Autoimmune Gastritis

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• ***Context.***—**Autoimmune gastritis (AG) is a corpus-restricted chronic atrophic gastritis associated with intrinsic factor deficiency, either with or without pernicious anemia. Autoimmune gastritis is a microscopic disease because patients present with no or vague symptoms, and clinicians rarely find endoscopic changes. Autoimmune gastritis only becomes a clinical disease when pathologists diagnose it in gastric biopsies performed for a variety of clinical indications. Unfamiliarity with this disease can result in misdiagnosis of patients, and thus inadequate patient management.**

Objective.—**To review the pathogenesis, clinical features, diagnostic criteria, differential diagnoses, sequelae, and surveillance recommendations for AG.**

Data Sources.—**The sources of the study include a review of the pertinent literature for AG.**

Conclusions.—**Autoimmune gastritis is an important disease characterized by a loss of oxyntic mucosa and presence of metaplastic epithelium and enterochromaffin-like cell hyperplasia. Awareness and proper diagnosis are critical to prevent mismanagement of patients.**

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PATHOGENESIS

Autoimmune gastritis (AG) is an immune-mediated disease, restricted to oxyntic (acid-producing) mucosa in the corpus (anatomic body and fundus) of the stomach.[1] Normally, the parietal cells in the oxyntic mucosa produce hydrochloric acid and intrinsic factor. The acidification of the stomach is managed by hydrochloric acid production by the H^+K^+ ATPase on the parietal cells in the oxyntic mucosa and gastrin by the G cells, or gastrin cells, in the antrum. Gastrin production by the G cells is regulated by acid in the antrum. Hence, low antral acid stimulates gastrin production, whereas high antral acid decreases G-cell production of gastrin. Enterochromaffin-like (ECL) cells are also found in the oxyntic mucosa and assist in the production of gastric acid through the production of histamine. Intrinsic factor is required for the absorption of vitamin B_{12} in the ileum. Chief cells are also found in oxyntic mucosa and produce pepsinogen and gastric lipase.

Autoimmune gastritis is a chronic gastritis where $CD4^+$ T cells target parietal cells; this leads to both parietal cell and chief cell loss with eventual atrophy of the mucosa. The loss of parietal cells creates a state of constant achlorhydria, prompting antral G cells to continuously produce gastrin.[1] Without parietal cells for the feedback loop, the result is a state of hypergastrinemia. Complete loss of parietal cells leads to a lack of intrinsic factor production that, if severe enough, may result in pernicious anemia. The hypergastrinemia leads to ECL cell hyperplasia. Gastric acid is also required for the absorption of inorganic iron, so patients with AG can also present with iron deficiency.[2]

Parietal cells, specifically their H^+K^+ ATPase, are the primary target by T cells in AG. The most sensitive marker, anti–parietal cell antibodies, are seen in 90% of patients with AG. A total of 50% to 70% of patients with AG also have antibodies to intrinsic factor and H^+K^+ATPase.[3] Intrinsic factor antibodies, in the correct clinical context, are considered diagnostic of pernicious anemia. The level of anti-intrinsic factor antibody does not correlate with severity of the disease, but presence of the antibody can be detected years before symptoms. Anti–H^+K^+ ATPase antibodies are not specific: the proton pump is the single major autoantigen in long-standing *Helicobacter pylori* gastritis.[4] In addition, serum levels of gastrin and pepsinogen are not specific for AG but can help predict the severity of the disease.

Although not entirely understood, there is a strong association between AG and *H pylori* gastritis. Both AG and *H pylori* gastritis can present with autoantibodies to peptides on the gastric H^+K^+ ATPase.[5] New evidence theorizes that some cases of AG may develop as a sequelae of chronic *H pylori* infection.[6] Both pathologically and clinically, chronic *H pylori* gastritis with autoantibodies and oxyntic mucosal atrophy resembles AG. A total of 83% of patients with AG have been shown to have antibodies to *H pylori*, indicating prior or current infection, although most biopsies do not demonstrate colonization of the bacteria.[4] This lack of bacteria is theorized to be due to the development of gastric atrophy over time clearing the bacterial colonization.[4] Also, it has been shown that histologically proven early stages of AG can be successfully treated with *H pylori* eradication therapy.[4] But considering how common *H pylori* infection is, it is worthwhile to note that hardly any cases of chronic *H pylori* gastritis develop into AG. Nevertheless, the similarities between *H pylori*–

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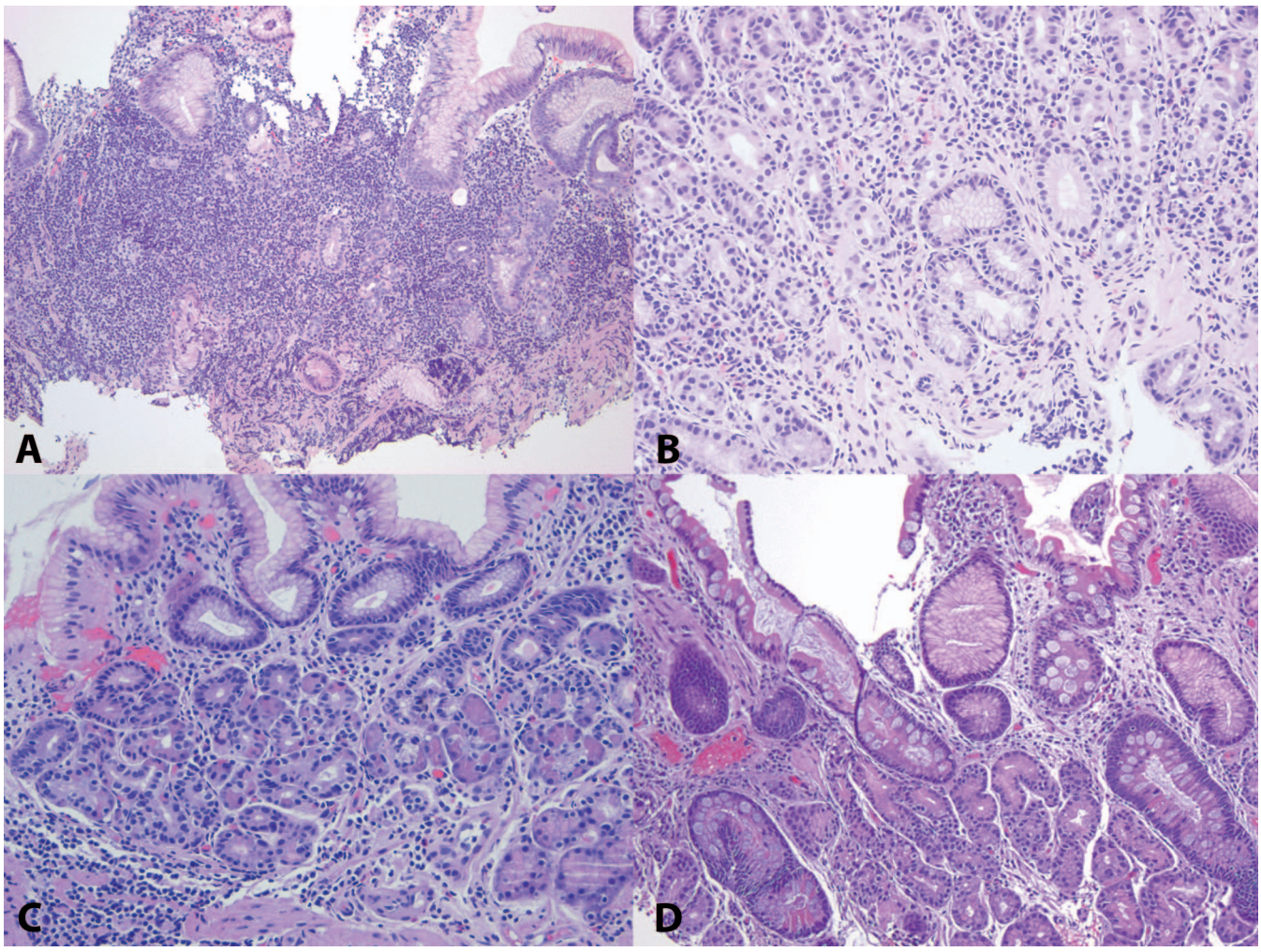

Figure 1. *Histologic findings of oxyntic mucosa in autoimmune gastritis. A, Lymphoplasmacytic inflammation more prominent at the base of the mucosa. B, Mucous metaplasia. C, Pancreatic acinar metaplasia. D, Intestinal metaplasia (hematoxylin-eosin, original magnifications ×100 [A and D] and ×200 [B and C]).*

infected patients who develop mucosal atrophy and patients with AG suggest a similar pathogenesis or that some AG patients may develop from a subgroup of the *H pylori* gastritides.

CLINICAL FEATURES

Historically, patients with AG presented with neurologic symptoms due to vitamin B_{12} deficiency and received a diagnosis of pernicious anemia. These cases could present with mild symptoms, such as pallor, weakness, and fatigue, or more severe cases, such as peripheral neuropathy or subacute combined degeneration.[3] In the present day, however, this presentation is very rare, and only patients with long-standing AG develop anemia, either from iron deficiency or vitamin B_{12} deficiency. More commonly, AG has no specific signs or symptoms, and it is diagnosed incidentally. The indication for endoscopy can be due to a variety of patient symptoms. In our institution, we find that patients with AG usually present with symptoms, such as dyspepsia, and have normal or minimal endoscopic findings of gastric erythema.

Autoimmune gastritis is more common in white individuals, especially those of Scandinavian descent.[3] The overall prevalence is 2%, with a predominance in the elderly female population.[1,7] Autoimmune gastritis occurs more commonly in patients with other autoimmune disorders, such as thyroiditis, type 1 diabetes, vitiligo, and Addison disease, and these patients usually represent the younger population.[7] Patients younger than 30 years with an isolated AG diagnosis are rare.

DIAGNOSIS

The diagnosis of AG is made histologically through endoscopic biopsy. Serologic testing for autoantibodies may or may not be used clinically as an adjunct for diagnosis.

In biopsies that include both antral and corpus mucosae, histologic diagnosis of AG will have 2 types of mucosa: normal antral mucosa and an inflamed, abnormal corpus mucosa. Histologic findings differ depending on whether the patient is in the early phase, florid phase, or end phase when they undergo biopsy.[1,8] The early phase is characterized by diffuse, basal-predominant inflammation within the lamina propria (Figure 1, A) of the oxyntic mucosa. The lymphocytes, which are predominantly $CD4^+$ T cells, are mixed with plasma cells, eosinophils, and mast cells. Patchy foci of lymphocytes infiltrating glands and secondary

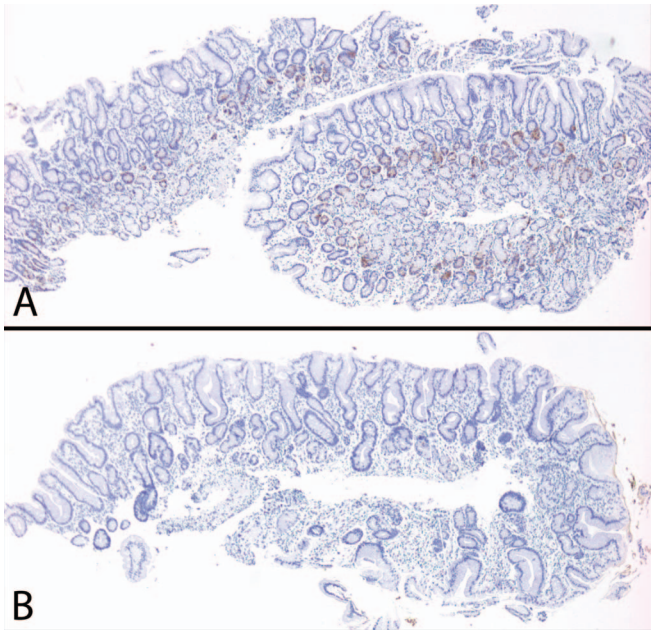

Figure 2. *A, Gastrin immunohistochemical stain highlighting G cells in normal antral mucosa. B, Negative gastrin staining on inflamed mucosa, indicating this is corpus mucosa (original magnification ×100).*

apoptotic bodies can be seen (Figure 1, B). A variety of epithelial metaplasia can also be seen in the early phase. This includes mucous metaplasia (also called pseudopyloric metaplasia), pancreatic acinar metaplasia (Figure 1, C), and proliferation of immature neck cells. The amount of atrophy can be variable, but residual parietal cells in the early stage can become hypertrophic because of the excess gastrin and form small polypoid nodules, called oxyntic gland pseudopolyps, which contain all the cells of this mucosa, including chief cells.[8]

The florid phase has marked atrophy of the oxyntic mucosa with diffuse lymphoplasmacytic inflammation. The basal-predominant location of the inflammation can be less intense in this stage. The metaplasia noted in the early phase persists, but intestinal metaplasia is also usually prominent (Figure 1, D). The ECL cells start to proliferate. The antral mucosa, if biopsied, will exhibit gastrin cell hyperplasia. Finally, the end stage is similar to the florid stage, with nearly complete oxyntic gland loss, marked epithelial metaplasia, and ECL-cell hyperplasia, but reduced inflammation.

The ECL-cell hyperplasia indicates a state of hypergastrinemia and increases parallel to the degree of atrophy. It only occurs with diffuse, profound body glandular atrophy, and therefore may or may not be present on an initial biopsy or early stage of the disease. The hyperplasia can be simple, linear, and nodular in pattern. The ECL cells are small, with clear cytoplasm, round nuclei, and finely dispersed chromatin.[8] Their presence is a diagnostic feature of AG. In addition, ECL-cell hyperplasia is a precursor of type 1 carcinoid tumor.

The most common lesions encountered endoscopically in AG are hyperplastic polyps, found in 10% to 40% of patients.[3] Most of the polyps are sessile, less than 2 cm in diameter, and are often multiple.[8] The polyps can be so numerous that they mimic a polyposis, and the diagnosis of AG can be missed if endoscopists do not biopsy the adjacent mucosa. Oxyntic gland pseudopolyps, mentioned earlier, can also be found endoscopically in the early stages of AG.

Identification of the location of the gastric biopsy can be difficult in AG if the endoscopist does not place the specimens in separately labeled jars for antrum and body/fundus. A complete loss of oxyntic mucosa in the corpus in a patient with AG can vaguely resemble antral mucosa because of the loss of oxyntic glands replaced by metaplastic mucous glands. In cases where both antral and oxyntic mucosa are put into the same specimen jar, a gastrin stain can be used to identify gastric location. G cells are only present in antral mucosa. A gastrin immunohistochemical stain highlights G cells in the antral mucosa (Figure 2, A) and is negative in the oxyntic mucosa (Figure 2, B).

DIFFERENTIAL DIAGNOSIS

Multifocal Atrophic Gastritis

Multifocal atrophic gastritis is a chronic gastritis with glandular atrophy similar to AG. Multifocal atrophic gastritis in our part of the world is limited to the antrum; however, in parts of the world where gastric carcinoma is endemic, it is usually a pangastritis. This is considered the precursor of gastric adenocarcinoma worldwide. The causative agent for this type of atrophic gastritis is *H pylori* in 75% of cases.[8] Multifocal atrophic gastritis has atrophy, mucous gland metaplasia, and intestinal metaplasia similar to AG, but ECL-cell hyperplasia is not present. Furthermore, serum autoantibodies are also absent in multifocal atrophic gastritis. The distinction between these entities is very important because of the risk of developing gastric adenocarcinoma in multifocal atrophic gastritis.

Helicobacter pylori Gastritis

Helicobacter pylori gastritis is a chronic gastritis caused by infection with a Gram-negative curved rod. *Helicobacter pylori* gastritis is much more common than AG, with a worldwide prevalence of 50%.[8] Although it is theorized that these 2 entities may be linked, they are still distinct entities that should be classified separately. Autoimmune gastritis is restricted to the oxyntic mucosa of the stomach, sparing the antrum. *Helicobacter pylori* gastritis is most intense in the antrum but may involve other areas of the stomach. Autoimmune gastritis has a basal-predominate chronic inflammatory infiltrate, whereas *H pylori* gastritis has a diffuse, superficial band of plasma cells in the lamina propria and neutrophils in the necks, marking active infection. Enterochromaffin-like–cell hyperplasia, seen in AG, is not a part of *H pylori* gastritis. Oxyntic gland destruction can be found in any chronic gastritis, but if present, it is focal in *H pylori* gastritis.

SEQUELAE OF AG

Vitamin B_{12} deficiency, and consequently pernicious anemia, is the most well-known sequelae of AG. Although uncommon in developed countries, some epidemiologic studies indicate that AG and pernicious anemia may be underdiagnosed in all parts of the world.[7] Not all patients with AG develop pernicious anemia, although every patient with pernicious anemia has AG.

Enterochromaffin-like–cell hyperplasia is a part of the hyperplasia-dysplasia-neoplasia sequence that leads to gastric carcinoid tumors. The hyperplasia aspect of this sequence has simple, linear, and nodular forms in AG.

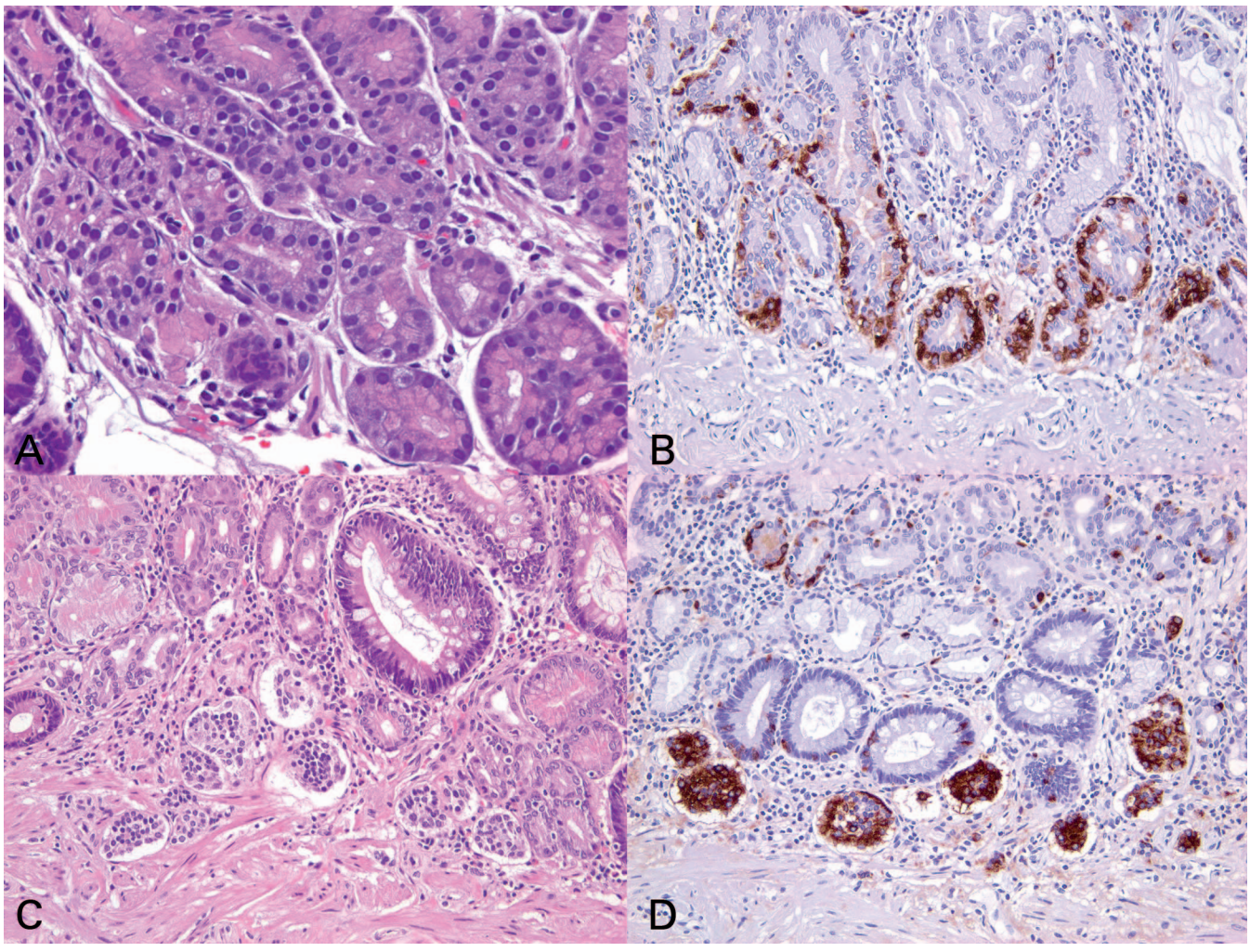

Figure 3. *A, Linear hyperplasia of the enterochromaffin-like (ECL) cells; note the clear cytoplasm, rimming the glands. B, Chromogranin immunohistochemical stain highlighting the ECL cells. C, Small clusters of ECL cells indicate nodular hyperplasia. D, Chromogranin immunohistochemical stain highlighting these nodules (hematoxylin-eosin, original magnifications ×400 [A] and ×200 [C]; original magnification ×200 [B and D]).*

Simple hyperplasia is defined as hypertrophied ECL cells occurring singly or in clusters of fewer than 5 cells, arranged in the lower third of the gastric pits. Linear hyperplasia consists of 5 or more ECL cells lining the base of the pits or in the glandular neck region (Figure 3, A and B).[7] Nodular hyperplasia is when 5 or more ECL cells form nodules, bounded by a basement membrane (Figure 3, C and D). Identification of ECL-cell hyperplasia can be identified on routine staining, but immunohistochemical stains for chromogranin or synaptophysin can be helpful in difficult cases. Dysplasia occurs when the cells enlarge, fuse into micronodules, or demonstrate microinvasion or newly formed stroma.[9] A carcinoid tumor is diagnosed when the ECL cells form nodules greater than 0.5 cm (Figure 4).[9] Type 1 carcinoid tumors are the type that arise in AG. These tumors are multifocal, small, indolent nodules, usually less than 1 cm, that have a low potential for metastasis.[10] Treatment is conservative and generally involves endoscopic removal.

Intestinal metaplasia, commonly found in AG, is a known precursor of gastric adenocarcinoma, particularly the intestinal type.[9] There are numerous studies documenting the link between intestinal metaplasia in the stomach and the subsequent development of gastric carcinoma, but these studies do not include patients with biopsy-proven AG. Murphy et al[11] demonstrated that elderly individuals with pernicious anemia were at an increased risk of developing noncardia gastric adenocarcinoma, with an odds ratio of 2.18. The study chose participants with pernicious anemia based on medical claim review, not biopsy-proven diagnosis of AG. This method of selecting patients is problematic because there could be many reasons for low vitamin B_{12} levels that have no correlation with AG. To our knowledge there are no formal studies analyzing the rate of gastric carcinoma in patients with biopsy-proven AG.

SURVEILLANCE

Prior to 2019, there were no formal recommendations for the endoscopic surveillance of patients with AG. In 2019, the management of epithelial precancerous conditions and lesions in the stomach (MAPS II) guidelines updated its

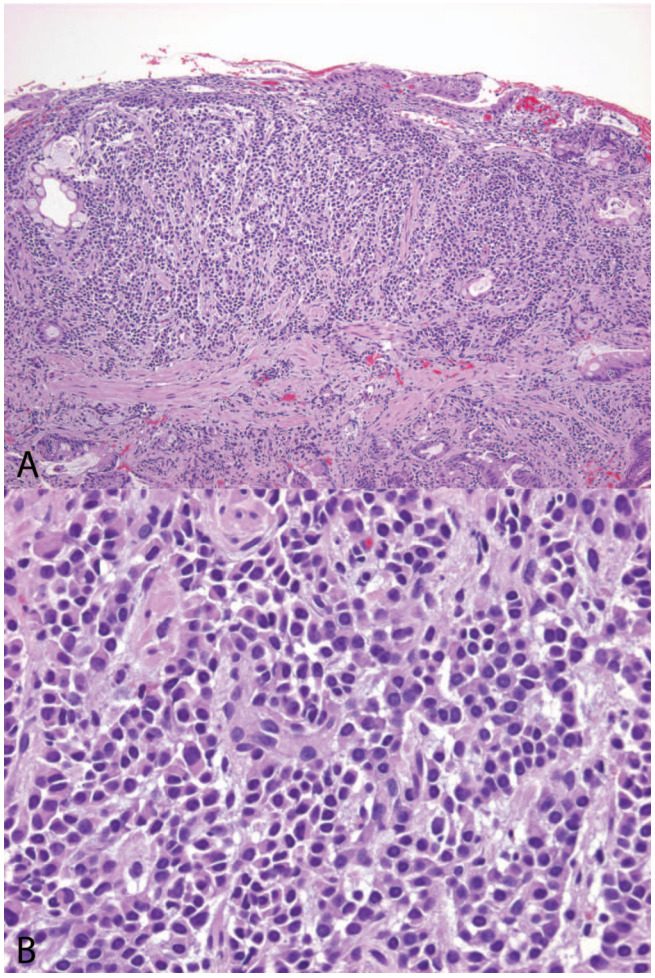

Figure 4. *A, Carcinoid tumor arising in autoimmune gastritis. Note the background intestinal metaplasia. B, Anastomosing cords and nests of plasmacytoid endocrine cells (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]).*

recommendations on diagnosis and management of patients with intestinal metaplasia and atrophic gastritis, and included AG in a systematic literature review. The guidelines' recommendation is endoscopic follow-up every 3 to 5 years to assess for epithelial dysplasia, carcinoid tumors, and gastric adenocarcinoma in patients with AG.[12] This is similar to surveillance recommendations for patients with non-autoimmune atrophic gastritis and intestinal metaplasia. According to the MAPS II guidelines, there is insufficient evidence in the current literature to assess the risk of carcinoma as a result of AG. Of note, the 2019 guidelines also recommend *H pylori* eradication therapy in all patients with nonatrophic chronic gastritis and AG.[12]

In conclusion, AG is an important disease that is diagnosed by histology. Loss of oxyntic mucosa; metaplastic epithelium, such as mucous cell or intestinal metaplasia; and ECL cell hyperplasia are the main diagnostic findings. Sequelae include indolent gastric carcinoids and a small risk of gastric adenocarcinoma.

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