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.


**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. 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 B12 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. 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.

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. 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. 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. New evidence theorizes that some cases of AG may develop as a sequelae of chronic *H pylori* infection. 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. This lack of bacteria is theorized to be due to the development of gastric atrophy over time clearing the bacterial colonization. Also, it has been shown that histologically proven early stages of AG can be successfully treated with *H pylori* eradication therapy. 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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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 B₁₂ 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 B₁₂ 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.²,⁷ 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 mucosa, 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
apolectic 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 polyloid 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.
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). 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. A carcinoid tumor is diagnosed when the ECL cells form nodules greater than 0.5 cm (Figure 4). 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. 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. 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 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 B12 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
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. 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.

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.

References