

## CLINICAL VIGNETTE

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# Atrophic Gastritis: An Underappreciated Cause of Iron Deficiency Anemia

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### Case

A 44-year-old female with a past medical history of congenital absence of a right kidney, obesity and lactose intolerance presented for an endoscopic evaluation due to a history of both iron and vitamin B12 deficiencies. Initially her primary care physician attributed her anemia to iron deficiency from her menstrual cycle and diet. Her hemoglobin was 11.3g/dL with a mean corpuscular volume of 70.6fL and ferritin 6ng/mL. She was started on ferrous sulfate 325mg twice daily and her anemia resolved a year later. Her primary care physician obtained repeat iron studies 1 year later which showed a persistently low ferritin at 15ng/mL as well as low vitamin B12 level, less than 150pg/mL. The patient was advised to get vitamin B12 shots for supplementation, but was not able to afford them. The following years hemoglobin remained normal, but had low vitamin B12 and ferritin. She was referred to gastroenterology for endoscopic evaluation. Upper endoscopy found atrophic appearing gastric mucosa and colonoscopy was normal. Gastric mapping was performed during her upper endoscopy. Pathology revealed gastric intestinal metaplasia confined to the gastric body. Serologies for serum gastrin, anti-parietal cell antibody, anti-intrinsic factor antibody, TSH were ordered post endoscopy. She was found to have a high titer anti-parietal cell antibody of 1:80. Gastric biopsies and helicobacter pylori stool antigen were both negative. She was diagnosed with having autoimmune atrophic gastritis and started on vitamin B12 shots and continued ferrous sulfate supplementation. Vitamin B12 deficiency resolved, her hemoglobin remained within normal range and ferritin also improved to 166ng/mL.

### Discussion

Atrophic gastritis (AG) is a condition characterized as chronic inflammation of the gastric mucosa. This inflammation leads to the loss of gastric glandular cells and their eventual replacement by intestinal and fibrous tissue. The replacement of gastric mucosa with intestinal mucosa results in a loss of hydrochloric acid, pepsin and intrinsic factor production. AG is thought to affect ~8% of the general population.<sup>1</sup> Atrophic gastritis patients are more commonly female and of east Asian or Andean origins. Atrophic gastritis is less common in north American and western European populations. Endoscopically, atrophic gastritis can range from very minimal to severe gastritis and atrophy. Atrophic gastritis is classified into two subtypes: Type A, autoimmune and Type B, environmental.<sup>2</sup>

Atrophic gastritis type A, known as autoimmune gastritis, is a result of autoimmune antibodies targeting the hydrogen-potassium-ATPase pumps on the luminal surface of parietal cells and intrinsic factor. These autoimmune antibodies target the  $\beta$  subunit of the hydrogen-potassium ATPase located within the plasma membrane of the parietal cell.<sup>2</sup> The loss of hydrochloric acid production by the parietal cells results in disruption of the negative feedback loop with the G cells in the gastric antrum, leading to hypersecretion of gastrin. Gastrin then goes on to overstimulate enterochromaffin cells within the gastric body which can lead to the formation of dysplastic cells. The loss of hydrochloric acid also leads to due malabsorption of iron. Iron requires a low pH for its ferric state to interact with ascorbic acid to bind a ligand in the gastric lumen in its ferrous state to facilitate transport into the duodenum where it is absorbed. Consequently, iron deficiency anemia is often one of the first signs of atrophic gastritis, in comparison to pernicious anemia, which is the more commonly associated type of anemia known to occur with atrophic gastritis.<sup>3</sup> Iron deficiency anemia often precedes pernicious anemia by several years. It is important to note that type A AG typically is confined to the gastric body and fundus, sparing of the antrum and poses a higher risk of causing gastric adenocarcinoma and carcinoid tumors than type B. Type A is also commonly associated with Hashimoto's thyroiditis (53%) and diabetes mellitus type 1.<sup>2</sup> A diagnosis of type 1 AG can be made with gastric biopsies, serum gastric level and anti-parietal cell and anti-intrinsic factor antibodies.<sup>4</sup>

Type B AG, also known as environmental atrophic gastritis, more common and caused by *Helicobacter pylori* infection. Type B AG can occur in any part of the stomach. It is hypothesized that *H. pylori* bacteria contains epitopes that mimic the hydrogen-potassium ATPase resulting molecular mimicry leading to antibody formation, which in turn leads to destruction of the parietal cells.<sup>2</sup> Of note, type 2 AG is not associated with pernicious anemia nor does serum gastrin become elevated. A diagnosis of type 2 AG can be made with gastric biopsies, serum pepsinogen level and anti-parietal cell and anti-intrinsic factor antibodies.<sup>4</sup>

An important reason for diagnosis and monitoring patients with atrophic gastritis is the increased risk of malignancy, particularly gastric carcinoids. Gastric carcinoids have 3 different subtypes with type 1 being the most common.<sup>5</sup> Gastric tissue follows "Correa's cascade", which is a histological progression

from normal gastric tissue to intestinal metaplasia, to dysplasia and ultimately intestinal adenocarcinoma.<sup>1</sup> Typically type 1 gastric carcinoids are seen as multifocal polyps, usually less than 5mm in size which are rarely functional (less than 5%). Approximately 50% of pernicious anemia cases are associated with it. Gastrin and chromogranin A serum levels also tend to be elevated. Type 2 gastric carcinoids are most commonly seen in multiple endocrine neoplasia (MEN) type 1. Type 2 gastric carcinoids are a result of hypersecretion of gastrin from the duodenal and pancreatic cells as opposed to gastric cells. Type 3 gastric carcinoids most commonly resemble gastric carcinomas. However, despite AG's associated increased risk of causing gastric malignancy, current guidelines recommend against routine endoscopic surveillance.<sup>6</sup> Finally, there is no treatment for atrophic gastritis, although endoscopic and medical therapies are available for carcinoid tumors.

### Conclusion

Iron deficiency anemia is the most common cause of anemia, affecting 6-12% of the general population.<sup>7</sup> Despite the routine evaluation of iron deficiency anemia, including serum iron, ferritin levels and endoscopic evaluation for gastrointestinal bleeding and luminal malignancies, iron malabsorption is less commonly evaluated. Patients who undergo endoscopic work up and appear endoscopically "normal" can fail to have the cause of their anemia determined without proper histological diagnoses. Undiagnosed atrophic gastritis can subject patients to unnecessary additional testing including gynecologic procedures and bone marrow biopsies which can lead to unnecessary costs and morbidity. Therefore, it is in the best interests of an endoscopist to obtain gastric mapping during an upper endoscopy, particularly in higher risk patients to make the diagnosis. While no treatment other than H. pylori eradication is available for atrophic gastritis, supplemental iron can reduce the burden or eliminate iron deficiency anemia.

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