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Giant type III well-differentiated neuroendocrine tumor of the stomach: A case report

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ABSTRACT

INTRODUCTION: We describe a case of a large type III neuroendocrine tumor of the stomach. Management and current literature are reviewed.
PRESENTATION OF CASE: A 37 year old female presented with upper gastrointestinal bleed and epigastric pain. Further workup demonstrated a large ulcerated gastric mass near the GE junction. Computer tomography scan and endoscopic ultrasound showed a 10 cm mass with no evidence of distant disease. Fine needle aspiration pathology was consistent with a well differentiated neuroendocrine tumor (Ki67 index <2%), with elevated levels of chromogranin A and serotonin levels but normal gastrin. The patient underwent an uneventful total gastrectomy. Final pathology analysis reported a higher KI67 index (7.54%) and a final pathology of grade 2 type III, T3 N3, neuroendocrine tumor of the stomach. The chromogranin levels normalized and no recurrent disease has been detected in one year follow up.
DISCUSSION: Gastric neuroendocrine tumors are extremely rare, accounting for 4% of all neuroendocrine tumors of the body and 1% of all neoplasms of the stomach. Based on histomorphologic characteristics and pathogenesis, gastric neuroendocrine tumors are classified into four types with differing prognosis and behavior. Current literature describes type 3 gastric neuroendocrine tumors as larger than 2 cm. However, there is no precedent in the literature for a tumor of this size.
CONCLUSION: The incidence of gastric neuroendocrine tumors has been increasing during the last decade, underscoring the need to improve our understanding of their biology and behavior. When identified histologically, patient outcomes depend on appropriate determination of tumor biology and subsequent choice of treatment.

1. Introduction

Gastroenteropancreatic neuroendocrine tumors (NETs) are rare lesions which originate in the enterocromaffin cells located in the gastrointestinal (GI) tract. Although they are considered indolent tumors, their clinical behavior is unpredictable and can range from benign to malignant. NETs are subdivided into foregut (gastric, duodenal and pancreatic) midgut (jejunal, ileal, cecal) and hindgut (distal colic and rectal) [1], with the most common site of origin being the ileum, followed by the rectum and the appendix [2,3]. We describe a case of a large type III neuroendocrine tumor of the stomach. Management and current literature are reviewed.

2. Presentation of case

A 37 year old female presented with sudden onset epigastric abdominal pain, and associated several episodes of hematemesis and melena over the 3 days prior to presentation. She describes intermittent epigastric discomfort over the past 3 years which improved with proton pump inhibitors. On physical exam, the abdomen was soft, non-tender, and non-distended. Rectal exam was positive for occult blood with no other abnormal findings. Normocytic anemia was the only abnormal routine test with a hemoglobin value of 10. A CT scan of the abdomen and pelvis was performed, displaying a $7 \times 7 \times 10$ cm mass in the left upper quadrant, the origin of which could be either gastric or pancreatic (Fig. 1), with no evidence of metastatic disease.

An esophagogastroduodenoscopy (EGD) was performed showing a mass with a large bleeding ulcer adjacent to the gastroesophageal junction (GEJ)(Fig. 2). Endoscopic ultrasound (EUS) revealed a 7 cm mass in the gastric wall arising from the mucosal layer, with no pancreatic involvement. Fine needle aspi-

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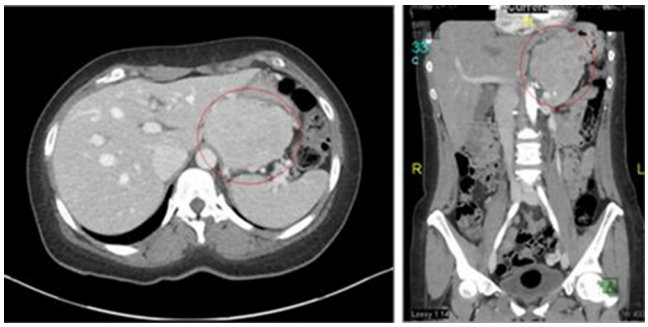

Fig. 1. Computed Tomography of the abdomen and pelvis (axial and coronal) showing a large gastric mass.

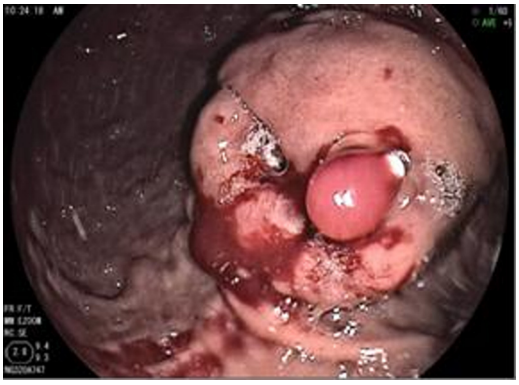

Fig. 2. Large gastric mass with bleeding ulcer on gastroscopy.

ration (FNA) was consistent with a grade I well-differentiated neuroendocrine tumor (NET) (Ki67 index < 2%). Pre-operative work up revealed elevated serotonin levels (460 ng/ml normal: 56–244 ng/ml) and chromogranin A (236 ng/ml normal: 1.9–15 ng/ml) with normal gastrin levels (33 pg—normal < 100 pg)

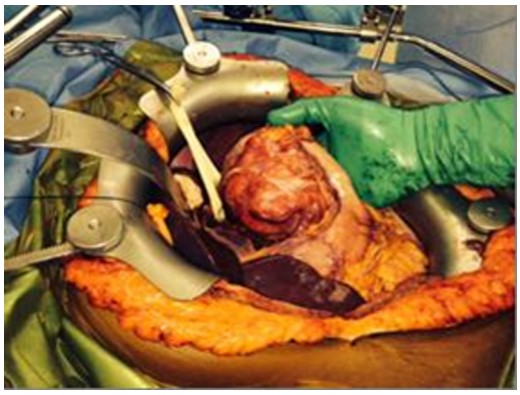

Fig. 3. Gastric mass near the gastroesophageal junction. Penrose drain around the esophagus.

The patient remained stable without any further bleeding and was discharged home, and later returned for an elective gastrectomy. At the time of operation, a large gastric mass was found 3 cm from the GEJ (Fig. 3). A total radical gastrectomy, including perigastric, left gastric and celiac lymph node dissection, was performed. Three centimeters of distal esophagus were also included. A Roux-en-Y reconstruction was performed and a feeding jejunostomy was placed. Negative margins were confirmed by frozen section. The patient had an uneventful postoperative course and was discharged home on postoperative day 6.

Final pathology analysis showed a 10 cm well-differentiated grade 2 type III gastric neuroendocrine tumor with subserosal and perineural invasion (T3). Margins were free of a tumor and 7/17 lymph nodes were positive for malignancy (N3). The tumor was solitary, with no endocrine cell hyperplasia or atrophic gastritis, consistent with a type III tumor (Fig. 4). Mitotic rate was 1 per

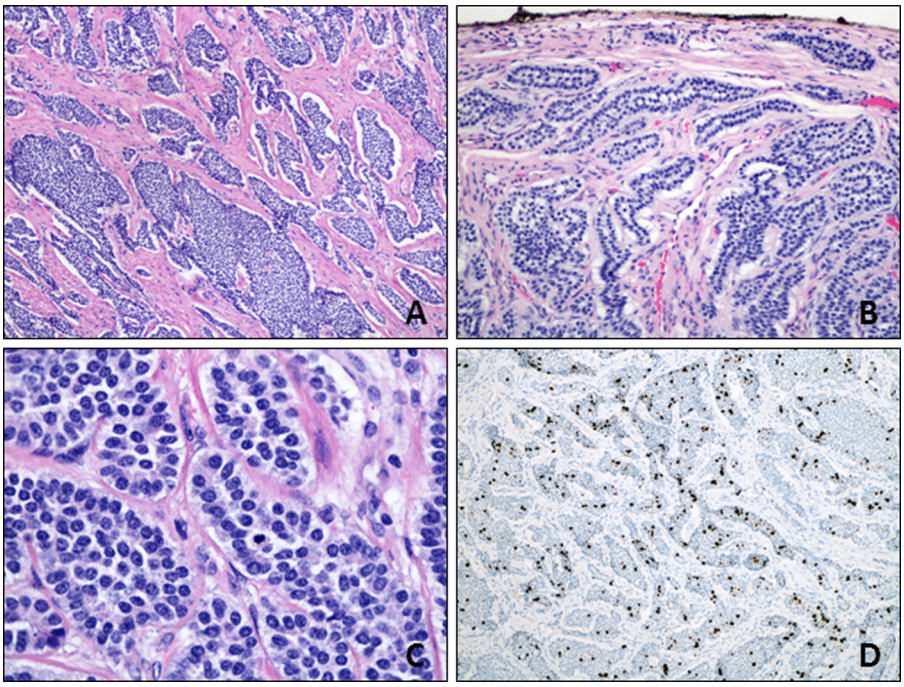

Fig. 4. (A) Insular growth pattern: Nests of monomorphous, small round neuroendocrine cells without atypia or necrosis, consistent with type III gastric neuroendocrine tumor (H&E, ×200 magnification). (B) Trabecular growth pattern: Tumor cells penetrate subserosa and grow in long cords one cell thick. Cytologic atypia, mitoses and necrosis are absent. (H&E, ×200 magnification). (C) Small polygonal cells with round to oval nuclei, inconspicuous nucleoli and finely dispersed chromatin. Rare mitotic figures are present. (H&E, ×600 magnification). (D) Ki-67 proliferative index is 7.54%, consistent with grade 2 tumor (Ki-67, ×100 magnification).

Table 1
GNET characteristics, classification, and prognosis [4,10,25].

	Type I	Type II	Type III	Type IV
Proportion	70–80%	5–6%	14–25%	Rare
Features	Multiple, 1–2 cm	Multiple, 1–2 cm	Single, >2 cm	Single, >2 cm
Ki-67	<2%	<2%	>2%	>30%
WHO classification	1a or 1b	1a or 1b	1b	2
5 Year Mortality	0.5–5%	0.5–5%	25–87%	100%

10 high power fields and Immunohistochemistry showed a Ki67 index of 7.54% assigning a grade 2 neuroendocrine tumor (G2 NET) according to the world health organization (WHO) classification (Fig. 4D). This represented a discrepancy with the prior FNA result which gave a Ki67 index of <2%. Chromogranin A level normalized one month after excision (from 240 to 4 ng/ml). CT scan of the chest and abdomen performed at 3, 6 and 12 months post-operatively have been negative for recurrence.

3. Discussion

NETs can be stratified using several classification systems, with the two most prevalent being the WHO and American Joint Committee on Cancer. The 2010 WHO classification is based on number of mitosis and the Ki67 index giving four categories: G1 NET, G2 NET, neuroendocrine carcinoma (NEC) and mixed adenoneuroendocrine carcinoma (MANEC) [4]. The 2009 American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) classification system uses tumor invasion, number of lymph nodes affected and metastases (TNM) [4]. However, these systems are not universally accepted, making it difficult to compare data from different centers [5].

Gastric NETs (GNETs) account for 4% of all neuroendocrine tumors of the body [6], represent between 8.7–23% of all GI tumors of this type [3,7], and only 1% of all neoplasms of the stomach [7]. Due to an increase in routine endoscopy, their incidence has increased substantially [8], and currently stands at 1–2 cases per 100,000 population per year with a female predominance and a mean age of diagnosis of 64 years [3,9] (Table 1).

Based on histomorphologic characteristics and pathogenesis, GNETs are classified into four types that differ in prognosis and biological behavior [10]. Type I (70–80%) is related to chronic atrophic gastritis, usually located at the gastric fundus or body with good prognosis after resection [11]. Type II (5–6%) is often associated with Zollinger Ellison syndrome and MEN1. Similarly to type I, types II GNETs are benign with a low risk of malignancy [12]. Type III (14–25%) GNETs are usually sporadic tumors that quite often infiltrate the muscularis propia and serosa conferring a malignant potential. They are also associated with vascular and lymph node invasion and liver metastasis [13]. Type IV GNETs are very rare, usually single, poorly differentiated and malignant, and associated with metastatic spread at the time of presentation [14]. Types I to III GNETs originate from enterochromaffin cells, while type IV originates from other endocrine cells that secrete gastrin, serotonin or adrenocorticotrophic hormone. Types I and II are associated with hypergastrinemia while type III and IV are gastrin independent tumors.

Type I GNETs frequently present with multiple small tumors. La Rosa et al., [15] reported an incidence of 77% of tumors less than 1 cm and 97% less than 1.5 cm in size. Type II GNETs are also multiple and less than 2 cm [9]. Type III GNETs are sporadic, isolated, and larger (>2 cm), with a mean of 5 cm in size, located at the body/fundus surrounded by normal (nonathrophic) mucosa [9]. There are currently no reports in the literature of a type III GNET with large dimensions as the one presented. Type IV GNETs are typically larger in size: Bordi et al. [16] presented a case of a type IV GNET measuring 16 cm, representing one of the largest tumor sizes ever reported.

Initial evaluation of patients with a suspected GNET should include a serum chromogranin A level. It is elevated in approximately 80% of patients with neuroendocrine tumors regardless of the site [17]. Elevations in Chromogranin A is frequently elevated in Type I to III but normal in type IV, likely related to the poorly differentiated nature of this tumor [10]. When the value is less than twice the upper normal range of baseline, Chromogranin A is a predictive factor for overall survival [18]. Measurement of gastrin levels is also recommended due to the association of types I and II and hypergastrinemia. Upper endoscopy represents an essential diagnostic tool as the majorities of GNETs are found on endoscopic examinations due to dyspeptic symptoms or anemia, and types I and II commonly present as polypoid lesions amenable to endoscopic resection. Biopsies of the lesions should be taken as well as biopsies from normal appearing stomach to determine the presence of atrophic gastritis [19]. Endoscopic ultrasound (EUS) is recommended in lesions greater than 2 cm to assess depth of invasion [20]. An Octreotide scan can be a useful adjunct in the diagnosis of gastric neuroendocrine tumors. FDG-PET scan is more sensitive in the detection of G3 NETs when compared with G1 or G2 tumors due to the highly metabolically active G3 NETs [21].

Endoscopic resection and surveillance is the treatment of choice in the majority of cases of type 1 GNET. Lesions less than one centimeter in size should be observed and carefully followed with annual endoscopy. Lesions greater than one centimeter in size are amenable to endoscopic resection (polypectomy, endoscopic mucosal resection) only if the lesion is confined to the mucosa or submucosa [21]. Gastric resection for a type I and type II GNET is recommended in patients with multifocal lesions (>4–6 lesions) or when invasive or recurrent disease is present [21]. Since Type III and IV GNETs behave similarly to gastric adenocarcinomas, with a high incidence of invasion beyond the submucosa and distant metastasis on presentation (50–100%), radical resection is recommended [21]. Chemotherapy and radiation therapy is indicated in advanced disease and as a palliative option on type IV GNET. Combination chemotherapy regimens are most commonly administered since single-agent chemotherapy has low response rates. The most common agents used are etoposide, cisplatin (CDDP), and carboplatin along with somatostatin analogues octreotide and pasireotide. Somatostatin analogues have shown a role in hormonal symptom control and tumor suppression [10].

In general, type I and II GNETs have good overall prognosis secondary to their benign biology with tumor-related mortality ranging from 0.5 to 5% [10]. Close surveillance is recommended for potential recurrence and malignant transformation. Type III tumor-related 5 year mortality is between 25 and 30% for well-differentiated and 75–87% for poorly-differentiated tumors [10]. Type IV GNETs have a mortality of 100% in 5 years and a mean survival of 6.5–14 months after diagnosis [10]. This case of GNET is notable for the size of the tumor. In review of the recent literature, the majority of cases discussed have an average diameter of 4 cm, in comparison with this case which was found to be 10 cm in greatest dimension [22–24].

4. Conclusion

The incidence of gastric neuroendocrine tumors has been increasing during the last decade, underscoring the need to improve our understanding of their biology and behavior. If a GNET is identified histologically, patient outcomes depend on appropriate determination of tumor biology and subsequent choice of treatment, surgical, medical, or both. As with all malignant neoplasms, treatment of GNETs must have a multi-faceted and team-based approach, utilizing multiple modalities to improve patient outcomes.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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Ethical approval

Not requested.

Consent

Written informed consent was obtained from the patient.Written informed consent was obtained from the patient.

Author contribution

All authors have been contributors.

Guarantors

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