasma cells, and epithelial infiltration by neutrophils and/or lymphocytes ('focally enhanced gastritis', see below). Superficial loose granulomas with or without giant cells may be seen. Their incidence ranges between 0 and 83% depending on the sampling and the age of the patients, since they are more common in the paediatric population with a short duration of disease.[56] Deep ulcerations and fissures are rare.

Although most patients with gastric Crohn's disease have concomitant duodenal and ileal involvement[58,59] or evidence of extensive colonic disease,[60] in rare instances the gastric lesions may precede the more diagnostic lower gastrointestinal manifestations. For example, Oren has reported a case of Crohn's colitis occurring more than 10 years after an initial presentation as granulomatous gastritis.[61]

FOCALLY ENHANCING GASTRITIS

Focally enhanced gastritis (FEG) is defined as presence of focal inflammatory lesions composed mainly of lymphocytes and histiocytes, and occasionally neutrophils, that involve either one or a few adjacent foveolae/glands.[62] More frequent in the antrum than in the gastric body mucosa, there is a single focus in 73.5% of cases that involves two to eight glands (Figure 6a,b).[63] The infiltrate is composed predominantly of CD3+ T lymphocytes and CD68+ histiocytes with admixed granulocytes in 62% of cases.[62,63]

First heralded as a lesion specific for Crohn's disease,[62,63] with a prevalence ranging from 43% to 76%,[63] subsequent studies have shown that FEG is also present in up to 21% of patients with ulcerative colitis.[64] FEG has since been noted in other settings too, including BMT patients.[63] In the general population, the incidence of FEG is of about 3% once *H. pylori* gastritis and reactive gastropathy are excluded.[63] The significance of FEG may be different in the adult and paediatric patient population, with FEG being a relatively good positive predictive marker for Crohn's disease in the latter.[65] Of note, FEG has also been reported in autistic children, where it may have a distinctive immunophenotype with dominance of CD8+ T lymphocytes.[66]

Miscellaneous forms of gastritis with a distinctive histology

Presented below are those inflammatory disorders of the stomach that present with distinctive histological

patterns but do not have a unifying aetiopathogenic mechanism.

GRANULOMATOUS GASTRITIS

This is a morphologically descriptive term applied to the presence of epithelioid histiocytic aggregates and is a manifestation of a diverse group of aetiologies. Gastric granulomas occur uncommonly, with a reported incidence of between 0.08% and 0.35%.[67–70] The granulomas vary in number, size, location and composition, and there are seldom any morphologically distinctive features that point to a specific diagnosis. Special stains for mycobacteria or fungi, or examination under polarized light for detection of foreign material, may be helpful at times in reaching a definitive diagnosis. However, in most instances clinical, endoscopic, radiological and serological correlation is needed to identify the underlying aetiology.

Crohn's disease remains the commonest cause of granulomatous gastritis in the Western population, being responsible for nearly half of all such cases.[67,68] Gastric manifestations of Crohn's disease are discussed in greater detail elsewhere in this review. Gastric involvement in sarcoidosis may occur in patients with an already established diagnosis or as a presenting manifestation of the disease (Figure 7). Gastric sarcoidosis is responsible for 1–21% of all cases of granulomatous inflammation in the stomach.[67,68] Most cases are clinically asymptomatic, and endoscopic abnormalities in the form of mucosal nodularity, polypoid changes, erosions and ulceration, as well as rigidity of gastric wall simulating linitis plastica, have been described in these patients.[71–76] The presence of compact granulomas in an otherwise normal mucosa is suggestive of sarcoidosis in the appropriate clinical setting, although a background of chronic active gastritis and positivity for *H. pylori* have also been reported in some patients with gastric sarcoidosis.[67] In the absence of pulmonary or mediastinal disease or other identifiable causes of granulomatous gastritis, the presence of hypergammaglobulinaemia, hypercalciuria, raised levels of angiotensin converting enzyme, a restrictive pattern on pulmonary function tests and an active uptake on gallium scan are indicative of sarcoidosis as the underlying aetiology.

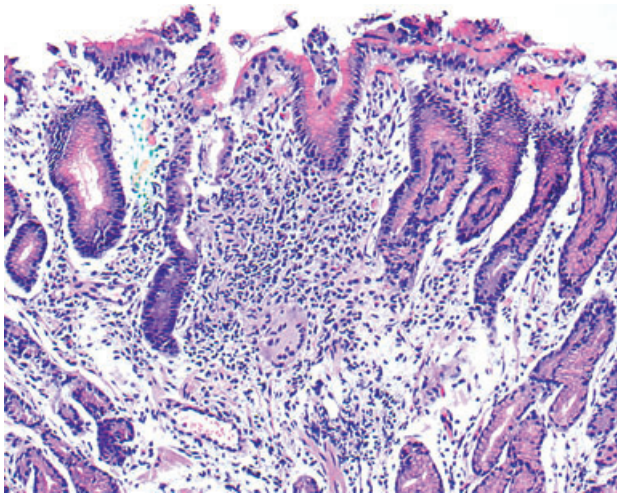

Figure 7. Granulomatous gastritis. The biopsy was obtained from an adolescent with documented ileal Crohn's disease.

The role of *H. pylori* as a causative organism for granulomatous gastritis is debatable. After the initial suggestions for such an association,[77] in a review of over 18 000 gastric biopsies, granulomas were found in 16 patients and *H. pylori* was identified in only six of those,[69] arguing for a fortuitous association. In a subsequent series of 71 patients with granulomatous gastritis associated with such diverse aetiologies as Crohn's disease, sarcoidosis, foreign body granulomas, tumours, etc., *H. pylori* was found in 92% of the biopsies.[68] Thus, while *H. pylori* infection may be responsible for granulomatous gastritis in a small number of cases, other causes of granulomatous inflammation must still be excluded even when the organisms are clearly identified.

Isolated granulomatous gastritis (IGG) has been described by Fahimi *et al*. as a clinicopathological entity distinct from regional enteritis and disseminated sarcoidosis.[78] In that series, most patients were symptomatic for more than a year and presented with weight loss, epigastric pain and vomiting, and this led to surgery on clinical suspicion of malignant obstruction. Since then, others have reported a good response to steroids[79] and even spontaneous resolution[80] in these cases. The concept of IGG has been questioned[67] due to lack of adequate clinical information and follow-up data in the initial study. Follow-up is especially important in view of cases in which granulomatous gastritis was a presenting manifestation of sarcoidosis[81,82] or Crohn's disease.[57,83] IGG should therefore not be regarded as a distinct clinicopathological entity. Thus, in the not uncommon scenario of granulomas in the stomach without an obvious aetiology (up to 25% of cases[68]), it is better to use a descriptive designation of 'granulomatous gastritis of uncertain aetiology' rather than IGG.

Although it extends beyond the scope of this review, one must be aware that bacterial, fungal and parasitic infections may also result in a granulomatous gastritis. Gastrointestinal tuberculosis may rarely present as an isolated infection of the stomach.[84,85] Such infections invariably occur in individuals residing in endemic

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areas or in severely immunocompromised patients. Diagnosis is usually established by the presence of necrotizing granulomas and the detection of acid-fast bacilli on special stains, or by culture or polymerase chain reaction methods allowing the sometimes difficult distinction from Crohn's disease.[86] Gastric involvement may occur in secondary or tertiary stages of syphilis, which may manifest endoscopically as rugal hypertrophy, mucosal erosions or ulcers, or luminal obstruction simulating malignancy. The histological appearance is characterized by a dense lymphoplasmacytic and granulomatous infiltrate often in a perivascular distribution.[87–89] Granulomatous gastritis associated with cryptococcal infection has also been described.[90] Acute gastric anisakiasis is caused by ingestion of raw fish. The larval nematodes of the family Anisakidae are usually removed endoscopically, but at times a granulomatous response to worm remnants with oedema and marked eosinophilia can be seen.[91–94] Gastric taeniasis causing a granulomatous gastritis has also been described.[95]

Gastric granulomas may also occur in association with adenocarcinomas and mucosa-associated lymphoid tissue (MALT) lymphomas.[96] In the former, they appear to be an inflammatory response to invasive tumour or extravasated mucin, similar to what has been described at other sites.

Foreign body granulomas may occur due to impacted food, suture material, or drugs, especially antacids, since magnesium, aluminium and silicon have been detected within granulomas by X-ray spectrometry[97] in rare instances. Xanthogranulomatous inflammation similar to that typically described in the gallbladder has also been reported in the stomach.[98] Other rare causes of granulomatous inflammation in the stomach include Langerhans cell histiocytosis,[99] chronic granulomatous disease[100] and common variable immunodeficiency.[55] An association with Whipple's disease[101] and with systemic vasculitides[102,103] has also been reported.

LYMPHOCYTIC GASTRITIS

Lymphocytic gastritis (LG) was described first by Haot as a peculiar endoscopic appearance, the so-called varioliform gastritis, characterized by thickened folds topped by small bumps with central aphthous ulcerations that was accompanied by an increased number of intraepithelial T lymphocytes (IELs) along the surface epithelium and in gastric pits.[104] A variety of other endoscopic appearances have been observed since. Affecting predominantly women, LG is an uncommon disorder found in 0.83% of patients undergoing an upper endoscopy and is present in 1.7–4.5% of cases of chronic active gastritis.[105] The symptomatology of LG can be variable and is not distinct from *H. pylori* gastritis, although it can be associated with anorexia and weight loss in a third of patients.[106] Other than the so-called varioliform gastritis described above, an impressive hypertrophic gastropathy with pit hyperplasia corresponding to severe diffuse lymphocytic infiltration may also be seen endoscopically. The changes may be seen throughout the stomach or may be more marked in the body or the antrum.[107] Interestingly, the endoscopic appearance can vary from one examination to another in the same patient.

Currently, the diagnostic threshold for LG is over 25 IELs per 100 epithelial cells, while the normal stomach shows a range of one to nine IELs.[108,109] Phenotypically, these IELs are predominantly CD3+ T cells coexpressing CD8.[110]

In addition to the increased number of intraepithelial T lymphocytes along the surface epithelium and in gastric pits, mild epithelial damage with mucin depletion and nuclear stratification is also seen. Marked elongation of the crypts has been described and the lamina propria may be variably expanded by a lymphoplasmacytic infiltrate (Figure 8). LG is pan-gastric in distribution in most (76%) cases but may be limited to the body (18%) or antrum (6%) in some patients.[105]

Multiple aetiologies can elicit the histological picture of LG. *Helicobacter pylori* infection is reported in about 20% of cases and coeliac sprue is present in 38% of cases.[105] In a series of patients with coeliac disease, 50% showed antral LG despite a normal gross appearance on endoscopy.[111] Other conditions have been associated with LG, and include Crohn's disease, HIV

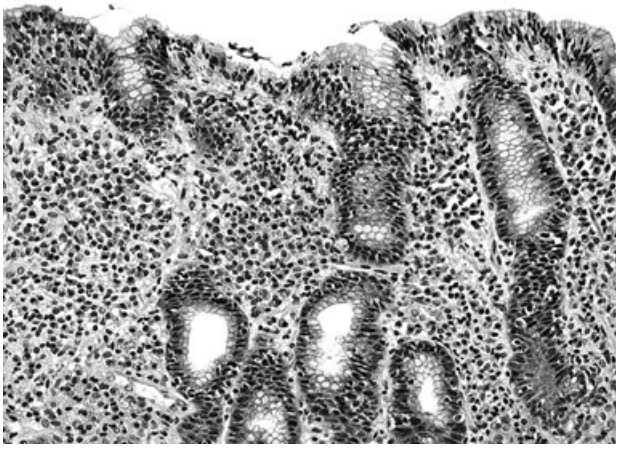

Figure 8. Lymphocytic gastritis. The lining surface epithelium shows distinctly increased lymphocytic exocytosis. Note the expansion of the lamina propria by a distinct lymphoplasmacytic infiltrate.

infection and lymphoma. In about one-fifth of cases, no aetiology is recognized.[105] Lymphocytic gastritis with Menetrier-like gastropathy and protein loss has also been reported in about 20% of the patients.[112,113]

Gastric lymphomas can present with prominent gastric folds that mimic the endoscopic appearance of LG and should always be excluded. A LG-like histology composed of benign T-cell IELs can be observed at the periphery of a gastric marginal zone B-cell lymphoma (MALT lymphoma). The vicinity of gastric adenocarcinoma has also been reported rarely to show a LG-like histology.

COLLAGENOUS GASTRITIS

Collagenous gastritis is rare and can involve either the antrum or the body/fundus. It is characterized microscopically by a chronic superficial gastritis composed of a lymphoplasmacytic infiltrate, scattered eosinophils and rare neutrophils, with subepithelial deposition of collagen bands in the superficial lamina propria (Figure 9).[114] Increased IELs have also been noted[115,116] in the setting of collagenous gastritis. The collagenous band is composed of type III, IV and VI collagen and can average 30–70 μm, but is often variably thick and discontinuous.[114,115,117] Similar to collagenous colitis, it entraps capillaries and is frequently associated with epithelial detachment. Glandular atrophy is rarely seen, and intestinal metaplasia is almost always absent.[117,118]

The clinical presentation is often as anaemia or chronic diarrhoea in a patient with synchronous collagenous or lymphocytic colitis or sprue.[119,120] A characteristic but not universal endoscopic appearance is that of diffuse nodularity of the gastric mucosa. Other patients may display a diffuse erythema only.[117]

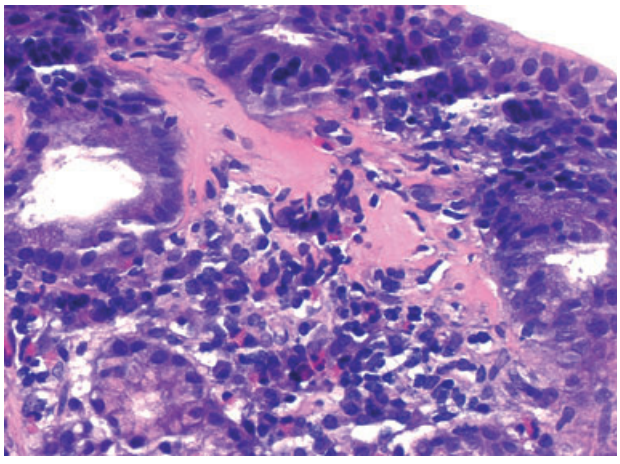

Figure 9. Collagenous gastritis. A distinct, thickened collagenous band underlines the surface (courtesy of Dr Mari Mino-Kenudson).

Notably, two distinct clinical subsets are emerging from the literature. Collagenous gastritis, predominantly in adult women, is commonly associated with a spectrum of lesions including coeliac disease or collagenous sprue or collagenous colitis, suggesting a pan-enteric pathogenic process. In contrast, paediatric patients frequently have the disease restricted to the stomach and present with gastrointestinal bleeding and anaemia.[115,117,119–121] The association with *H. pylori* infection sometimes reported in the literature appears to be fortuitous.

EOSINOPHILIC GASTRITIS

A few eosinophils may normally be present in the lamina propria of the stomach. Eosinophilic gastritis (EG) is defined by a prominent eosinophilic infiltrate, involving the gastric wall or more commonly the gastric epithelium (Figure 10).[122]

An allergic mechanism may underlie EG in some patients, whereas in others it is idiopathic in nature.[123] Although EG is seen most often in the setting of an eosinophilic gastroenteritis, it can also be associated with a diverse array of disorders. These include food allergies, mostly in paediatric patients (e.g. cow's milk, soy protein), collagen vascular disease and systemic connective tissue disorders (e.g. scleroderma and polymyositis) and parasitic infections. Other underlying conditions may include gastric cancer and lymphoma, Crohn's disease, vasculitis, drug allergy and *H. pylori* infection.[122–126]

When EG occurs in the setting of an eosinophilic gastroenteritis, the nature and severity of symptoms is

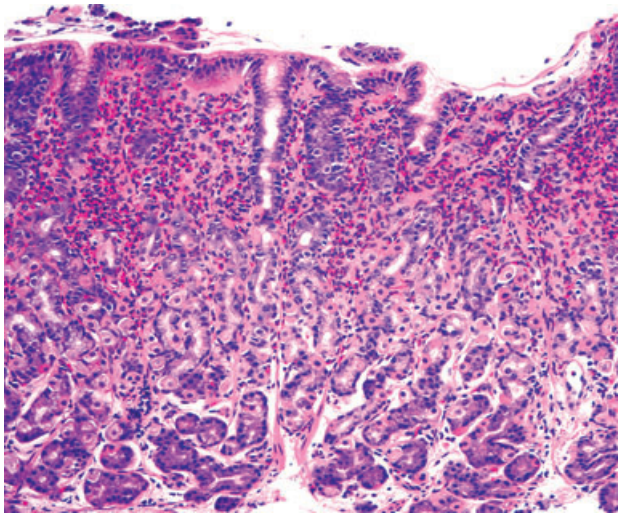

Figure 10. Eosinophilic gastritis. The superficial lamina propria is expanded by marked eosinophilic infiltrate. Mild regenerative epithelial changes are seen.

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related to the distribution and intensity of the inflammatory infiltrate. Serosal involvement is usually associated with eosinophilic ascites, while coexisting small bowel disease may result in iron deficiency anaemia and protein loss. In addition, peripheral blood eosinophilia is also characteristically but not universally present.[127]

With regard to the stomach, the endoscopy may show hypertrophic gastric folds or vesicles in the mucosal form of EG.[128] The eosinophilic infiltration is commonly observed in the antrum, and may be patchy, underlining the importance of obtaining biopsy specimens from multiple sites. Non-specific epithelial changes such as mucin depletion may be seen in severe cases that exhibit a marked intraepithelial eosinophilic infiltration.

Vascular gastropathies

Vascular gastropathies are characterized histologically by abnormalities of the gastric mucosal and/or submucosal blood vessels in the absence of a conspicuous inflammatory component. The endoscopic appearances may overlap with those of gastritis of other causes and hence biopsy is often necessary to establish the diagnosis. The two main entities that we will review here are portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE). Other rare lesions such as gastric lymphocytic phlebitis are not discussed.[129]

PHG is an important cause of chronic upper gastrointestinal bleeding and occurs in about 65% of all patients with cirrhosis and portal hypertension. Approximately two-thirds of these patients with PHG have mild disease while another 10–25% show severe disease.[130] The presence of PHG correlates with more severe liver disease, presence, and size of esophageal varices, and a previous history of sclerotherapy.[131,132] Changes similar to PHG have also been described in the setting of non-cirrhotic portal hypertension, extrahepatic portal vein obstruction and in Budd–Chiari syndrome.[133] The exact pathophysiological mechanisms involved in PHG are unclear at present. However, there is clearly an increased susceptibility of the gastric mucosa in the setting of PHG to damage by drugs or other noxious agents, as shown in both animal and human studies.[134–136] Changes in nitric oxide production, tumour necrosis factor-alpha synthesis and sensitivity to prostaglandin inhibition have been postulated as playing a role in the pathogenesis of PHG.[137–139]

Unlike GAVE, the endoscopic and histological changes in PHG are most often confined to the gastric corpus and fundus. The endoscopic appearance of PHG is variable. An oedematous red mucosa with a mosaic pattern is seen in early and mild disease, while friable, cherry-red mucosal red spots that actively bleed on touch are present in severe disease.[140] Marked vascular ectasia, irregularity and tortuosity, and variable mural thickening of mucosal and submucosal capillaries and veins[141,142] are the morphological hallmarks of PHG. However, it must be emphasized that: (i) changes in PHG may at times be more marked in deeper submucosal vessels[141] and therefore a normal mucosal biopsy by no means rules out a diagnosis of PHG, and (ii) the presence of capillary dilation in gastric mucosal biopsies is a non-specific finding that may be seen in patients with and without portal hypertension[142] and, if used in isolation, is not a reliable diagnostic criterion for PHG.

Gastric antral vascular ectasia or GAVE syndrome was initially described in 1953[143] and the now well-known endoscopic appearance of a 'watermelon stomach' was characterized in greater detail subsequently.[144,145] The typical patient with GAVE is usually an elderly woman with some form of autoimmune connective tissue disease and a history of chronic occult blood loss.[146] The syndrome has been associated with Raynaud's phenomenon, sclerodactyly, atrophic gastritis and hypergastrinaemia,[146] scleroderma, and CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) syndrome, BMT and chronic renal failure.[147–151] About 30% of patients with GAVE may have cirrhosis[152] and, in the setting of portal hypertension, the distinction between GAVE and severe PHG not only can be challenging but is also of clinical relevance for patient management.[153] The classical endoscopic appearance is that of raised, red mucosal stripes of dilated and tortuous blood vessels involving the antrum and converging on the pylorus, but is present in only about half the cases. Other described patterns are essentially a variable combination of flat and linear stripes.[146] While the antrum is affected most often, proximal extension into the corpus and involvement of the cardia have also been described.[154]

Degenerative changes and prolapse of the antral mucosa have been proposed as possible mechanisms for occurrence of GAVE.[144,145,155] Vasoactive intestinal peptide and serotonin-positive neuroendocrine cells have been reported in some cases close to blood vessels, leading to suggestions that the vascular dilation may be endogenous peptide mediated.[156] Typical morphological features are those of vascular dilation, intravascular microthrombi which are present in about 50% of cases (Figure 11)[153] and a variable component of spindle cell myofibroblastic proliferation in the lamina propria.[157] The latter two findings are particularly useful in distinguishing GAVE from PHG in the setting of cirrhosis and portal hypertension. Foveolar hyperplasia and regenerative epithelial changes are also present in most cases.

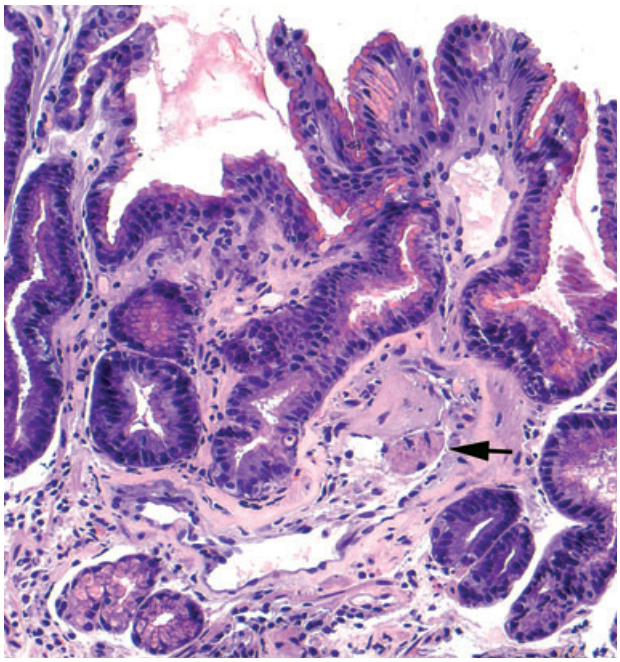

Figure 11. Gastric antral vascular ectasia (GAVE). Distended capillaries extend within the lamina propria. A single fibrin thrombus is seen (arrow). The surface epithelium shows foveolar hyperplasia.

Unlike severe PHG, reduction of portal pressures by β-blockers, transjugular intrahepatic portosystemic shunt or surgery is not an effective treatment for GAVE-associated bleeding.[158–160] Endoscopic laser coagulative therapies[161,162] are most useful in its management.

In conclusion, there is a rich non-tumoral pathology of the stomach beyond *H. pylori* gastritis which, at least in Western nations, is becoming less common. Non-infective forms of gastritis may present with a diverse array of clinical, endoscopic and histological manifestations. Surgical pathologists in clinical practice can be assisted greatly by knowledge of common aetiological associations, of distinctive morphological patterns (e.g. granulomatous, lymphocytic gastritis) and of reactive patterns that may mimic a malignant process (e.g. reactive gastropathy, chemotherapy). This information can be readily put to the test in a systematic approach to diagnosis (Table 1). The increase in endoscopic examinations being performed, along with greater collaborative efforts between gastroenterologists and pathologists, will surely lead to a better understanding of known entities and help distinguish currently uncharacterized diseases.

Table 1. Schematic approach to the diagnosis of non-*Helicobacter pylori* gastritis

Lamina propria expanded with inflammation

Diffuse

Autoimmune gastritis
- Corpus predominant
- Lymphoplasmacytic infiltrate
- Parietal cell destruction
- ECL cell hyperplasia

Lymphocytic gastritis
- Increased IELs
- *H. pylori* +/–
- History of celiac sprue +/–
- Others: Crohn, HIV, etc…

Eosinophilic gastritis
- Increased intra-epithelial or lamina propria eosinophils
- History of allergy, connective tissue disease, parasites etc.

Collagenous gastritis
- Subepithelial collagen band
- Increased IEL's +/–
- History of sprue, collagenous colitis

Focal

Focally Enhancing Gastritis
- Admixed lymphohistiocytic and neutrophilic infiltrate
- IBD, autism, bone marrow transplant

Granuloma(s)

Granulomatous Gastritis
- Crohn disease
- Sarcoidosis
- Others: Parasite, Foreign body, Mycobacteria, etc
- Unknown (25%)
- Rule out other causes even if *H. pylori* positive

Lamina propria with little or no inflammation

Acute Gastritis
- Erosion, edema, hemorrhage
- Caustic injury, Alcohol
- Shock, hypotension
- Iatrogenic: Iron, etc...
- Radiation

Reactive Gastropathy
- Foveolar hyperplasia w/ "Corkscrew appearance"
- NSAID, other drugs
- Bile reflux
- (Alcohol)

GAVE
- Antrum predominant vascular ectasia
- Intravascular thrombi
- Myofibroblastic proliferation

PHG
- Corpus predominant vascular ectasia
- Edema, congestion
- Mural thickening
- History of cirrhosis/portal HT

GVHD
- Increased apoptosis
- Similar changes secondary to cytoreductive regimens
- Difficult diagnosis within 3 weeks of transplantation

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References

1. Sugawa C, Lucas CE. Caustic injury of the upper gastrointestinal tract in adults: a clinical and endoscopic study. *Surgery* 1989; **106;** 802–806; discussion 806–807.
2. Garcia Diaz E, Castro Fernandez M, Romero Gomez M, Castilla Higuero L. [Upper gastrointestinal tract injury caused by ingestion of caustic substances]. *Gastroenterol. Hepatol.* 2001; **24;** 191–195.
3. Poley JW, Steyerberg EW, Kuipers EJ *et al.* Ingestion of acid and alkaline agents: outcome and prognostic value of early upper endoscopy. *Gastrointest. Endosc.* 2004; **60;** 372–377.
4. Chamberlain CE. Acute hemorrhagic gastritis. *Gastroenterol. Clin. North Am.* 1993; **22;** 843–873.
5. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N. Engl. J. Med.* 1999; **340;** 1888–1899.
6. Franzin G, Manfrini C, Musola R, Rodella S, Fratton A. Chronic erosions of the stomach—a clinical, endoscopic and histological evaluation. *Endoscopy* 1984; **16;** 1–5.
7. Isaacson P. Biopsy appearances easily mistaken for malignancy in gastrointestinal endoscopy. *Histopathology* 1982; **6;** 377–389.
8. Owen DA. Gastritis and carditis. *Mod. Pathol.* 2003; **16;** 325–341.
9. Dixon MF, O'Connor HJ, Axon AT, King RF, Johnston D. Reflux gastritis: distinct histopathological entity? *J. Clin. Pathol.* 1986; **39;** 524–530.
10. Warshaw AL. Bile gastritis without prior gastric surgery: contributing role of cholecystectomy. *Am. J. Surg.* 1979; **137;** 527–531.
11. Sobala GM, King RF, Axon AT, Dixon MF. Reflux gastritis in the intact stomach. *J. Clin. Pathol.* 1990; **43;** 303–306.
12. Quinn CM, Bjarnason I, Price AB. Gastritis in patients on nonsteroidal anti-inflammatory drugs. *Histopathology* 1993; **23;** 341–348.
13. Haber MM, Lopez I. Gastric histologic findings in patients with nonsteroidal anti-inflammatory drug-associated gastric ulcer. *Mod. Pathol.* 1999; **12;** 592–598.
14. Wallace JL. Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. *Gastroenterology* 1997; **112;** 1000–1016.
15. DeNardi FG, Riddell RH. Reactive (chemical) gastropathy and gastritis. In Graham DY, Genta RM, Dixon MF eds. *Gastritis.* Philadelphia: Lippincott Williams & Wilkins 1999.
16. Lauwers GY, Furman J, Michael LE, Balis UJ, Kubilis PS. Cytoskeletal and kinetic epithelial differences between NSAID gastropathy and *Helicobacter pylori* gastritis: an immunohistochemical determination. *Histopathology* 2001; **39;** 133–140.
17. Mino-Kenudson M, Tomita S, Lauwers GY. Mucin expression in reactive gastropathy: an immunohistochemical analysis. *Arch. Pathol. Lab. Med.* 2007; in press.
18. Sobala GM, O'Connor HJ, Dewar EP *et al.* Bile reflux and intestinal metaplasia in gastric mucosa. *J. Clin. Pathol.* 1993; **46;** 235–240.
19. El-Zimaity HM, Genta RM, Graham DY. Histological features do not define NSAID-induced gastritis. *Hum. Pathol.* 1996; **27;** 1348–1354.
20. Rubio CA, Slezak P. Foveolar cell vacuolization in operated stomachs. *Am. J. Surg. Pathol.* 1988; **12;** 773–776.
21. Janunger KG, Domellof L, Eriksson S. The development of mucosal changes after gastric surgery for ulcer disease. *Scand. J. Gastroenterol.* 1978; **13;** 217–223.
22. Offerhaus GJ, van de Stadt J, Huibregtse K, Tersmette AC, Tytgat GN. The mucosa of the gastric remnant harboring malignancy. Histologic findings in the biopsy specimens of 504 asymptomatic patients 15–46 years after partial gastrectomy with emphasis on nonmalignant lesions. *Cancer* 1989; **64;** 698–703.
23. Geboes K, Rutgeerts P, Broeckaert L, Vantrappen G, Desmet V. Histologic appearances of endoscopic gastric mucosal biopsies 10–20 years after partial gastrectomy. *Ann. Surg.* 1980; **192;** 179–182.
24. Abraham SC, Yardley JH, Wu TT. Erosive injury to the upper gastrointestinal tract in patients receiving iron medication: an underrecognized entity. *Am. J. Surg. Pathol.* 1999; **23;** 1241–1247.
25. Marginean EC, Bennick M, Cyczk J, Robert ME, Jain D. Gastric siderosis: patterns and significance. *Am. J. Surg. Pathol.* 2006; **30;** 514–520.
26. Greenson JK, Trinidad SB, Pfeil SA *et al.* Gastric mucosal calcinosis. Calcified aluminum phosphate deposits secondary to aluminum-containing antacids or sucralfate therapy in organ transplant patients. *Am. J. Surg. Pathol.* 1993; **17;** 45–50.
27. Stroehlein KB, Stroehlein JR, Kahan BD, Gruber SA. Gastric mucosal calcinosis in renal transplant patients. *Transplant Proc.* 1999; **31;** 2124–2126.
28. Saab S, Venkataramani A, Behling CA, Savides TJ. Gastric mucosal calcinosis in a patient with dyspepsia. *J. Clin. Gastroenterol.* 1996; **22;** 156–164.
29. Iacobuzio-Donahue CA, Lee EL, Abraham SC, Yardley JH, Wu TT. Colchicine toxicity: distinct morphologic findings in gastrointestinal biopsies. *Am. J. Surg. Pathol.* 2001; **25;** 1067–1073.
30. Abraham SC, Bhagavan BS, Lee LA, Rashid A, Wu TT. Upper gastrointestinal tract injury in patients receiving kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. *Am. J. Surg. Pathol.* 2001; **25;** 637–644.
31. Doria MI Jr, Doria LK, Faintuch J, Levin B. Gastric mucosal injury after hepatic arterial infusion chemotherapy with floxuridine. A clinical and pathologic study. *Cancer* 1994; **73;** 2042–2047.
32. Choi HY, Takeda M. Gastric epithelial atypia following hepatic arterial infusion chemotherapy. *Diagn. Cytopathol.* 1985; **1;** 241–244.
33. Petras RE, Hart WR, Bukowski RM. Gastric epithelial atypia associated with hepatic arterial infusion chemotherapy. Its distinction from early gastric carcinoma. *Cancer* 1985; **56;** 745–750.
34. Novak JM, Collins JT, Donowitz M *et al.* Effects of radiation on the human gastrointestinal tract. *J. Clin. Gastroenterol.* 1979; **1;** 9–39.
35. Berthrong M, Fajardo LF. Radiation injury in surgical pathology. Part II. Alimentary tract. *Am. J. Surg. Pathol.* 1981; **5;** 153–178.
36. Toh BH, van Driel IR, Gleeson PA. Pernicious anemia. *N. Engl. J. Med.* 1997; **337;** 1441–1448.
37. Waters HM, Dawson DW, Howarth JE, Geary CG. High incidence of type II autoantibodies in pernicious anaemia. *J. Clin. Pathol.* 1993; **46;** 45–47.
38. Krasinskas AM, Abraham SC, Metz DC, Furth EE. Oxyntic mucosa pseudopolyps: a presentation of atrophic autoimmune gastritis. *Am. J. Surg. Pathol.* 2003; **27;** 236–241.
39. Torbenson M, Abraham SC, Boitnott J, Yardley JH, Wu TT. Autoimmune gastritis: distinct histological and immunohistochemical findings before complete loss of oxyntic glands. *Mod. Pathol.* 2002; **15;** 102–109.

40. Annibale B, Azzoni C, Corleto VD *et al.* Atrophic body gastritis patients with enterochromaffin-like cell dysplasia are at increased risk for the development of type I gastric carcinoid. *Eur. J. Gastroenterol. Hepatol.* 2001; **13;** 1449–1456.
41. Lahner E, Caruana P, D'Ambra G *et al.* First endoscopic-histologic follow-up in patients with body-predominant atrophic gastritis: when should it be done? *Gastrointest. Endosc.* 2001; **53;** 443–448.
42. Rindi G, Bordi C, Rappel S *et al.* Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. *World J. Surg.* 1996; **20;** 168–172.
43. Lauwers GY. Epithelial neoplasms of the stomach. In Odze RD, Goldblum JR, Crawford JM eds. *Surgical pathology of the gastrointestinal tract: liver, biliary tract, and pancreas.* Philadelphia: Saunders 2004.
44. Weisdorf DJ, Snover DC, Haake R *et al.* Acute upper gastrointestinal graft-versus-host disease: clinical significance and response to immunosuppressive therapy. *Blood* 1990; **76;** 624–629.
45. Roy J, Snover D, Weisdorf S *et al.* Simultaneous upper and lower endoscopic biopsy in the diagnosis of intestinal graft-versus-host disease. *Transplantation* 1991; **51;** 642–646.
46. Cox GJ, Matsui SM, Lo RS *et al.* Etiology and outcome of diarrhea after marrow transplantation: a prospective study. *Gastroenterology* 1994; **107;** 1398–1407.
47. Washington K, Bentley RC, Green A *et al.* Gastric graft-versus-host disease: a blinded histologic study. *Am. J. Surg. Pathol.* 1997; **21;** 1037–1046.
48. Snover DC, Sibley RK, Freese DK *et al.* Orthotopic liver transplantation: a pathological study of 63 serial liver biopsies from 17 patients with special reference to the diagnostic features and natural history of rejection. *Hepatology* 1984; **4;** 1212–1222.
49. Snover DC, Weisdorf SA, Vercellotti GM *et al.* A histopathologic study of gastric and small intestinal graft-versus-host disease following allogeneic bone marrow transplantation. *Hum. Pathol.* 1985; **16;** 387–392.
50. Epstein RJ, McDonald GB, Sale GE, Shulman HM, Thomas ED. The diagnostic accuracy of the rectal biopsy in acute graft-versus-host disease: a prospective study of thirteen patients. *Gastroenterology* 1980; **78;** 764–771.
51. Lavilla P, Gil A, Rodriguez MC *et al.* X-linked agammaglobulinemia and gastric adenocarcinoma. *Cancer* 1993; **72;** 1528–1531.
52. Casis B, Fernandez-Vazquez I, Barnardos E *et al.* Autoimmune enteropathy in an adult with autoimmune multisystemic involvement. *Scand. J. Gastroenterol.* 2002; **37;** 1012–1016.
53. Mitomi H, Tanabe S, Igarashi M *et al.* Autoimmune enteropathy with severe atrophic gastritis and colitis in an adult: proposal of a generalized autoimmune disorder of the alimentary tract. *Scand. J. Gastroenterol.* 1998; **33;** 716–720.
54. Jevremovic D, Torbenson M, Murray JA, Burgart LJ, Abraham SC. Atrophic autoimmune pangastritis: a distinctive form of antral and fundic gastritis associated with systemic autoimmune disease. *Am. J. Surg. Pathol.* in press.
55. Washington K, Stenzel TT, Buckley RH, Gottfried MR. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. *Am. J. Surg. Pathol.* 1996; **20;** 1240–1252.
56. Wright CL, Riddell RH. Histology of the stomach and duodenum in Crohn's disease. *Am. J. Surg. Pathol.* 1998; **22;** 383–390.
57. Cary ER, Tremaine WJ, Banks PM, Nagorney DM. Isolated Crohn's disease of the stomach. *Mayo Clin. Proc.* 1989; **64;** 776–779.
58. Danzi JT, Farmer RG, Sullivan BH Jr, Rankin GB. Endoscopic features of gastroduodenal Crohn's disease. *Gastroenterology* 1976; **70;** 9–13.
59. Nugent FW, Richmond M, Park SK. Crohn's disease of the duodenum. *Gut* 1977; **18;** 115–120.
60. Priebe WM, Simon JB. Crohn's disease of the stomach with outlet obstruction: a case report and review of therapy. *J. Clin. Gastroenterol.* 1983; **5;** 441–445.
61. Oren R, Harats N, Polak A, Libson E, Naparstek Y. Granulomatous colitis 10 years after presentation with isolated Crohn's gastritis. *Am. J. Gastroenterol.* 1989; **84;** 449–450.
62. Oberhuber G, Puspok A, Oesterreicher C *et al.* Focally enhanced gastritis: a frequent type of gastritis in patients with Crohn's disease. *Gastroenterology* 1997; **112;** 698–706.
63. Xin W, Greenson JK. The clinical significance of focally enhanced gastritis. *Am. J. Surg. Pathol.* 2004; **28;** 1347–1351.
64. Sharif F, McDermott M, Dillon M *et al.* Focally enhanced gastritis in children with Crohn's disease and ulcerative colitis. *Am. J. Gastroenterol.* 2002; **97;** 1415–1420.
65. McHugh JB, Ruiz RE, Greenson JK. Significance of focally enhanced gastritis in the pediatric population. *Mod. Pathol.* 2006; **19;** 112A (abstract 514).
66. Torrente F, Anthony A, Heuschkel RB *et al.* Focal-enhanced gastritis in regressive autism with features distinct from Crohn's and *Helicobacter pylori* gastritis. *Am. J. Gastroenterol.* 2004; **99;** 598–605.
67. Shapiro JL, Goldblum JR, Petras RE. A clinicopathologic study of 42 patients with granulomatous gastritis. Is there really an 'idiopathic' granulomatous gastritis? *Am. J. Surg. Pathol.* 1996; **20;** 462–470.
68. Ectors NL, Dixon MF, Geboes KJ *et al.* Granulomatous gastritis: a morphological and diagnostic approach. *Histopathology* 1993; **23;** 55–61.
69. Genta RM. Granulomatous gastritis. In Graham DY ed. *Gastritis.* Philadelphia: Lippincott Williams & Wilkins 1999.
70. Maeng L, Lee A, Choi K, Kang CS, Kim KM. Granulomatous gastritis: a clinicopathologic analysis of 18 biopsy cases. *Am. J. Surg. Pathol.* 2004; **28;** 941–945.
71. Farman J, Ramirez G, Rybak B *et al.* Gastric sarcoidosis. *Abdom. Imaging* 1997; **22;** 248–252.
72. Fireman Z, Sternberg A, Yarchovsky Y *et al.* Multiple antral ulcers in gastric sarcoid. *J. Clin. Gastroenterol.* 1997; **24;** 97–99.
73. Fung WP, Foo KT, Lee YS. Gastric sarcoidosis presenting with haematemesis. *Med. J. Aust.* 1975; **2;** 47–49.
74. Ona FV. Gastric sarcoid: unusual cause of upper gastrointestinal hemorrhage. *Am. J. Gastroenterol.* 1981; **75;** 286–288.
75. Ferrucci JT Jr, Janower ML. Localized infiltrating lesions of the stomach. *Semin. Roentgenol.* 1971; **6;** 168–181.
76. Bellan L, Semelka R, Warren CP. Sarcoidosis as a cause of linitis plastica. *Can. Assoc. Radiol. J.* 1988; **39;** 72–74.
77. Dhillon AP, Sawyerr A. Granulomatous gastritis associated with *Campylobacter pylori*. *APMIS* 1989; **97;** 723–727.
78. Fahimi HD, Deren JJ, Gottlieb LS, Zamcheck N. Isolated granulomatous gastritis: its relationship to disseminated sarcoidosis and regional enteritis. *Gastroenterology* 1963; **45;** 161–175.
79. Brown KM, Kass M, Wilson RSr. Isolated granulomatous gastritis. Treatment with corticosteroids. *J. Clin. Gastroenterol.* 1987; **9;** 442–446.
80. Weinstock JV. Idiopathic isolated granulomatous gastritis: spontaneous resolution without surgical intervention. *Dig. Dis. Sci.* 1980; **25;** 233–235.
81. Berens DL, Montes M. Gastric sarcoidosis. *NY State J. Med.* 1975; **75;** 1290–1293.

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82. Croxon S, Chen K, Davidson AR. Sarcoidosis of the stomach. *Digestion* 1987; **38;** 193–196.
83. Khan MH, Lam R, Tamoney HJ. Isolated granulomatous gastritis. Report of a case simulating gastric carcinoma. *Am. J. Gastroenterol.* 1979; **71;** 90–94.
84. Palmer ED. Tuberculosis of the stomach and the stomach in tuberculosis; a review with particular reference to gross pathology and gastroscopic diagnosis. *Am. Rev. Tuberc.* 1950; **61;** 116–130.
85. Chazan BI, Aitchison JD. Gastric tuberculosis. *BMJ* 1960; **5208;** 1288–1290.
86. Bhansali SK. Abdominal tuberculosis. Experiences with 300 cases. *Am. J. Gastroenterol.* 1977; **67;** 324–337.
87. Besses C, Sans-Sabrafen J, Badia X *et al.* Ulceroinfiltrative syphilitic gastropathy: silver stain diagnosis from biopsy specimen. *Am. J. Gastroenterol.* 1987; **82;** 773–774.
88. Beckman JW, Schuman BM. Antral gastritis and ulceration in a patient with secondary syphilis. *Gastrointest. Endosc.* 1986; **32;** 355–356.
89. Anai H, Okada Y, Okubo K *et al.* Gastric syphilis simulating linitis plastica type of gastric cancer. *Gastrointest. Endosc.* 1990; **36;** 624–626.
90. Chalasani N, Wilcox CM, Hunter HT, Schwartz DA. Endoscopic features of gastroduodenal cryptococcosis in AIDS. *Gastrointest. Endosc.* 1997; **45;** 315–317.
91. Sugimachi K, Inokuchi K, Ooiwa T, Fujino T, Ishii Y. Acute gastric anisakiasis. Analysis of 178 cases. *JAMA* 1985; **253;** 1012–1013.
92. Kakizoe S, Kakizoe H, Kakizoe K *et al.* Endoscopic findings and clinical manifestation of gastric anisakiasis. *Am. J. Gastroenterol.* 1995; **90;** 761–763.
93. Muraoka A, Suehiro I, Fujii M *et al.* Acute gastric anisakiasis: 28 cases during the last 10 years. *Dig. Dis. Sci.* 1996; **41;** 2362–2365.
94. Gomez B, Tabar AI, Tunon T *et al.* Eosinophilic gastroenteritis and Anisakis. *Allergy* 1998; **53;** 1148–1154.
95. Uygur-Bayramicli O, Yavuzer D, Dolapcioglu C, Sensu S, Tuncer K. Granulomatous gastritis due to taeniasis. *J. Clin. Gastroenterol.* 1998; **27;** 351–352.
96. Bigotti G, Coli A, Magistrelli P *et al.* Gastric adenocarcinoma associated with granulomatous gastritis. Case report and review of the literature. *Tumori* 2002; **88;** 163–166.
97. Gumaste VV, Janowitz HD, Waye JD. Granulomatous gastritis: a case report and review of the literature. *Am. J. Gastroenterol.* 1989; **84;** 1315–1318.
98. Zhang L, Huang X, Li J. Xanthogranuloma of the stomach: a case report. *Eur J. Surg. Oncol.* 1992; **18;** 293–295.
99. Groisman GM, Rosh JR, Harpaz N. Langerhans cell histiocytosis of the stomach. A cause of granulomatous gastritis and gastric polyposis. *Arch. Pathol. Lab. Med.* 1994; **118;** 1232–1235.
100. Varma VA, Sessions JT, Kahn LB, Lipper S. Chronic granulomatous disease of childhood presenting as gastric outlet obstruction. *Am. J. Surg. Pathol.* 1982; **6;** 673–676.
101. Ectors N, Geboes K, Wynants P, Desmet V. Granulomatous gastritis and Whipple's disease. *Am. J. Gastroenterol.* 1992; **87;** 509–513.
102. Temmesfeld-Wollbrueck B, Heinrichs C, Szalay A, Seeger W. Granulomatous gastritis in Wegener's disease: differentiation from Crohn's disease supported by a positive test for antineutrophil antibodies. *Gut* 1997; **40;** 550–553.
103. O'Donovan C, Murray J, Staunton H, Doyle JS, Leader M. Granulomatous gastritis: part of a vasculitic syndrome. *Hum. Pathol.* 1991; **22;** 1057–1059.
104. Haot J, Hamichi L, Wallez L, Mainguet P. Lymphocytic gastritis: a newly described entity: a retrospective endoscopic and histological study. *Gut* 1988; **29;** 1258–1264.
105. Wu TT, Hamilton SR. Lymphocytic gastritis: association with etiology and topology. *Am. J. Surg. Pathol.* 1999; **23;** 153–158.
106. Haot J, Jouret-Maurin A, Delos M. Anatomo-clinical study of a series of chronic gastritis characterized by intraepithelial lymphocytic infiltration. *Acta Endoscopica* 1986; **16;** 69–74.
107. Haot J, Jouret A, Mainguet P. Lymphocytic gastritis. In Graham DY, Genta RM, Dixon MF eds. *Gastritis.* Philadelphia: Lippincott Williams & Wilkins 1999.
108. Haot J, Jouret A, Willette M, Gossuin A, Mainguet P. Lymphocytic gastritis—prospective study of its relationship with varioliform gastritis. *Gut* 1990; **31;** 282–285.
109. Wolfsen HC, Carpenter HA, Talley NJ. Menetrier's disease: a form of hypertrophic gastropathy or gastritis? *Gastroenterology* 1993; **104;** 1310–1319.
110. Oberhuber G, Bodingbauer M, Mosberger I, Stolte M, Vogelsang H. High proportion of granzyme B-positive (activated) intraepithelial and lamina propria lymphocytes in lymphocytic gastritis. *Am. J. Surg. Pathol.* 1998; **22;** 450–458.
111. Wolber R, De Owen DI, Buono L, Appelman H, Freeman H. Lymphocytic gastritis in patients with celiac sprue or spruelike intestinal disease. *Gastroenterology* 1990; **98;** 310–315.
112. Haot J, Bogomoletz WV, Jouret A, Mainguet P. Menetrier's disease with lymphocytic gastritis: an unusual association with possible pathogenic implications. *Hum. Pathol.* 1991; **22;** 379–386.
113. Wolber RA, Owen DA, Anderson FH, Freeman HJ. Lymphocytic gastritis and giant gastric folds associated with gastrointestinal protein loss. *Mod. Pathol.* 1991; **4;** 13–15.
114. Kajino Y, Kushima R, Koyama S, Fujiyama Y, Okabe H. Collagenous gastritis in a young Japanese woman. *Pathol. Int.* 2003; **53;** 174–178.
115. Vesoulis Z, Lozanski G, Ravichandran P, Esber E. Collagenous gastritis: a case report, morphologic evaluation, and review. *Mod. Pathol.* 2000; **13;** 591–596.
116. Cote JF, Hankard GF, Faure C *et al.* Collagenous gastritis revealed by severe anemia in a child. *Hum. Pathol.* 1998; **29;** 883–886.
117. Lagorce-Pages C, Fabiani B, Bouvier R *et al.* Collagenous gastritis: a report of six cases. *Am. J. Surg. Pathol.* 2001; **25;** 1174–1179.
118. Winslow JL, Trainer TD, Colletti RB. Collagenous gastritis: a long-term follow-up with the development of endocrine cell hyperplasia, intestinal metaplasia, and epithelial changes indeterminate for dysplasia. *Am. J. Clin. Pathol.* 2001; **116;** 753–758.
119. Groisman GM, Meyers S, Harpaz N. Collagenous gastritis associated with lymphocytic colitis. *J. Clin. Gastroenterol.* 1996; **22;** 134–137.
120. Stolte M, Ritter M, Borchard F, Koch-Scherrer G. Collagenous gastroduodenitis on collagenous colitis. *Endoscopy* 1990; **22;** 186–187.
121. Pulimood AB, Ramakrishna BS, Mathan MM. Collagenous gastritis and collagenous colitis: a report with sequential histological and ultrastructural findings. *Gut* 1999; **44;** 881–885.
122. Johnstone JM, Morson BC. Eosinophilic gastroenteritis. *Histopathology* 1978; **2;** 335–348.
123. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J. Allergy Clin. Immunol.* 2004; **113;** 11–28; quiz 29.
124. Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. *Am. J. Surg. Pathol.* 1986; **10;** 75–86.

125. Papadopoulos AA, Tzathas C, Polymeros D, Ladas SD. Symptomatic eosinophilic gastritis cured with *Helicobacter pylori* eradication. *Gut* 2005; **54;** 1822.
126. Seve P, Stankovic K, Michalet V *et al.* Carbimazole induced eosinophilic granulomatous vasculitis localized to the stomach. *J. Intern. Med.* 2005; **258;** 191–195.
127. Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut* 1990; **31;** 54–58.
128. Goldman H. Gastrointestinal mucosal biopsy. In Goldman H ed. *Inflammatory diseases of the stomach.* New York: Churchill Livingstone 1996.
129. Abraham SC, Solem CA, Hauser SC, Smyrk TC. Chronic antral ulcer associated with gastroduodenal lymphocytic phlebitis. *Am. J. Surg. Pathol.* 2004; **28;** 1659–1663.
130. Pique JM. Portal hypertensive gastropathy. *Baillieres Clin. Gastroenterol.* 1997; **11;** 257–270.
131. Zoli M, Merkel C, Magalotti D *et al.* Evaluation of a new endoscopic index to predict first bleeding from the upper gastrointestinal tract in patients with cirrhosis. *Hepatology* 1996; **24;** 1047–1052.
132. Primignani M, Carpinelli L, Preatoni P *et al.* Natural history of portal hypertensive gastropathy in patients with liver cirrhosis. The New Italian Endoscopic Club for the study and treatment of esophageal varices (NIEC). *Gastroenterology* 2000; **119;** 181–187.
133. Sarin SK, Sreenivas DV, Lahoti D, Saraya A. Factors influencing development of portal hypertensive gastropathy in patients with portal hypertension. *Gastroenterology* 1992; **102;** 994–999.
134. Payen JL, Cales P, Pienkowski P *et al.* Weakness of mucosal barrier in portal hypertensive gastropathy of alcoholic cirrhosis. Effects of propranolol and enprostil. *J. Hepatol.* 1995; **23;** 689–696.
135. Beck PL, Lee SS, McKnight GW, Wallace JL. Characterization of spontaneous and ethanol-induced gastric damage in cirrhotic rats. *Gastroenterology* 1992; **103;** 1048–1055.
136. Beck PL, McKnight GW, Kelly JK, Wallace JL, Lee SS. Hepatic and gastric cytoprotective effects of long-term prostaglandin E1 administration in cirrhotic rats. *Gastroenterology* 1993; **105;** 1483–1489.
137. El-Newihi HM, Kanji VK, Mihas AA. Activity of gastric mucosal nitric oxide synthase in portal hypertensive gastropathy. *Am. J. Gastroenterol.* 1996; **91;** 535–538.
138. Ohta M, Tarnawski AS, Itani R. *et al.* Tumor necrosis factor alpha regulates nitric oxide synthase expression in portal hypertensive gastric mucosa of rats. *Hepatology* 1998; **27;** 906–913.
139. Beck PL, McKnight W, Lee SS, Wallace JL. Prostaglandin modulation of the gastric vasculature and mucosal integrity in cirrhotic rats. *Am. J. Physiol.* 1993; **265;** G453–458.
140. Carpinelli L, Primignani M, Preatoni P *et al.* Portal hypertensive gastropathy: reproducibility of a classification, prevalence of elementary lesions, sensitivity and specificity in the diagnosis of cirrhosis of the liver. A NIEC multicentre study. New Italian Endoscopic Club. *Ital. J. Gastroenterol. Hepatol.* 1997; **29;** 533–540.
141. Viggiano TR, Gostout CJ. Portal hypertensive intestinal vasculopathy: a review of the clinical, endoscopic, and histopathologic features. *Am. J. Gastroenterol.* 1992; **87;** 944–954.
142. Misra SP, Dwivedi M, Misra V *et al.* Endoscopic and histologic appearance of the gastric mucosa in patients with portal hypertension. *Gastrointest. Endosc.* 1990; **36;** 575–579.
143. Rider JA, Klotz AP, Kirsner JB. Gastritis with veno-capillary ectasia as a source of massive gastric hemorrhage. *Gastroenterology* 1953; **24;** 118–123.
144. Lee FI, Costello F, Flanagan N, Vasudev KS. Diffuse antral vascular ectasia. *Gastrointest. Endosc.* 1984; **30;** 87–90.
145. Jabbari M, Cherry R., Lough JO *et al.* Gastric antral vascular ectasia: the watermelon stomach. *Gastroenterology* 1984; **87;** 1165–1170.
146. Gostout CJ, Viggiano TR, Ahlquist DA *et al.* The clinical and endoscopic spectrum of the watermelon stomach. *J. Clin. Gastroenterol.* 1992; **15;** 256–263.
147. Liberski SM, McGarrity TJ, Hartle RJ, Varano V, Reynolds D. The watermelon stomach: long-term outcome in patients treated with Nd:YAG laser therapy. *Gastrointest. Endosc.* 1994; **40;** 584–587.
148. Murphy FT, Enzenauer RJ, Cheney CP. Watermelon stomach. *Arthritis Rheum.* 1999; **42;** 573.
149. Schoonbroodt D, Horsmans Y, Hoang P *et al.* Vascular gastric anomalies, CREST syndrome and primary biliary cirrhosis: efficacy of ethinyl estradiol-norethisterone combination. *Gastroenterol. Clin. Biol.* 1994; **18;** 649–651.
150. Tobin RW, Hackman RC, Kimmey MB *et al.* Bleeding from gastric antral vascular ectasia in marrow transplant patients. *Gastrointest. Endosc.* 1996; **44;** 223–229.
151. Herman BE, Vargo JJ, Baum S, Silverman ED, Eisold J. Gastric antral vascular ectasia: a case report and review of the literature. *J. Nucl. Med.* 1996; **37;** 854–856.
152. Payen JL, Cales P. [Gastric modifications in cirrhosis]. *Gastroenterol. Clin. Biol.* 1991; **15;** 285–295.
153. Payen JL, Cales P, Voigt JJ *et al.* Severe portal hypertensive gastropathy and antral vascular ectasia are distinct entities in patients with cirrhosis. *Gastroenterology* 1995; **108;** 138–144.
154. Stotzer PO, Willen R, Kilander AF. Watermelon stomach: not only an antral disease. *Gastrointest. Endosc.* 2002; **55;** 897–900.
155. Rawlinson WD, Barr GD, Lin BP. Antral vascular ectasia—the 'watermelon' stomach. *Med. J. Aust.* 1986; **144;** 709–711.
156. Lowes JR, Rode J. Neuroendocrine cell proliferations in gastric antral vascular ectasia. *Gastroenterology* 1989; **97;** 207–212.
157. Suit PF, Petras RE, Bauer TW, Petrini JL Jr. Gastric antral vascular ectasia. A histologic and morphometric study of 'the watermelon stomach'. *Am. J. Surg. Pathol.* 1987; **11;** 750–757.
158. Spahr L, Villeneuve JP, Dufresne MP *et al.* Gastric antral vascular ectasia in cirrhotic patients: absence of relation with portal hypertension. *Gut* 1999; **44;** 739–742.
159. Cales P, Voigt JJ, Payen JL *et al.* Diffuse vascular ectasia of the antrum, duodenum, and jejunum in a patient with nodular regenerative hyperplasia. Lack of response to portosystemic shunt or gastrectomy. *Gut* 1993; **34;** 558–561.
160. Kamath PS, Lacerda M, Ahlquist DA *et al.* Gastric mucosal responses to intrahepatic portosystemic shunting in patients with cirrhosis. *Gastroenterology* 2000; **118;** 905–911.
161. Bourke MJ, Hope RL, Boyd P *et al.* Endoscopic laser therapy for watermelon stomach. *J. Gastroenterol. Hepatol.* 1996; **11;** 832–834.
162. Yusoff I, Brennan F, Ormonde D, Laurence B. Argon plasma coagulation for treatment of watermelon stomach. *Endoscopy* 2002; **34;** 407–410.

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