Clinical Case Report

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Well-differentiated neuroendocrine tumor of the stomach

A rare case at an uncommon site

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Abstract

Introduction: A 13-year-old African–American female presented to her primary care physician's office with fatigue, syncope, and hematemesis. After initial evaluation, the patient was referred to pediatric gastroenterology clinic for further evaluation.

Main concerns, important findings: An upper gastrointestinal endoscopy was performed to evaluate the source of her bleeding. Endoscopy revealed a 3-cm mass in the lesser curvature of the stomach, and a biopsy of the mass revealed a concern for carcinoid (neuroendocrine) features.

Diagnosis: She underwent an open gastrectomy. Post-surgical pathology reports confirmed a well-differentiated neuroendocrine tumor of the stomach.

Conclusion: Neuroendocrine tumors of the stomach in children are rare and we presently do not have pediatric-specific diagnostic and treatment guidelines. Although adult-based The North American Neuroendocrine Tumor Society (NANETS) guidelines are helpful, they are clearly not geared toward pediatric patients. To establish pediatric guidelines and to assess effectiveness of treatments, multicenter data collection is essential. In the long run, accumulation of clinically useful treatment information and long-term follow-up guidelines should enable clinicians to improve standard of care given to children with neuroendocrine tumors.

Abbreviations: CT = computed tomography, ECL = enterochromaffin-like, EGD = esophagogastroduodenoscopy, ENET = The European Neuroendocrine Tumor Society, EUS = endoscopic ultrasound, HIAA = hydroxyindoleacetic acid, LOH = loss of heterozygosity, NANETS = The North American Neuroendocrine Tumor Society, NET = neuroendocrine tumor, NJ = nasojejunal.

Keywords: carcinoid, gastrointestinal, neuroendocrine tumor (NET)

1. Introduction

Well-differentiated neuroendocrine tumors (NETs) are exceedingly rare in children and adults[1,2] with the vast majority of them developing in the gastrointestinal (GI) tract. Although rare, NETs are the most common GI epithelial tumors in children, comprising 2% of diagnosed cases. Because of the rarity of NETs in children, there are no established pediatric management guidelines. Present recommendations for diagnosis, treatment, and long-term follow-up vary and are primarily derived from The North American Neuroendocrine Tumor Society (NANETS) adult guidelines.[3–7]

NETs, which originate from neuroendocrine cells, are found throughout the body. NETs were first described by Lubarsch, from multiple tumors in the distal ileum of two patients at autopsy, over a century ago.[8] These tumors were named carcinoid tumors (Karzinoide) in 1907 by Oberndorfer.[9] Historically, these tumors were described as originating from the foregut, midgut, or hindgut. The midgut location is the most common primary site in the majority of patients.[10] The annual incidence of NET both in adults and children is estimated to be roughly 2 to 5 cases per 100,000 population.[6,7,10–12]

Over the past 2 decades, various classification systems have sub-grouped NETs histologically by their differentiation and grade. Tumor differentiation refers to the similarity of the neoplastic cells to their non-neoplastic counterparts. Tumor grade refers to the tumor's degree of biological aggressiveness and is measured by proliferation rate.[11] Until recently there has been little consensus on the classification and the management of NETs. Before the 2010 update, World Health Organization (WHO) used a combined classification system that incorporated both staging and grading information. Because of several limitations, including limited information for therapeutic decision making, WHO has discontinued the use of the hybrid system and adapted the new classification system that allows staging and grading separately.[6] WHO released the present classification system for the digestive system based on histologic grade in

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2010.[5–7] This classification divides NETs into well differentiated, including low-grade (G1) and intermediate-grade (G2) neuroendocrine neoplasms, and poorly differentiated, high-grade (G3) neuroendocrine carcinoma. This present classification system brought the WHO system more closely in line with other widely used systems including the European Neuro Endocrine Tumors (ENETs) classification system.[5–7]

There are three distinct groups of neuroendocrine neoplasms in the stomach. Of these, 70% to 80% are Type 1 gastric NETs. The majority are < 1 to 2 cm, multiple, polypoid lesions and well differentiated (G1), with a predominance in female to male patients. These gastric NETs are usually asymptomatic, but can present with anemia. Type 1 NETs develop on the background of chronic atrophic gastritis, which is a consequence of *Helicobacter pylori* infection or of autoimmune gastritis. The atrophy of the fundic glands leads to hyperplasia of enterochromaffin-like (ECL) cells. The majority of Type 1 NETs have excellent survival rates; however, a small percentage of patients develop distant metastases.[6,7,10,12,13] Type 2 gastric NETs are associated with Zollinger–-Ellison syndrome, within the MEN-1 syndrome, and account for 2% to 5% of gastric NETs. Distant metastases can be found in 10% to 30% of cases.[6,10,12] Finally, Type 3 gastric NETs are the second-largest group, constituting 15% to 20% of the cases, and occur as sporadic tumors. They are large (>1–2 cm), usually single and invasive. The majority of them are poorly differentiated, have lymph node involvement, and distant metastases.[6,10,12]

Most NETs are indolent and asymptomatic leading to a delay in diagnosis. The development of various biomarker assays, including peptides and amines produced by NETs such as 5-HIAA (primary metabolite of serotonin), histamine, gastrin, and chromogranin A, and the development of immunohistochemistry panels have facilitated blood and tissue diagnosis.[10] The combination of these biomarker assays and pathological characterization of NETs has enhanced early surgical and pharmacological intervention to improve quality of life and survival.[10]

Endoscopic resection is the mainstay of the therapy for Type 1 and Type 2 NETs, measuring <2 cm in size. Tumors >2 cm, polypoid, or recurrent tumors require a more aggressive approach with local surgical resection. Type 3, high-grade tumors are treated with a combination of surgery, chemotherapy, targeted therapy, and somatostatin analogues to control symptoms that result from the release of peptides and neuroamines.[6,10,12]

We report on a 13-year-old patient with a well-differentiated NET of the stomach, diagnosed after upper GI endoscopy and successfully removed via gastrectomy.

2. Case report

A 13-year-old African–American female presented to the emergency department on referral from her pediatrician for acute hematemesis and syncopal episodes 24 hours before admission. The patient reported having limited to no epigastric pain or nausea. She reported near-syncope at school the day before admission and presented to her pediatrician's office for further evaluation. During the evaluation she had acute hematemesis with tar-like color and clots. She had a syncopal event lasting 1 minute shortly after her hematemesis and was

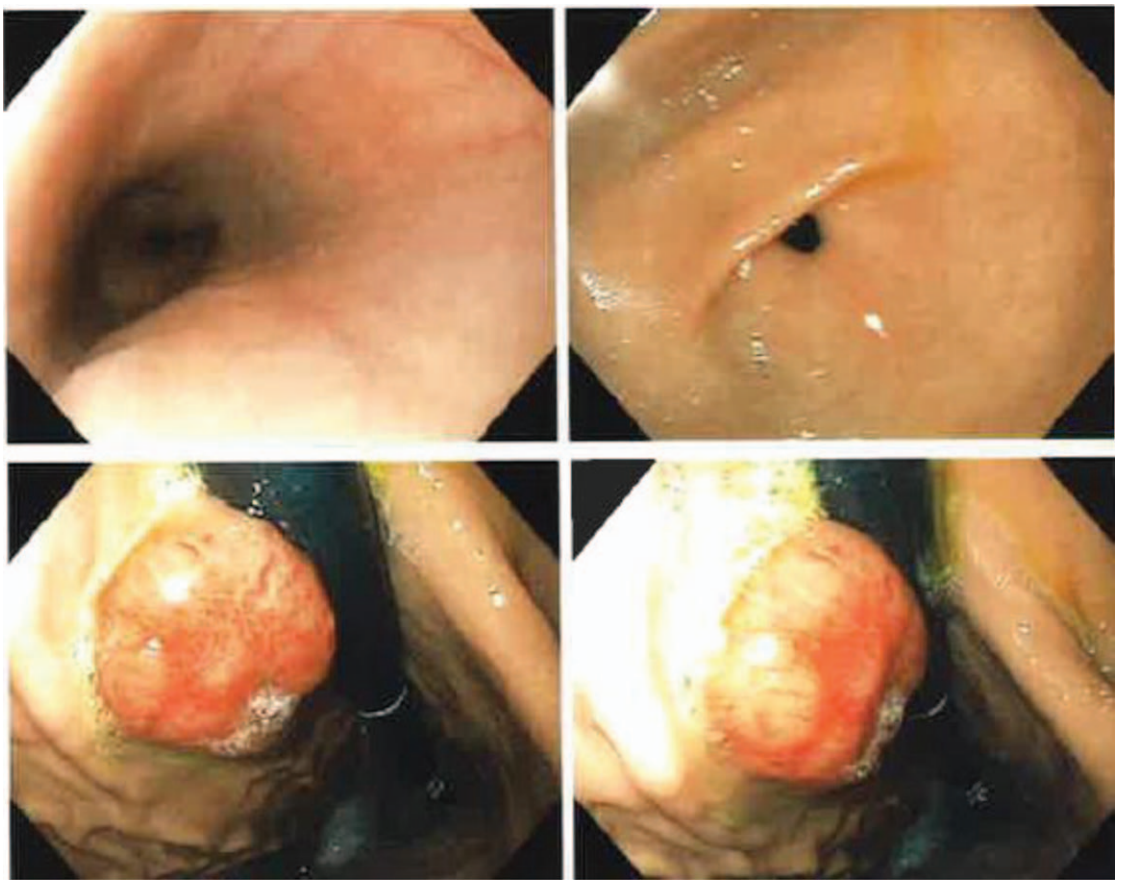

Figure 1. Endoscopic ultrasound identified a solitary mass without extension beyond the stomach with pathology concerning for a neuroendocrine tumor.

directed to the nearest emergency department for care. In the emergency department, her hemoglobin was found to be 9.3 g/dL. On examination, she had no abdominal tenderness and no masses palpated. She was administered 20 mg of pantoprazole IV and admitted to the pediatric floor for further diagnosis and management.

Following admission, an upper endoscopy evaluation revealed a mass in the lesser curvature of the stomach, with friable mucosa and central ulceration, but no active bleeding. The initial pathology, using cold biopsy technique, revealed benign reactive gastric mucosa with no evidence of *H pylori*.

A CT scan of the abdomen revealed a 2.7-cm mass involving the gastric mucosa and possibly gastric wall of the lesser curvature of the central stomach. There was no adenopathy or evidence of extension of the mass through the gastric wall and into the serosa or surrounding soft tissues.

Endoscopic ultrasound (EUS)-guided fine-needle aspiration identified a solitary mass without extension beyond the stomach with pathology concerning a NET (Fig. 1). At the time of surgical exploration, she was found to have the index lesion along the lesser curvature of the stomach; in addition, there were multiple lymph nodes along the lesser curvature of the stomach past the incisura. To resect these in continuity, a total gastrectomy was required and 15 lymph nodes resected. The final pathology report demonstrated a 3-cm polypoid primary tumor with 6 out of 15 lymph nodes involved with the tumor T2, N1, Mx (Fig. 2). After

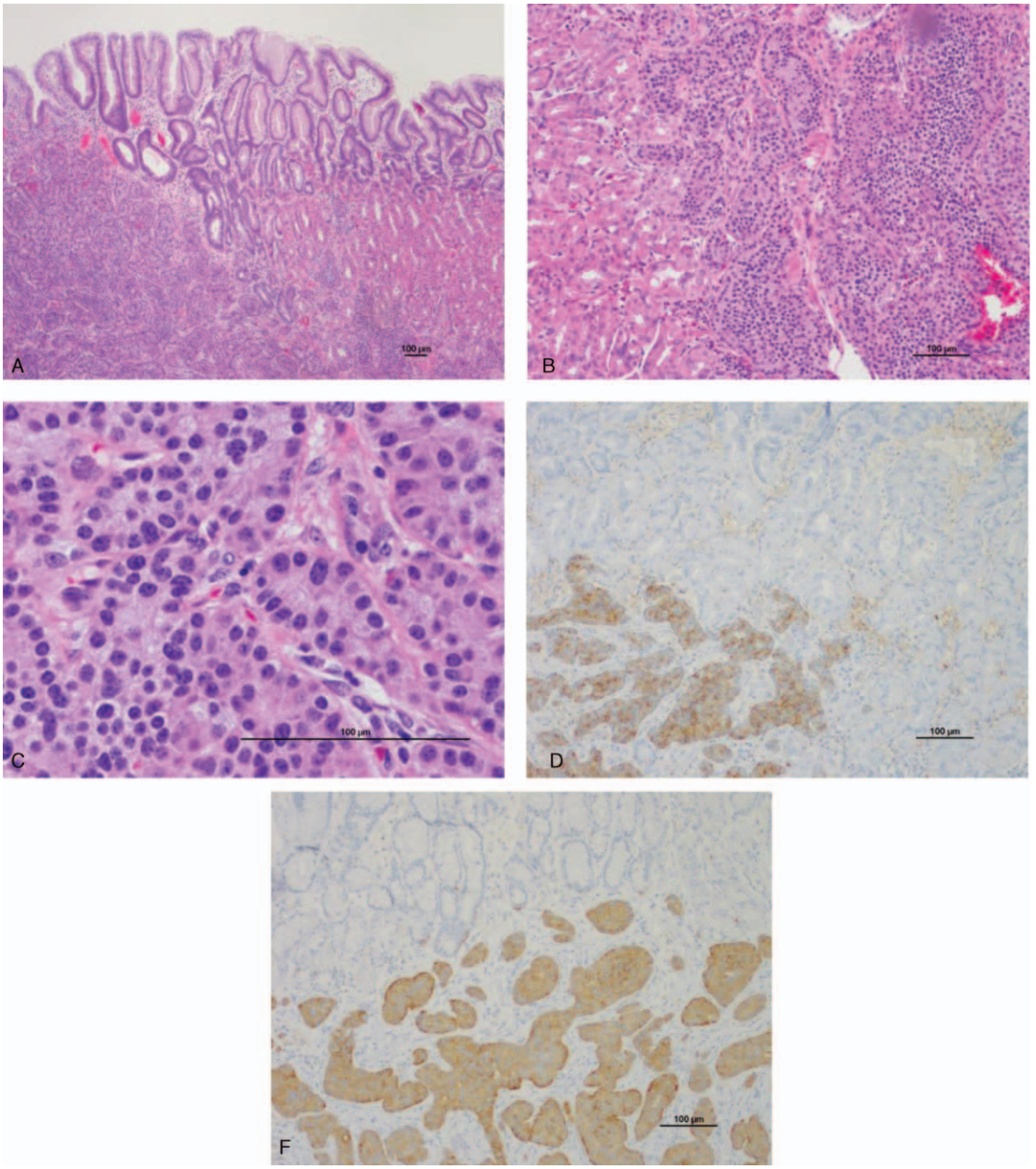

Figure 2. Section of the mass from the lesser curvature of the stomach. (A) Submucosal/mucosal mass. H & E stain, original magnification 40×. (B) Submucosal/mucosal mass. H & E, original 100×. (C) Submucosal/mucosal mass. H & E, original magnification 400×. (D) Diffuse cytoplasmic granular decoration of nests of tumor cells with chromogranin A, original magnification 200×. (E) Diffuse cytoplasmic decoration of nests of tumor cells with synaptophysin, original magnification 400×. H & E=hematoxylin and eosin.

the confirmation of NET, octreotide scintigraphy was performed and was found to be negative for distant metastasis. Urine 5-hydroxyindoleacetic acid (HIAA) and chromogranin A, plasma chromogranin A, gastrin, and histamine levels were analyzed and did not demonstrate any abnormalities. MEN 1 syndrome was excluded and chromosome analysis did not reveal *11q13* abnormality.

Post-operatively, the patient developed dysphagia and stricture at the esophagojejunostomy site. This stricture required esophagogastroduodenoscopy (EGD) with balloon dilation and a nasojejunal (NJ) feeding tube for nutritional support. Six months following the initial gastrectomy she developed vitamin B_{12} deficiency (179 pg/mL with normal 211–946 pg/mL), and iron deficiency anemia (ferritin 11 ng/mL with normal 15–77 ng/mL and soluble transferrin receptor 50.9 nmol/L with normal 12.2–27.3 nmol/L). Both conditions were successfully treated through supplementation. She is presently 22 months post gastrectomy and continues to be followed by gastroenterology and oncology. Her routine follow-up visit includes biomarker assays (chromogranin A, gastrin, and histamine) every 3 months and abdominal imaging (CT) every 6 months. She will be followed-up closely for the next 5 years.

3. Conclusion

Our knowledge of GI neuroendocrine neoplasms has evolved over the last 4 decades, primarily through pediatric case series of carcinoid tumors involving the appendix and bronchial tract. NETs arise from neuroendocrine cells of the GI tract and tracheobronchial tree, historically defined as gastric carcinoids and regarded as a single group of neoplasms[14,15] NET classifications arose according to their presumed embryologic tissue of origin: foregut, midgut, or hindgut tumors with the nomenclature being *carcinoid tumor*, *NET*, or *neuroendocrine carcinoma*. However, there is clinical and biological variability in these tumor subgroups requiring a newer classification that takes histologic characteristics into account as well. NANETS tackled this issue and started categorizing, NETs as well- or poorly-differentiated tumors, with the vast majority being of the well-differentiated histology.[16]

Well-differentiated tumors are uniform and produce neurosecretory granules with diffuse immunoexpression of neuroendocrine markers such as chromogranin A and synaptophysin. Most well-differentiated tumors are composed of ECL cells. Poorly differentiated tumors are rare and have a high rate of metastasis, noted as a neuroendocrine carcinoma.[5,6,16–18]

As with most NETs, these tumors can secrete a number of substances including: 5-serotonin, 5-hydroxytryptophan, kallikrein, adrenocorticothrophic hormone, P-substance, catecholamines, prostaglandin, and gastrin. The risk of classic carcinoid syndrome, diarrhea, flushing, and episodic hypotension can occur, but it too is rare in children, as carcinoid syndrome is associated with metastasis to the liver which is extremely rare in children.[7]

Additionally, NETs are associated with syndromes like multiple endocrine neoplasia 1 (MEN1), may show loss of heterozygosity (LOH) at *11q13,* LOH for *p53 and adenomatous polyposis coli* tumor-suppressor gene have been reported in poorly-differentiated NETs. Because of these associations, the physician can anticipate NETs and institute early intervention, while providing genetic counseling to all of the patients.[5,7]

In 2010, NANETS published guidelines to improve NET management. These guidelines include management of well-differentiated, poorly differentiated, and unusual forms of NETs in adults. These guidelines are presently serving as a reference to pediatric providers with pediatric NET cases. The specific treatment modality used for NETs is decided by the tumor location, and the best chance for cure comes from a complete resection of all known diseases.

In conclusion, NETs of the stomach in children are rare. We presently do not have pediatric-specific diagnostic and treatment guidelines. Although NANETS guidelines are helpful, they are clearly not geared toward pediatric patients. To establish pediatric guidelines and to assess effectiveness of treatments, multicenter data collection is essential. In the long run, accumulation of clinically useful treatment information and long-term follow-up guidelines should enable clinicians to improve standard of care given to children with NETs.

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