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CASE REPORT

Well-Differentiated Grade 3 Gastric Neuroendocrine Tumors: Diagnostic Challenges and Therapeutic Perspectives

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ABSTRACT

The most common digestive neuroendocrine tumors (NETs) arise from the small intestine, pancreas, or appendix, followed by those originating in the stomach. Among these, type 1 gastric neuroendocrine tumors (g-NETs) generally carry a favorable prognosis owing to their low proliferative activity. However, a recently recognized entity — well-differentiated grade 3 neuroendocrine tumors — is characterized by preserved morphological differentiation despite an elevated Ki-67 proliferation index. These tumors represent a borderline category between low-grade NETs and neuroendocrine carcinomas (NECs). Although exceedingly rare, their management remains controversial and challenging, particularly when cytotoxic chemotherapy is contraindicated or refused by the patient. We report the case of a 51-year-old woman diagnosed with a well-differentiated, high-grade (grade 3) gastric neuroendocrine tumor (type 1) arising in the setting of autoimmune gastritis. The tumor displayed a Ki-67 proliferation index of 25%, reflecting significant metastatic potential. A hepatic metastasis was identified at the time of diagnosis. Treatment with lanreotide achieved a prolonged partial response, allowing consideration of deferred surgical intervention.

Keywords: Gastric neuroendocrine tumor, Well-differentiated, Grade 3, autoimmune gastritis.

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1. INTRODUCTION

Gastric neuroendocrine neoplasms (g-NENs) are rare tumors, with an incidence of approximately 4.97 cases per million in the U.S. (1). They arise from enterochromaffin-like cells and constitute about 5-15% of digestive neuroendocrine neoplasms (dig-NENs). g-NENs are classified as Type 1 (linked to chronic atrophic gastritis), Type 2 (Zollinger–Ellison syndrome), and Type 3 (sporadic), with Type 1 being the most common, accounting for 80-90% of cases (2-4).

In 2010, the WHO categorized well-differentiated dig-NENs as low (G1) or intermediate grade (G2), while poorly differentiated tumors are classified as high grade (G3). Subsequent studies introduced a new category of well-differentiated grade 3 neuroendocrine tumors (G3 NET), which are classified based on the Ki-67 proliferation index (< 3%, 3-20%, > 20%). Although aggressive, G3 NETs, primarily found in the pancreas, can also occur in the stomach (8-29%), colon, or rectum (8-24%) (5, 6). Diagnosis relies on histopathology and immunohistochemistry with markers like chromogranin A and synaptophysin, though up to 25% of gastric neuroendocrine carcinomas (g-NECs) may not express these markers (5).

Clinical presentations are often nonspecific, making endoscopy and targeted biopsies essential. Staging involves endoscopic ultrasound (EUS) to assess tumor depth and lymph node involvement. Despite their high grade, well-differentiated G3 gastric NETs generally have a better prognosis than poorly differentiated NECs. Their rarity and diagnostic challenges hinder management, with limited literature and no consensus guidelines available; treatment recommendations are often derived from other G3 NETs and

guidelines from the North American Neuroendocrine Tumor Society (6). Management should be individualized through multidisciplinary consultations, taking into account factors like differentiation, vascular and lymph node invasion, and metastases. The case report aims to highlight the atypical presentation, diagnostic difficulties, and treatment implications of a well-differentiated G3 gastric NET, emphasizing the need to differentiate between NET G3 and NEC and its effect on management strategies.

2. CASE PRESENTATION

A 51-year-old woman presented with persistent atypical epigastric pain. Laboratory tests showed a vitamin B12 deficiency and iron-deficiency anemia. Endoscopy identified a 20-mm polypoid lesion in the gastric fundus (Figure 1) with surrounding atrophic mucosa and multiple nodules. Histology demonstrated atrophic gastric mucosa with intestinal metaplasia and no Helicobacter pylori infection. Finally, findings of enterochromaffin-like cell hyperplasia, fundic atrophy associated with hypergastrinemia, and positive anti-parietal cell and intrinsic factor antibodies confirm autoimmune atrophic gastritis and the diagnosis of type 1 g-NET.

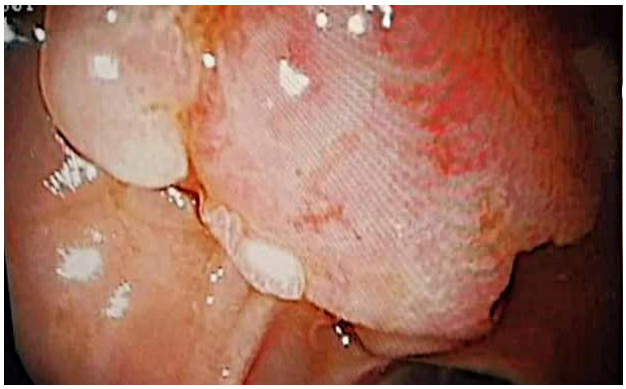

Figure 1. Appearance of a centimeter-sized polypoid lesion.

EUS identified a hypoechoic lesion infiltrating the submucosa and muscularis, measuring 19 × 9.7 mm (Figure 2). The lesion was vascularized by a 1.2 mm pedicle, exhibiting heterogeneous enhancement with areas of necrosis. EUS also identified two perigastric lymph nodes measuring between 17 and 23 mm, along with a hypoechoic, oval lesion in segment II of the liver, measuring 13 × 11.7 mm. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) was performed on both the perigastric lymphadenopathy and the hepatic nodule.

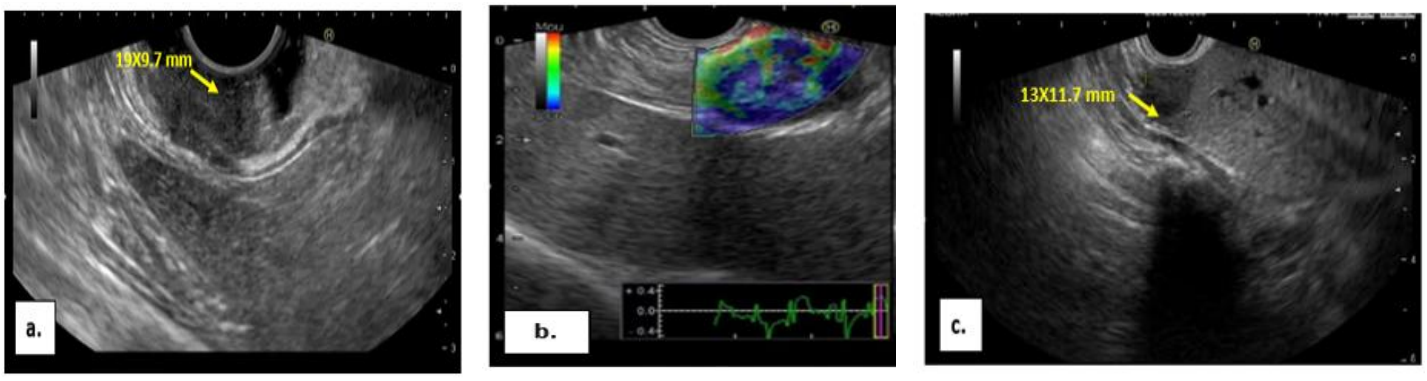

Figure 2. Endoscopic ultrasound features of the g-NET. a. Hypoechoic lesion of the deep part of the gastric mucosa, infiltrating the submucosa and even the muscularis, vascularized by a central pedicle. b. Perigastric lymphadenopathy, presplenic. c. Hypoechoic metastatic lesion in segment II of the liver.

The pathological analysis revealed a diffuse tumor proliferation with an organoid or insular, trabecular pattern, in a thin and hypervascular stroma. The tumor had monomorphic cells with granular eosinophilic cytoplasm, oval to round nuclei, and salt-and-pepper chromatin with small nucleoli (Figure 3). Immunohistochemical analysis demonstrated strong expression of synaptophysin and chromogranin A. The proliferation index was estimated at 25%. Hepatic biopsy revealed well-differentiated neuroendocrine metastases morphologically consistent with the primary gastric tumor.

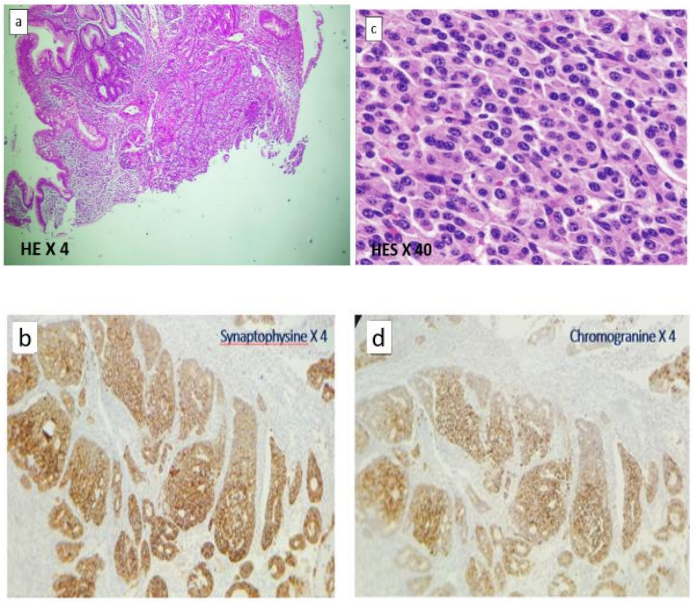

Figure 3. Histological and immunohistochemical features of NET: a. Severe atrophic gastritis with intestinal metaplasia. b. Tumor cells showing diffuse immunostaining for synaptophysin. c. Diffuse tumor proliferation composed of monomorphic tumor cells with abundant eosinophilic cytoplasm, arranged in nests as small solid clusters; nuclei are oval or regularly round. d. Tumor cells showing diffuse immunostaining for synaptophysine. and chromogranin A.

Based on histopathological and immunohistochemical findings, a well-differentiated high-grade (G3) gastric neuroendocrine tumor was diagnosed, consistent with 2019 WHO criteria.

During staging, a computed tomography (CT) scan revealed a well-defined thickening of the gastric fundus wall, measuring 17 mm, exhibiting characteristic tissue density and post-contrast enhancement, and perigastric lymph nodes were observed, with the largest measuring 22 mm. No secondary lesions were identified in the lungs, liver, or bones. However, MRI revealed a single subcapsular nodule in segment II measuring 12.2 mm. The lesion appeared hypointense on T1, hyperintense on T2, and on diffusion, with ADC restriction. Post-contrast T1 fat-saturated sequences demonstrated annular peripheral enhancement.

Somatostatin receptor scintigraphy (SRS-CT) showed no suspicious uptake beyond the known lesions. Due to the metastatic stage (M1 hepatic) and the high tumor grade, chemotherapy was recommended; however, the patient declined this treatment option. Instead, she was administered Lanreotide Autogel® 120 mg every four weeks for a total of 16 cycles. The treatment was well tolerated and led to a total regression of the hepatic lesion, although there was persistent mild thickening of the fundic wall, measuring 4 mm in thickness over a length of 9 mm. Following a prolonged disease management period, oncological surgery was considered the next therapeutic step during a multidisciplinary consultation meeting (MCM). The histological characteristics and the absence of distant metastases supported the surgical approach. Additionally, the evaluation of the patient's clinical progression and her response to lanreotide further reinforced the decision to regard surgery as a viable option.

3. DISCUSSION

The incidence of gastric neuroendocrine tumors (g-NETs) is rising due to enhanced diagnostic techniques, with G3 g-NETs being relatively uncommon, comprising approximately 5% of digestive neuroendocrine neoplasms (dig-NENs) and 15-20% of all G3 NETs (5).

These tumors are heterogeneous, including both well-differentiated and poorly differentiated forms. Distinguishing well-differentiated G3 g-NETs from poorly differentiated neuroendocrine carcinomas (NECs) presents significant diagnostic challenges, prompting a reevaluation of current classification and treatment protocols. Guidelines specify that "neuroendocrine tumor" should refer solely to well-differentiated neoplasms. Well-differentiated G3 NETs are characterized by maintained morphology (trabecular, organoid, or gyriform patterns) and minimal pleomorphism or necrosis. They typically express at least two neuroendocrine markers, such as chromogranin A and synaptophysin, with positivity rates ranging from 91% to 100%, compared to 75% to 96% in NECs (6).

This case highlights an unusual form of g-NETs characterized by small size (<20 mm), a high proliferation index despite well-differentiated morphology, and aggressive behavior including submucosal invasion, lymph node involvement, and hepatic metastasis. Such cases are rare and not well understood, necessitating a tailored management approach. Endoscopic ultrasound (EUS) is crucial for characterizing lesions and allows for fine-needle aspiration, especially in tumors >10 mm. In high-grade g-NETs, where the risk of progression and metastasis is significant, EUS plays a vital role in early management decisions (3).

Hepatic metastases from NETs are typically multiple and hypervascular. A triphasic CT scan is recommended for optimal detection, although rare features such as hypovascular, pseudocystic, pseudoangiomatous, or purely fibrotic lesions can complicate radiological interpretation. Hepatic MRI, utilizing both morphological and diffusion-weighted sequences, provides superior detection of liver metastases. Features like larger size, heterogeneous and low contrast enhancement, vascular invasion, and distant metastases are more prevalent in grade 3 NETs compared to grades 1 or 2 (6,7).

Routine radiological evaluations are generally unnecessary for type 1 g-NETs, which are typically low-grade. Imaging is recommended only if EUS indicates metastases or if high-risk features, such as grade 2 histology, lymphovascular invasion, tumor size ≥10 mm, or suspected T2 involvement, are present. Metastasis from gastric NETs primarily affects the liver and lymph nodes, warranting a comprehensive staging workup to ensure appropriate therapeutic management(7-9). The prognosis for well-differentiated G3 g-NETs is variable; while it is poorer than that for G1 or G2 NETs, it remains more favorable than for NECs. Currently, 62-70% of G3 g-NETs are metastatic at diagnosis. Metastases primarily affect the liver and lymph nodes, with tumor grade being a significant prognostic factor related to the risk of distant metastases (8).

Several hypotheses address tumor grade progression, including increased Ki-67 index, sampling errors, or associated carcinomatous components; however, a definitive Ki-67 cutoff for guiding resection has not been established. This progression indicates the aggressive potential of NETs and correlates with a significant decrease in overall survival, with reported survival for G3 NETs reaching 55 months compared to less than 18 months for NECs .

The lack of standardized protocols highlights the need for treatment validation through specialized NET boards. Treatment options depend on tumor size, number, invasion depth, presence of metastases, and differentiation. For type 1 g-NETs, endoscopic surveillance is suitable for small, non-aggressive lesions, while endoscopic or surgical resection is recommended for larger or high-grade tumors, especially with suspected lymphovascular invasion or muscularis propria infiltration on EUS (6-10).

In advanced or metastatic cases, first-line chemotherapy, specifically a combination of temozolomide and capecitabine (CapTem), is recommended for its efficacy, particularly in pancreatic neuroendocrine tumors (11). This approach is advised when the Ki-67 index is below 55% and is based primarily on proliferation rates rather than on histological differentiation, thereby allowing alternative treatment options for patients who decline cytotoxic chemotherapy. Somatostatin analogs may also have a role in treating NETs beyond grades 1 and 2; the CLARINET study demonstrated the antiproliferative efficacy of lanreotide in non-functional G1-G2 NETs (12). Although G3 patients were excluded from this study, some retrospective series suggest potential benefits of somatostatin analogs in well-differentiated G3 NETs with intermediate proliferation rates (Ki-67 index between 20% and 55%).

This clinical case underscores the potential role of somatostatin analogs, such as Lanreotide, in the long-term management of certain well-differentiated G3 NETs. The observed prolonged treatment response suggests that this option is promising but still under-researched. It is crucial to implement rigorous, personalized follow-up for patients to facilitate treatment adjustments based on clinical and biological changes.

In cases of objective tumor response despite initial unresectable hepatic metastasis, the management strategy can be reconsidered, leading to a multidisciplinary consultation (NET-MCM) to tailor a personalized treatment plan (15-17). Surgical resection for metastatic NETs may be viable for carefully chosen patients, particularly those with sustained disease control through medical therapy or those who may benefit from a delayed curative approach. While this surgical strategy is well established for pancreatic NETs, its application is increasingly recognized for well-differentiated gastric NETs (18). Additionally, annual endoscopic surveillance is recommended for type 1 g-NETs that do not require resection, given the heightened risk of gastric adenocarcinoma associated with chronic atrophic gastritis (18).

4. CONCLUSION

Well-differentiated grade 3 gastric neuroendocrine tumors constitute a rare and complex entity that remains insufficiently characterized in the literature. Most available epidemiological data derive from retrospective studies, which are frequently limited by nonspecific differentiation criteria and the challenge of reclassifying poorly differentiated neuroendocrine carcinomas. This gap highlights the urgent need for comprehensive expert reevaluation of cases, particularly within specialized networks such as TEN-path. Future prospective studies are necessary to define the true incidence of these tumors accurately and to provide detailed clinical data that enhance understanding and underscore the importance of close collaboration among experts in this field. To address the diagnostic and therapeutic challenges posed by these complex and rare tumors, a multidisciplinary, personalized, case-by-case approach guided by MCM is essential to optimize therapeutic decisions and improve patient outcomes.

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