CLINICAL VIGNETTE

Autoimmune Gastritis

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Case Presentation

A 36-year old woman with recent diagnosis of systemic lupus erythematosis presented with several months of burning epigastric abdominal pain. Recently, the pain was waking her up at night. She also reported fatigue and weakness. On exam she had normal vital signs and BMI of 223kg/m^2. Her abdomen was not distended with normal bowel sounds. It was soft but diffusely tender to palpation, without guarding hepatosplenomegaly. There was no skin rash, normal gait and normal sensory exam. Labs included normal thyroid function tests and negative celiac panel. B12 was 265 pg/mL at the lower end of normal. EGD showed a normal esophagus, however, the body and the antrum of the stomach appeared erythematous (Figures 1 and 2). A nodule was biopsied in the antrum. The proximal duodenum appeared normal. Random biopsies obtained in the gastric antrum and body showed complete loss of oxyntic glands in the body of the stomach. Minimal inflammation was seen in the antrum, while severe atrophy was seen in the body of the stomach. The nodule biopsy also showed chronic gastritis. This pattern was highly suggestive of autoimmune gastritis. A gastrin level, off proton pump inhibitors, was elevated at 321 pg/mL. Intrinsic factor antibody was negative. The parietal cell antibody titer was 1:320 (positive test is over 1:20). The constellation of the patient's autoantibodies to parietal cells, low B12, elevated gastrin and gastric biopsies all suggested diagnosis of autoimmune gastritis.

Discussion

Autoimmune gastritis is a chronic progressive inflammatory condition, which is mostly asymptomatic until it progresses to chronic atrophic gastritis.[1] Autoimmune atrophic gastritis results from parietal cell destruction, mediated by autoantibody binding to the H+K+- ATPase on the cell surface.[2] Destroyed parietal cells are replaced with atrophic and metaplastic mucosa. The destruction of parietal cells induces hypochlorhydria, and eventual achlorhydria. Autoantibodies against intrinsic factor result in impaired cobalamin (B12) absorption.

Historically, atrophic gastritis was defined as two subtypes: Type A and Type B. Type A referred to atrophy of the gastric body, with preservation of the antrum, in the presence of anti-parietal cell antibodies. Type A is now known as autoimmune atrophic gastritis. Type B includes antrum-predominant gastritis without the anti-parietal cell antibodies, and is now known to be associated with Helicobacter pylori gastritis.[2] According to the most recent classification of atrophic gastritis, The Updated Sydney System Classification, the categories are multifocal and corpus-predominant. Multifocal atrophic gastritis is associated with H. pylori as well as other environmental factors. It is now termed environmental metaplastic atrophic gastritis. Corpus-predominant atrophic gastritis is now coined autoimmune metaplastic atrophic gastritis (AMAG). Metaplasia is now included in both terms as it is the key histological change found in atrophic gastritis.[3]

The prevalence of AMAG reported to be 0.1% in the general population, and close to 2% in the over 60 year old population.[3] The diagnosis may be missed if pathology results show diagnosis of "chronic gastritis," but the cause is not investigated further. AMAG is reported in similar prevalence among all ethnicities, but seen more commonly in women than in men (3:1). Studies have shown pernicious anemia to be underdiagnosed. Diagnosis is likely delayed because pernicious anemia symptoms are non-specific, while AMAG can remain asymptomatic in its earlier stages.[3]

Serological markers are very useful in making the diagnosis of AMAG. Anti-intrinsic factor (Anti-IF) antibodies are more specific, but less sensitive than anti-parietal cell antibodies. Anti- IF antibodies have a 27% sensitivity and 90% specificity. On the other hand, anti-parietal cell antibodies are 81% sensitive and 90% specific in biopsy proven AMAG.[1,2] However, anti-parietal cell antibodies can be found in other autoimmune disorders, such as Hashimoto's thyroiditis, without AMAG. Anti-IF antibodies play a clear role in pernicious anemia, but do not contribute to the pathophysiology of gastritis.[4]

Endoscopic appearance of early AMAG is generally normal. With progression of the disease, mucosa appears atrophic, pale with readily visible sub-epithelial vessels, predominantly in the body and fundus, as well as pseudopolyps, islands of normal oxyntic mucosa. The antrum typically appears uninvolved.[2]

Parietal cell loss, seen with AMAG, results in decrease in production of acid and intrinsic factor, which is required for absorption of cobalamin (B12) in the terminal ileum. Pernicious anemia (or megaloblastic anemia) due to B12 deficiency, results after progression of gastritis, to gastric fibrosis and finally to gastric atrophy.[2] Iron deficiency has also been reported; often preceding pernicious anemia. The pathophysiology of iron deficiency in AMAG is due to decreased

bioavailable iron in the setting of achlorhydria. Gastric acid is required to maintain iron in its ferrous state, which is more readily absorbable.[1,2]

Clinically, AMAG is often silent. If present, gastrointestinal symptoms can include heartburn, regurgitation and dyspepsia. Some patients have reported post-prandial fullness and early satiety.[5] Neurological symptoms can be present in those with B12 deficiency, which results in neuropathy. Demyelination occurs at the central nervous system level, resulting in sensory ataxia, visual disturbances and altered reflexes.[5]

There may be an association between *Helicobacter pylori* (*H. pylori*) infection and autoimmune gastritis. The group with evidence of both autoimmune gastritis and H. pylori infection, suggests that H. pylori infection may lead to development of autoimmune gastritis. H. pylori infection can cause influx of B cells and T cells into the epithelium of the body of the stomach, as well as severe inflammatory and atrophic changes seen in the oxyntic mucosa. Decreased gastric acid secretion, with increased gastrin levels are also found with H. pylori. Eradication of H. pylori infection can reverse early signs of autoimmune gastritis.[6] The relationship with H. pylori infection continues to be an area of research.

Autoimmune gastritis, like other immune mediated disorders, has been associated with other autoimmune disorders. Most commonly, it has been associated with autoimmune thyroid disease. Other autoimmune disease include type 1 diabetes, vitiligo and Addison disease. Several susceptibility genes Gasa 1, 2, 3, and 4 have been discovered in mouse models. Three of the genes are located on the same locus as susceptibility genes for diabetes in non-obese mice. This genetic association may contribute to the 3-5 fold increased risk of autoimmune gastritis in patients with type 1 diabetes mellitus.[7]

Reduced parietal cell mass due to autoantibody mediated destruction results in decreased acid production. Subsequent hypochlorhydria, and eventual achlorhydria cause sustained hypergastrinemia. Persistently elevated gastrin levels continuously stimulate endocrine-like cells to proliferate. This proliferation results in changes ranging from initial hyperplasia to eventual neuroendocrine tumor formation. The neuroendocrine tumors associated with autoimmune atrophic gastritis are typically small (less than 1-cm) and numerous. This type of neuroendocrine tumors have very rare malignant potential.[6]

Risk of gastric adenocarcinomas is increased to 1.4% in patients with autoimmune gastritis. The Surveillance, Epidemiology, and End Results (SEER) program reports annual incidence of gastric cancer in the US of 0.073 cases per 1000 person-years. Adenocarcinoma has been reported in patients typically with end stage autoimmune gastritis with manifested pernicious anemia.[8]

Conclusion

Autoimmune gastritis is a chronic progressive inflammatory condition, which is mostly silent in its early stages. The pathophysiology is atrophy and destruction of a result of parietal cells mediated by autoantibodies, with atrophy and achlorhydria. Symptoms can be silent, but upper gastrointestinal symptoms have been reported. End stage gastritis results in B12 deficiency due to autoantibodies against intrinsic factor, which results in neurological symptoms. Iron deficiency can be seen even prior to B12 deficiency, due to decreased bioavailability of iron in the setting of achlorhydria. Autoimmune gastritis can be seen associated with *H. pylori* infection, as well as multiple autoimmune disorders. Due to achlorhydria there is state of hypergastinemia, which results in hyperplasia, metaplasia, and eventual carcinoid formation. There is also an increased risk of gastric adenocarcinoma. Diagnosis of autoimmune gastritis can be missed without endoscopic evaluation and proper biopsies. Due to the risk of adenocarcinoma, surveillance is suggested, however, there are no current guidelines on timing.

Figures

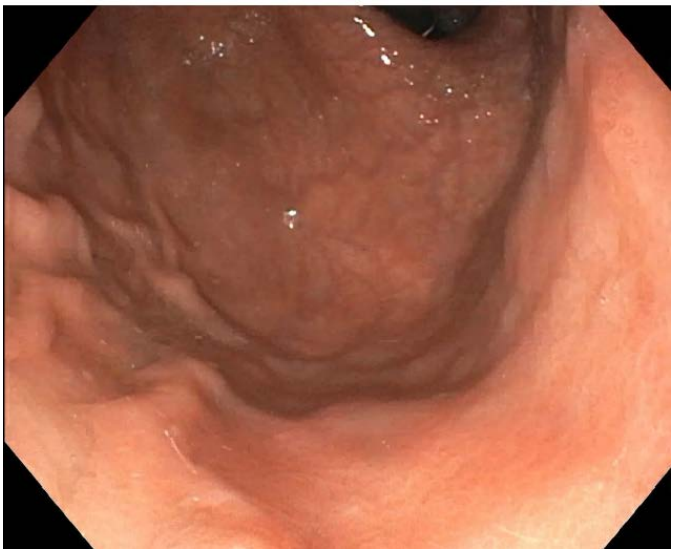

Figure 1. Gastric fundus and body.

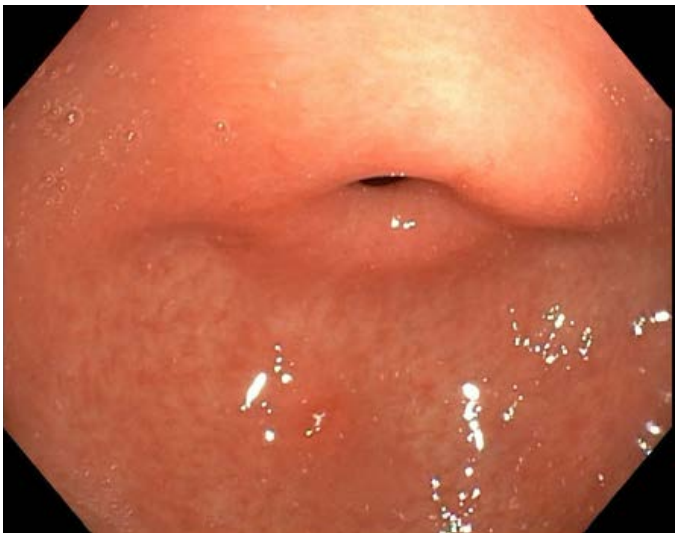

Figure 2. Gastric antrum.

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