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(CASE REPORT)

Autoimmune gastritis associated with well-differentiated type 1 gastric neuroendocrine tumor: A Case Report and Brief Literature Review

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Abstract

Autoimmune gastritis (AIG) is an immune-mediated inflammatory disorder characterized by the progressive destruction of gastric parietal cells, leading to achlorhydria, intrinsic factor deficiency, and compensatory hypergastrinemia. This condition predisposes patients to severe micronutrient deficiencies and significantly increases the risk of developing type 1 gastric neuroendocrine tumors.

We present the case of a 58-year-old female with a history of Hashimoto's thyroiditis who presented with progressive fatigue, early satiety, and neurologic symptoms initially managed as irritable bowel syndrome. Diagnostic evaluation revealed severe vitamin B12 and iron deficiency anemia, hypergastrinemia, and positive anti-parietal cell antibodies. Upper endoscopy demonstrated severe corpus-restricted atrophic gastritis with multiple small polyps. A multidisciplinary tumor board guided the management, leading to the endoscopic mucosal resection of the dominant 8-millimeter lesion, which was histologically confirmed as a well-differentiated type 1 gastric neuroendocrine tumor (G-NET) with enterochromaffin-like cell hyperplasia.

This case highlights the gradual, often subtle progression of autoimmune gastritis and the importance of recognizing the thyro-entero-gastric autoimmune association. It also underscores the need for early endoscopic screening and surveillance in patients with combined iron and vitamin B12 deficiency anemia, as timely intervention may prevent progression from enterochromaffin-like cell hyperplasia to neuroendocrine neoplasia and reduce the risk of gastric adenocarcinoma.

Keywords: Autoimmune gastritis; Gastric neuroendocrine tumor; Gastric neoplasia; Hypergastrinemia; Intrinsic factor antibodies; Gastrin level

1. Introduction

Autoimmune gastritis (AIG) is a chronic, progressive, organ-specific autoimmune disease that targets the oxyntic mucosa of the stomach. [1] Despite an estimated global prevalence of 1% to 2%, the condition remains substantially underdiagnosed, frequently presenting with non-specific dyspepsia or delayed hematologic and neurologic manifestations. [2] The clinical significance of autoimmune gastritis lies not only in its profound impact on micronutrient absorption but also in its well-established potential to drive gastric neoplasia. The autoimmune

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destruction of parietal cells invariably leads to profound hypochlorhydria, which subsequently triggers a compensatory, unabated secretion of gastrin from antral G cells. [3,4] This chronic hypergastrinemia acts as a potent trophic factor for enterochromaffin-like cells, initiating a cascade from hyperplasia to dysplasia and ultimately resulting in the formation of type 1 G-NET. [5] Patients with AIG carry an estimated 13-fold increased risk of developing these indolent yet potentially progressive neoplasms compared to the general population. [5]

We report a case of a 58-year-old female whose protracted fatigue and subtle neurologic symptoms masked an underlying thyro-entero-gastric autoimmune syndrome, culminating in the diagnosis of a well-differentiated gastric neuroendocrine tumor, Grade 1. This report aims to elucidate the intricate pathogenesis linking autoimmune gastritis to neuroendocrine tumorigenesis and to advocate for heightened clinical vigilance and multidisciplinary management in this vulnerable patient population.

2. Case Presentation

2.1. Clinical Presentation

A 58-year-old female presented with a three-year history of progressive fatigue, episodic epigastric discomfort, and intermittent loose stools that worsened after meals. She had been managed empirically for suspected irritable bowel syndrome with dietary modifications and a trial of a proton pump inhibitor, which provided no sustained relief. Over the preceding six months, she noticed early satiety and unintentional weight loss of 12 pounds. She also described occasional tingling on her feet and a persistent sensation of a "full tongue." She sought medical attention because her fatigue had become debilitating, and she had started bruising easily after minor bumps.

2.2. Physical Examination, History, Labs, Imaging, and Differential Diagnosis

Physical examination revealed pale conjunctivae and smooth, erythematous patches on the dorsal aspect of the tongue, consistent with glossitis. Neurologic exam showed diminished vibration sense in the distal lower extremities. Her personal history included Hashimoto's thyroiditis diagnosed ten years earlier, and her family history was notable for a sister with pernicious anemia.

Laboratory studies showed macrocytic anemia (hemoglobin 9.2 g/dL, MCV 104 fL), low serum vitamin B12 (145 pg/mL), elevated gastrin (950 pg/mL), and positive anti-parietal cell and anti-intrinsic factor antibodies. Iron studies revealed mild iron deficiency. Upper endoscopy showed diffuse moderate to severe atrophic changes in the gastric body and fundus with sparing of the antrum, and multiple small, pale-yellow polyps in the corpus (Largest 8 mm). Endoscopic ultrasound confirmed the polyps as intramucosal, well-circumscribed lesions. Computed tomography (CT) of the abdomen showed no lymphadenopathy or metastatic disease.

The clinical differential diagnosis included functional dyspepsia with incidental autoimmune metaplasia, pernicious anemia with reactive neuroendocrine hyperplasia, and, less likely, multiple sporadic gastric neuroendocrine tumors or type 2 in the setting of Zollinger-Ellison syndrome (though gastrin levels were not extremely high and gastric acid studies were not performed). Radiologic differential diagnosis focused on benign hyperplastic polyps versus low-grade neuroendocrine tumors.

2.3. Multidisciplinary Tumor Board Discussion

The tumor board, comprising gastroenterology, endocrine pathology, medical oncology, pathology, and general surgery, convened with a focused question: whether the patient required endoscopic resection of all visible polyps or surveillance alone, given the underlying autoimmune gastritis. The pathologist confirmed the presence of enterochromaffin-like (ECL) cell hyperplasia. The gastroenterologist argued that type 1 G-NETs have a low metastatic potential but carry a risk of progression over the years.

The surgeon noted that, given the small size (the largest 8 mm) and lack of invasion, an endoscopic mucosal resection (EMR) of the dominant polyp was preferred over surgical resection. The team agreed that the patient should not undergo antrectomy because hypergastrinemia was driven by autoimmune achlorhydria, not gastrinoma. They recommended endoscopic surveillance with resection of lesions >1 cm or those with atypical endoscopic features.

2.4. Special Studies, Pathology, Immunohistochemistry, and Molecular Studies

The dominant polyp was removed by EMR and submitted for histology. Microscopic examination showed a well-differentiated neuroendocrine tumor forming trabecular and ribbon-like patterns within the deep mucosa, with

uniform round nuclei and finely stippled chromatin. No lymphovascular invasion was seen. (**Figure 1 A, B**) IHC was strongly positive for chromogranin A, synaptophysin, and gastrin, with a low Ki-67 proliferation index of 2%. Cytokeratin staining highlighted the entrapped gastric glands. Further, IHC for CDX2 was negative, consistent with a foregut origin. The adjacent non-neoplastic gastric mucosa demonstrated loss of parietal cells with replacement by epithelium resembling antral-type mucosa. The lamina propria contained a prominent lymphoplasmacytic infiltrate. The presence of goblet cells identified intestinal metaplasia. Together with the presence of anti-parietal cell antibodies, these histomorphologic findings were diagnostic of autoimmune gastritis (AIG) (**Figure 1 C**),

Molecular studies using next-generation sequencing showed no MEN1 mutations, and serum MENIN immunohistochemistry (IHC) on the tumor was retained, ruling out sporadic MEN1-related G-NET. The patient underwent genetic counseling and declined MEN1 germline testing, given no family history of neuroendocrine tumors.

2.5. Development of Gastric Neuroendocrine Tumor: Diagnosis, Treatment, and Outcome

The diagnosis of AIG with type 1 G-NET was confirmed. The patient started on intramuscular vitamin B12 replacement, which gradually improved her macrocytic anemia and neurologic symptoms. Oral iron supplementation corrected the iron deficiency. Regarding the G-NET, the tumor board recommended a conservative endoscopic approach. The dominant 8 mm polyp was resected with negative margins. The remaining five micronodules (<5 mm each) were left in situ. Follow-up endoscopy at six months showed no new large lesions; the residual micronodules were unchanged. At 12 months, one micronodule had grown to 7 mm and was resected by cold snare polypectomy.

The patient remained free of neuroendocrine symptoms, and annual CT scans showed no metastatic disease. Her gastrin level gradually fell from 950 pg/mL to 420 pg/mL after vitamin B12 and iron replacement, although it remained elevated. She was advised to continue lifelong endoscopic surveillance every 12 to 24 months. She was also counseled that her underlying atrophic gastritis carries a separate risk of gastric adenocarcinoma, which also requires ongoing surveillance. At the 3-year follow-up, no additional G-NETs exceeded 5 mm, and her quality of life remained normal.

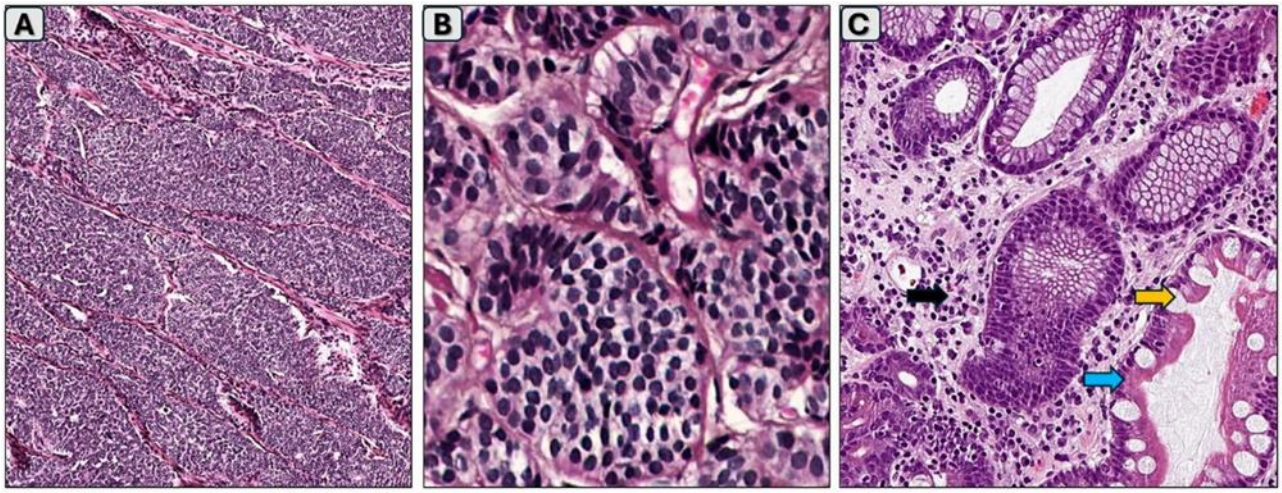

Figure 1 Microscopic features of autoimmune gastritis associated with type 1 gastric neuroendocrine tumor

- 1A**:** Low-power view showing neuroendocrine tumor with solid, trabecular, and ribbon-like patterns within the deep mucosa (H&E X20)
- 1B**:** High-power view showing neuroendocrine tumor with uniform round nuclei and finely stippled chromatin (H&E X40)
- 1C**:** High-power view showing autoimmune gastritis with intestinal metaplasia (Blue arrow), Goblet cells (Yellow arrow), and lymphoplasmacytic infiltrate (Black arrow) (H&E X40)

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification):

AIG, historically termed type A chronic atrophic gastritis, primarily affects women, with a female-to-male ratio approaching 3:1, and its incidence rises significantly with advancing age. [3,6] Epidemiologic data indicate that the disease frequently coexists with other autoimmune disorders, most notably Hashimoto's thyroiditis and type 1 diabetes mellitus, forming a complex polyautoimmune phenotype. [7]

The World Health Organization (WHO) classifies gastric neuroendocrine neoplasms based on their differentiation and proliferative grading (Ki-67 index and mitotic rate). [8] Type 1 gastric neuroendocrine tumors represent 70% to 80% of all gastric neuroendocrine tumors; they are typically small, multifocal, low-grade (Grade 1 or 2) lesions confined to the gastric body and fundus and are exclusively driven by the hypergastrinemia secondary to autoimmune achlorhydria. [9] In contrast to sporadic type 3 tumors, type 1 lesions generally exhibit an indolent clinical course and a very low metastatic rate. [10] However, the background atrophic mucosa also carries a distinct, elevated risk of developing gastric adenocarcinoma, necessitating comprehensive and lifelong endoscopic surveillance. [11]

3.2. Pathogenesis, Pathophysiology

The pathogenesis involves CD4+ T-cell-mediated destruction of the H+/K+-ATPase pump on parietal cells, leading to a loss of gastric acid secretion and intrinsic factor production. [12] The development of type 1 G-NETs in the setting of AIG represents a classic paradigm of hormone-driven tumorigenesis. The initiating event is immune-mediated destruction of oxyntic glands, leading to parietal cell loss and the abolition of gastric acid secretion. [1,13] The resulting achlorhydria disrupts the normal negative feedback loop, causing antral G cells to continuously secrete gastrin in a futile attempt to stimulate acid production. [10] Gastrin exerts a profound trophic effect by binding to cholecystokinin-2 (CCK2) receptors on the enterochromaffin-like (ECL) cells located in the gastric body and fundus. [14] This chronic stimulation induces ECL cell proliferation, manifesting initially as linear or nodular hyperplasia. [14]

Over time, and likely facilitated by secondary somatic mutations, this hyperplastic state can progress to dysplasia and eventually transform into an overt type 1 G-NET. [9,10] Concurrently, the loss of intrinsic factor leads to the depletion of vitamin B12, causing defective DNA synthesis and pernicious anemia. At the same time, the lack of gastric acid impairs the reduction of dietary iron, leading to early iron deficiency anemia. [3] This intricate chain reaction underscores how a localized autoimmune insult translates into systemic hematologic deficits and localized neuroendocrine neoplasia.

3.3. Comparative Analysis of Our Case with Existing Literature, And What Have We Learned from This Case?

Our patient's presentation is consistent with current literature describing the association between AIG and type 1 G-NETs. Like patients in reported cohorts, she was a middle-aged woman with a pre-existing autoimmune disorder (Hashimoto's thyroiditis) and combined iron and vitamin B12 deficiencies. [7,15] Although pernicious anemia is classically associated with AIG, recent studies show that iron deficiency anemia may precede macrocytosis by several years, as reflected in this case. [3,16] The endoscopic finding of multiple small polyps in the setting of severe corpus atrophy with antral sparing represents a characteristic macroscopic feature of the disease. [9]

The multidisciplinary management of our case also reflects current European Neuroendocrine Tumor Society (ENETS) guidelines, which advocate conservative, organ-sparing approaches for small type 1 tumors. [17] The decision to perform endoscopic mucosal resection of the dominant 8-millimeter lesion, while employing surveillance for the smaller micronodules, safely balanced oncologic control with preservation of gastric anatomy. [17,18]

This case imparts several critical clinical lessons. First, it highlights the diagnostic peril of attributing chronic gastrointestinal and constitutional symptoms to functional disorders like irritable bowel syndrome without thoroughly investigating objective red flags, such as progressive anemia and new-onset neurologic deficits. Second, it reinforces the concept of polyautoimmunity; the history of thyroid disease should lower the threshold for investigating AIH in patients with unexplained anemia. Finally, the case demonstrates that hypergastrinemia in the presence of achlorhydria is a potent oncogenic driver.

We encourage clinicians to recognize that diagnosing AIG mandates a commitment to long-term endoscopic surveillance, not only to monitor the recurrence or progression of neuroendocrine tumors but also to detect early dysplastic changes that may herald gastric adenocarcinoma.

Abbreviations:

- Autoimmune gastritis (AIG)
- Gastric neuroendocrine tumor (G-NET)
- Immunohistochemistry (IHC)

4. Conclusion

This case illustrates the profound clinical consequences of AIG, culminating in the development of a well-differentiated type 1 G-NET. We presented this case to emphasize that AIG is not merely a benign cause of vitamin deficiency but a complex, precancerous condition driven by a predictable cascade of achlorhydria, hypergastrinemia, and enterochromaffin-like cell hyperplasia that carries a 13-fold increased risk of neuroendocrine tumorigenesis.

The value of this report to the medical community lies in its demonstration of the thyro-entero-gastric autoimmune link and the necessity of looking beyond isolated symptoms. By recognizing the early hematologic warning signs and employing a multidisciplinary, conservative endoscopic approach, clinicians can effectively manage these indolent tumors while maintaining a high index of suspicion for concurrent gastric malignancies, thereby optimizing long-term patient outcomes and quality of life.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

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Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

This work did not involve any studies on human or animal subjects performed by the authors. It was a retrospective review of archival pathology material collected during routine clinical care, and all data were fully de-identified before analysis.

Statement of informed consent

The patient was lost to follow-up, and all attempts to reach the patient were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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