

When Variants Collide: An Unusual Presentation of Metastatic Gastric Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm

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ABSTRACT

Gastrointestinal neuroendocrine neoplasms were recently reclassified into the 2019 World Health Organization schema into well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine carcinomas, and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). Among these, gastric MiNENs are exceedingly rare and often metastasize quickly without diagnostic clues. We present a refractory gastric MiNEN with unique presenting features. This case highlights the clinical spectrum of these tumors, the importance of accurate histochemical interpretation, and clinical management in the absence of formalized guidelines. Future therapies looking at novel targets and palliative symptom relief are needed.

INTRODUCTION

The neuroendocrine cells of the gastrointestinal tract produce numerous hormones with effects on acid secretion, motility, pancreatic stimulation, and storage.¹ Neuroendocrine neoplasms (NENs) are epithelial overgrowths confined to neuroendocrine differentiation. In 2019, the World Health Organization released a significant update and reclassified the digestive system tumors. It divides NENs into well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine carcinomas, or mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). This classification largely depends on molecular profiling, histochemical analysis, and proliferation markers such as Ki-67 and the mitotic index.² Traditionally, gastric tumors display a hyperplasia-dysplasia-neoplasia sequence under hypergastrinemia states; however, neuroendocrine carcinomas have demonstrated unique tumorigenesis from endocrine cells.³ NENs are underestimated, and clinical data lack because these patients are often excluded from clinical trials. This places importance on the reporting of newly diagnosed MiNENs that often require a multidisciplinary consensus to design the most optimal treatment strategy.⁴ Over the years, these groups of digestive tumors have undergone frequent classification changes because more sophisticated immunohistochemical methods are used. Although pathologists have recognized this entity for quite some time, there seems to be a lag in its clinical understanding as its presentation occurs late. We present an exceedingly rare case of a gastric MiNEN presenting with atypical features not noted previously in the literature. This case aims to broaden the clinical understanding of this tumor, highlighting its paraneoplastic and locoregional effects.

CASE REPORT

A 59-year-old woman presented to her primary care physician with dizziness, fatigue, anorexia, bloating, and hoarseness for months despite lifestyle measures and omeprazole. She had a history of hypertension and a family history significant for cardiovascular disease. She never used tobacco products, alcohol, or illicit substances. She began workup with an abdominal ultrasound that revealed

a 2.2-cm solid lesion in the liver but was lost to follow-up until she presented to the emergency department with complaints of abdominal pain, anorexia, night sweats, and recurrent near syncopal episodes.

On arrival, she was hypotensive to 77/34 mm/hg, normocardic to 83 beats per minute, afebrile, tachypneic, and not requiring supplemental oxygen. She appeared ill, dehydrated, and uncomfortable unable to stand for extended periods without feeling dizzy. After a fluid bolus, repeated blood pressure was 94/67 mm Hg with a heart rate of 98 beats/min. Complete blood counts and metabolic panels were unremarkable. Reviewing her history from centralized electronic records, the mass on her ultrasound prompted a magnetic resonance imaging, which revealed numerous lesions in the liver and bulky adenopathy along the stomach, pancreas, and gastrohepatic ligaments (Figure 1). A coronal computed tomography scan revealed a tortuous inferior vena cava (IVC) with surrounding mass effect with the left renal vein being compressed by para-aortic nodes, while the IVC was wrapped by anterior and posterior lymph nodes (Figure 2). No biliary or ductal abnormalities were noted. Symptoms were controlled with esomeprazole, prophylactic low-molecular-weight heparin, ondansetron, prochlorperazine, and frequent hydration to the extent tolerable. An esophagogastroduodenoscopy revealed a 4-cm ulcerative mass at the gastroesophageal junction extending into the fundus, with biopsy revealing an MiNEN with sheets of high-grade tumor cells and glands with underlying squamous epithelium (Figure 3). *Helicobacter pylori* staining was negative, and gastrin was not obtained because of the nature of the diagnosis. Liver biopsy confirmed metastatic MiNEN with medium to large tumor cells and scattered adenocarcinoma of gastric origin (Figure 4).

On disclosing her results, the patient decided to go back home to pursue staging, molecular profiling, and candidacy for clinical

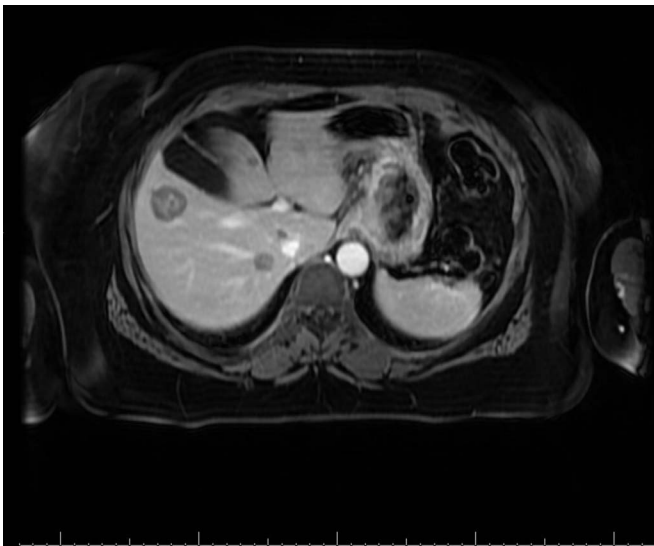


Figure 1. Abdominal magnetic resonance imaging reveals the index hepatic lesion measuring 2.8 × 2.7 cm and thickening of the lesser curvature of the stomach.



Figure 2. Abdominal and pelvic coronal computed tomography revealing the 2.8 × 2.7-cm index lesion of the liver and a distorted inferior vena cava vasculature from anterior and posterior lymph node compression (arrowhead) with left para-aortic lymph nodes compressing the left renal vein.

trials, ultimately undergoing palliative chemotherapy with carboplatin and etoposide. After assessing fit, she received a chest port to initiate chemotherapy with carboplatin 750-mg and etoposide 220-mg infusions, pretreated with aprepitant 130 mg, ondansetron 8 mg, and dexamethasone 12 mg. Despite 2 cycles over 2–3 months and relief in stomach pain, repeat imaging revealed diffuse osseous metastatic involvement of the thoracolumbar spine and pelvis. Hopeful for life prolongation, the next treatment line was initiated with capecitabine 1,000 mg twice a day from days 1–14 and temozolomide 400 mg on days



Figure 3. Esophagogastroduodenoscopy revealing a 4-cm large ulcerative mass extending into the gastric fundus.

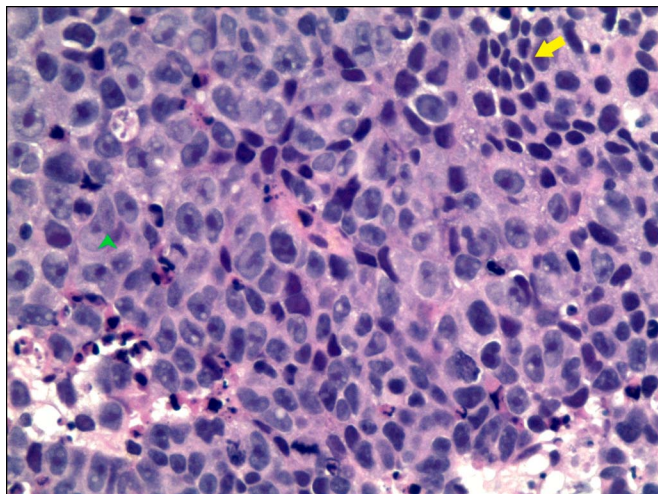


Figure 4. Histopathology of the liver, revealing high-grade tumor cells, with rare tumor cells having moderate cytoplasm and occasional nucleoli (hematoxylin and eosin stain, 40× magnification).

10–14. During subsequent outpatient visits, she was found to be repeatedly hypotensive, with increasing occurrences of presyncope. After ruling out other etiologies, interventional radiology was consulted for IVC stent placement, although it was decided that chemotherapy would continue, with the possibility of stent placement if adequate tumor shrinkage was not achieved. During a subsequent admission for renal failure and severe thrombocytopenia, her hemodynamics and course rapidly worsened, eventually passing away in hospice care.

DISCUSSION

The unique element of our case remains the rarity of this tumor and its atypical clinical presentation, often seen in advanced stages. MiNENs have an overall poor prognosis presenting with metastatic and paraneoplastic components at the time of diagnosis. Gastric MiNENs constitute a small fraction of digestive tumors, most commonly affecting men in their fifth or sixth decade.^{4,5} The most extensive report on MiNEN trends comes from the Surveillance, Epidemiology, and End Results registry between 1975 and 2016. It reports an incidence of 5.6%, mostly in the appendix, colon, cecum, rectum, or small intestine.⁵ Compared with other tumors, gastric MiNENs are discovered at advanced stages, and very little is known about them.

Our patient experienced recurrent dizziness, intolerance to standing for prolonged periods, and presyncope consistent with orthostatic hypotension, and alternative causes were ruled out, including anemia, volume depletion, and arrhythmia. Autonomic failure seemed less likely due to her response in heart rate. We attributed her symptoms to IVC compression by extensive lymphadenopathy consistent with IVC syndrome, a presentation consistent with the literature.^{6–8} A similar case of IVC compression has been described, eluding to the propensity of these tumors to metastasize in a disorganized way risking compression of vital structures.⁷

Recommendations for therapy guidance, surveillance patterns, and treatment duration are lacking, placing precedence on isolated reports.⁹ The challenge for pathologists remains to identify both elements because it has prognostic implications.¹⁰ In most cases, the neuroendocrine component is represented by small or large cell NEC, which in itself renders a poor prognosis, while the non-neuroendocrine component is represented by carcinoma of the primary site.^{7,11} A recent systematic review noted that the neuroendocrine component determines the clinical trajectory. Most diagnostic and therapeutic data come from advanced cases, while isolated reports achieving success with long-term survival are sparse.^{11,12} The general approach in patients identified with a metastatic spread at diagnosis is palliative chemotherapy initiation with combination cisplatin or carboplatin with etoposide before deterioration limits chemotherapy. These tumors respond to platinum-based regimens, often administered for 4 cycles, while surgical metastasectomy offers no further benefit.⁶ In a multinetwork cohort, platinum-based regimens demonstrated higher efficacy than folinic acid, fluorouracil, and irinotecan and folinic acid, fluorouracil, and oxaliplatin regimens for progression-free and median overall survival. Platinum-based therapy is highly individualized but often administered as cisplatin 25 mg/m² on days 1–3 or carboplatin 300 mg/m² followed by etoposide 100 mg/m² on days 1–3 every 21 days.¹³

Interestingly, a 3-drug regimen derived from small-cell lung cancer models consisting of paclitaxel, carboplatin, and etoposide reflected a longer median survival, with nearly 25% of patients alive at 3 years.¹⁴ Despite the study limitations and unvalidated paclitaxel benefits in this setting, any benefit in outcome must be explored in these aggressive tumors. Future research looking into novel molecular targets is vital in quelling its progression. Equally important are therapies that provide palliative symptom relief, especially in tumors that have a mass effect on vital structures.^{3,15,16} In conclusion, through this report, we want to highlight the formation of a rare mixed neuroendocrine-non-neuroendocrine neoplasm and its unique presentation.¹⁷

DISCLOSURES

Author contributions: S. Deliwala wrote the manuscript and is the article guarantor. A. Ponnappalli, I. Gakhal, and V. Modi edited the manuscript. T. Haykal, G. Bachuwa, and S. Chawla edited the manuscript and revised it for intellectual content.

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