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CASE REPORT | PATHOLOGY

Progression From Antral G-Cell Hyperplasia to Gastric Neuroendocrine Tumor in a Patient With Autoimmune Gastritis

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ABSTRACT

Autoimmune metaplastic atrophic gastritis is caused by immune-mediated destruction of gastric parietal cells. This leads to the absence of gastric acid production, which causes compensatory hyperplasia of gastric antral G-cells leading to hypergastrinemia. The excess gastrin binds to enterochromaffin-like cells causing hyperplasia, which may progress to dysplasia and rarely to gastric neuroendocrine tumors. We present a rare case of autoimmune metaplastic atrophic gastritis associated with G-cell hyperplasia showing the full developmental spectrum of enterochromaffin-like cell proliferation from hyperplasia to dysplasia to neuroendocrine tumor.

INTRODUCTION

Autoimmune metaplastic atrophic gastritis (AMAG) is a chronic inflammatory disease characterized by immune-mediated replacement of gastric parietal cells with atrophic and metaplastic mucosa.[1] Patients with AMAG often present with dyspepsia or symptomatic anemia; however, many remain asymptomatic in the early stages of the disease. AMAG is associated with other autoimmune diseases and is a risk factor for the development of type 1 gastric neuroendocrine tumor (GNET).[2] Previous studies have reported an annual incidence of type 1 GNET ranging from 0.4% to 0.68% in patients with AMAG.[3,4] Lately, the incidence of AMAG and type 1 GNET has increased globally, partly owing to improved awareness of these diseases.[5] Type 1 GNET comprises 70%–80% of all GNETs and generally has an excellent prognosis after resection, with a metastatic potential between 2% and 5%.[6] Despite the relatively benign course of type 1 GNET, careful consideration should be placed on diagnosis and management, given the increasing incidence of these tumors. We present a case of AMAG in a patient with dyspepsia who was diagnosed with G-cell hyperplasia with progression to type 1 gastric microneuroendocrine tumor. This case exemplifies a thorough diagnostic workup for AMAG with GNET and reviews the pathophysiology behind the development of this condition.

CASE REPORT

A 63-year-old African American woman with a medical history of diabetes mellitus classified as latent adult autoimmune diabetes complicated by diabetic gastroparesis, Hashimoto's thyroiditis, pernicious anemia on B12 supplementation, and hypertension was referred for nausea, vomiting, weight loss, and dyspepsia. She underwent esophagogastroduodenoscopy (EGD) with random gastric biopsies showing grossly normal mucosa, was consistent with chronic inflammation and focal foveolar hyperplasia, and negative for *Helicobacter pylori* (Figure 1). By immunohistochemistry, biopsies demonstrated G-cells by gastrin immunostaining, confirming antral-type mucosal origin. Cells were positive for synaptophysin present in aggregates measuring up to 0.9 mm (Figure 2). MIB1 immunohistochemical stain showed a Ki-67 proliferation index of less than 3% within these aggregates, which was pathologically suggestive of a type 1 microneuroendocrine tumor (Figure 2).

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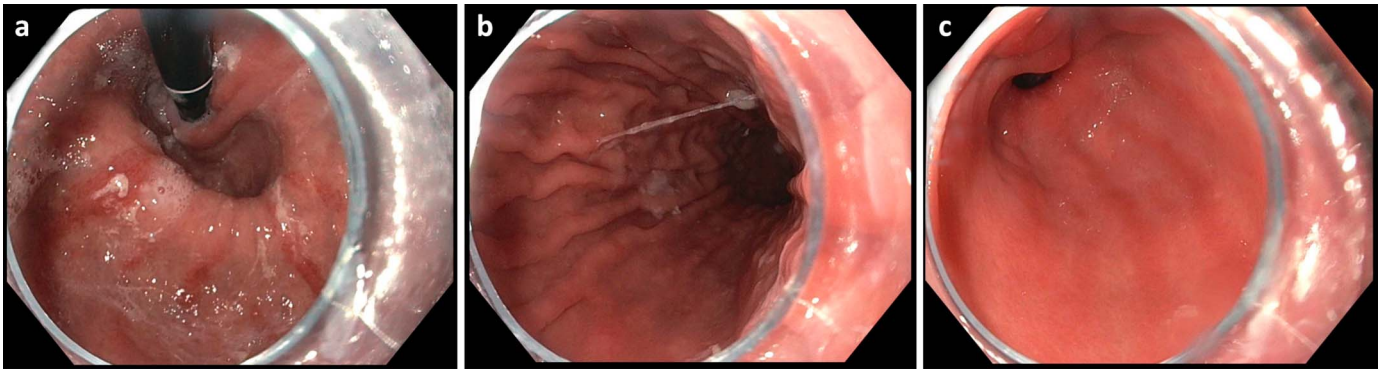

Figure 1. Endoscopic images of the (A) gastric fundus, (B) body, and (C) antrum.

Laboratory results showed elevated serum gastrin levels to 2,068 pg/mL. Given concern for type 1 GNET, she underwent a gallium-68 DOTATATE positron emission tomography scan, which was negative. Next, EGD with endoscopic ultrasound (EUS) of the gastrinoma triangle was performed. EUS was grossly normal without findings of a primary tumor or mucosal abnormalities. Random mucosal biopsies confirmed neuroendocrine tumor of the gastric body composed of small clusters/nodules of neuroendocrine hyperplasia with an estimated proliferation index less than 3%.

Additional workup revealed elevated chromogranin-A of 211 ng/mL, positive glutamic acid decarboxylase antibodies >120 IU/mL, positive gastric parietal cell antibody of 46.9 units, and positive intrinsic factor antibodies. The patient was diagnosed with AMAG based on her histologic and laboratory findings, although it remained unclear when she initially developed this condition.

After 6 months, the patient underwent surveillance EGD, and random biopsies were assessed with immunohistochemistry. EGD showed diffuse moderate inflammation, and biopsies from the gastric antrum demonstrated G-cell hyperplasia, again highlighted by gastrin immunostaining (Figure 3). Biopsies of the gastric body showed hallmark features of AMAG, including antralization with loss of oxyntic glands and the full spectrum of disordered enterochromaffin-like (ECL) cell proliferation from hyperplasia to dysplasia to microneuroendocrine tumor (1 mm, MIB1 < 3%) (Figure 3C). At the time of this writing, our patient is being treated for pernicious anemia and is undergoing further endoscopic surveillance to evaluate for progression of microneuroendocrine tumor through serial EGD with EUS.

DISCUSSION

In this case, our patient with diabetes, autoimmune thyroiditis, and pernicious anemia was found to have positive antigastric parietal cell and anti-intrinsic factor antibodies with gastric biopsy findings consistent with AMAG. She was subsequently diagnosed with a type 1 microneuroendocrine tumor with reconfirmation of AMAG and G-cell hyperplasia, and she is currently undergoing surveillance endoscopy for cancer progression. Although few previous cases have reported autoimmune gastritis and its association with G-cell hyperplasia and hypergastrinemia,[7–9] this is the first known report of endoscopic findings of AMAG associated with G-cell hyperplasia showing the full developmental spectrum of ECL cell proliferation from hyperplasia to dysplasia to neuroendocrine tumor.

To understand the progression of this patient's disease and symptoms, it is essential to understand the pathophysiology.

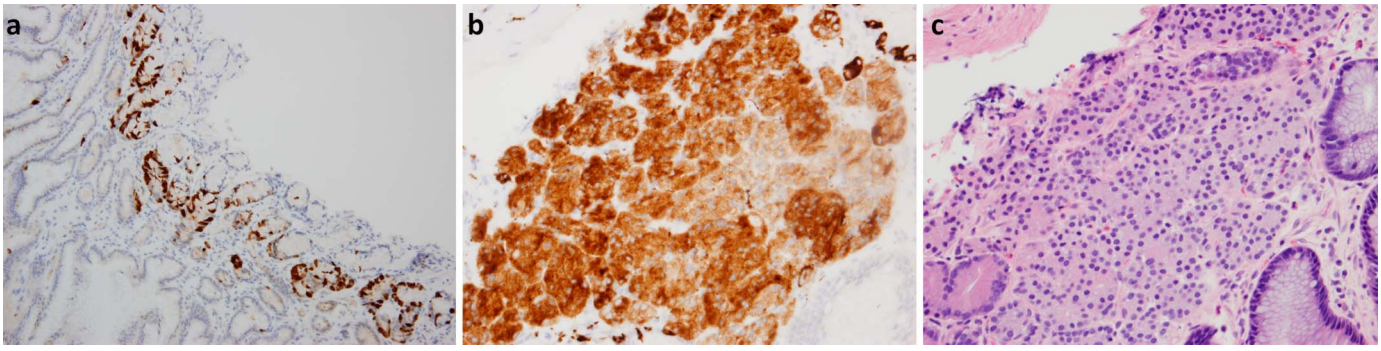

Figure 2. Random biopsies were obtained of the gastric antrum and body with immunohistochemistry demonstrating G cells by (A) gastrin immunostaining, (B) positive synaptophysin present in aggregates measuring up to 0.9 mm, and (C) Ki-67 proliferation index of less than 3% within these aggregates with MIB1 staining.

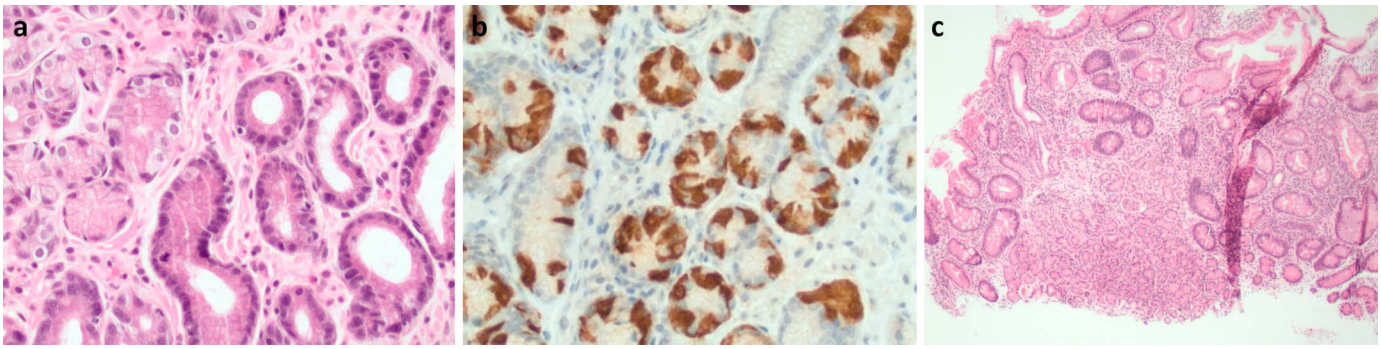

Figure 3. Random biopsies were obtained in the gastric antrum with immunohistochemistry redemonstrating G-cell hyperplasia highlighted by (A) gastrin immunostaining. (B) Biopsies of the gastric body revealed hallmark features of autoimmune gastritis including antralization with loss of oxyntic glands and showed (C) the full spectrum of disordered enterochromaffin-like cell proliferation from hyperplasia to dysplasia to microneuroendocrine tumor (1 mm, MIB1 < 3%).

AMAG is characterized by immune-mediated destruction of gastric parietal cells. This leads to the absence of gastric acid production causing compensatory hyperplasia of gastric antral G-cells with hypergastrinemia.[10] Furthermore, there is potentially decreased inhibition from gastric D-cells, contributing to increased gastrin production. When serum gastrin levels are >1,000 pg/mL, Zollinger-Ellison syndrome is often the first diagnosis to be suspected; however, keeping G-cell hyperplasia on the differential diagnosis is important to avoid subjecting these patients to unnecessary surgical procedures. For our patient, G-cell hyperplasia was confirmed by gastrin immunohistochemistry. As a result, the marked hypergastrinemia was considered to have been caused by G-cell hyperplasia related to a block in the negative feedback mechanism of somatostatin against achlorhydria with autoimmune gastritis.

At increased levels, gastrin binds to ECL cells through the cholecystokinin-2 receptor and causes ECL cell hyperplasia,[1] which may progress to dysplasia and type 1 GNET, occurring in 1%–12.5% of cases.[6] Furthermore, it has been reported that AMAG and type 1 GNET can occur with or without the presence of other autoimmune diseases including type 1 diabetes mellitus, autoimmune thyroiditis, and pernicious anemia, as seen in our patient.[11] The current medical literature does not routinely recommend surveillance endoscopy for patients with AMAG. However, our patient had AMAG with G-cell hyperplasia that had progressed to type 1 GNET, thereby increasing the risk of developing metastatic disease. Thus, for patients with atrophic gastritis and associated G-cell hyperplasia, consideration should be given to evaluate with interval surveillance endoscopy with gastric mapping biopsies to assess for gastric intestinal metaplasia and stomach cancer. One review article suggests that surveillance every 6–12 months with endoscopic mucosal resection is sufficient for tumors less than 2 cm vs surgical antrectomy for larger or progressive tumors; however, data are limited on the optimal management of microneuroendocrine tumors.[2] Some options to consider include EGD with EUS as was performed for our patient or potentially using virtual chromoendoscopy, an imaging technique that evolving research has shown to be beneficial in identifying and classifying neuroendocrine tumors.[12,13]

In conclusion, AMAG is a rare but important condition to consider on the differential diagnosis in patients with dyspepsia, especially in the setting of other autoimmune comorbidities. Given the potential to develop type 1 GNET and metastatic disease, these patients may benefit from routine endoscopy for dysplasia surveillance.

DISCLOSURES

Author contributions: P. Brown and B. Tetali wrote the manuscript. P. Brown, B. Tetali, S. Suresh, and A. Varma revised the manuscript for intellectual content and approved the final manuscript. A. Varma is the article guarantor.

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