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Case report

Advanced gastric neuroendocrine tumor with hepatic metastasis - A case report

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ABSTRACT

Introduction and importance: Gastric neuroendocrine tumors (NETs) are rare neoplasms that originate from enterochromaffin cells in the gastric mucosa and pose a diagnostic dilemma due to their non-specific presentation.

Case presentation: We present a 79-year-old woman, who came with complaints of abdominal pain associated with loss of pain and appetite. Although on the first look multiple differentials could be listed, upon complete evaluation she was diagnosed to have type III Gastric NET. Histopathology and immunohistochemistry allowed diagnostic confirmation of the disease along with strong clinical suspicion. The patient however succumbed to the illness due to advanced disease and lack of established protocol for its management.

Clinical discussion: The treatment of Gastric NETs primarily involves surgical resection of the tumor and is especially helpful in type I and II cases. For advanced metastatic type III NETs, lines of therapy have not been established although surgical resection can be done if the majority (~90 %) of the tumor is resectable. Patients should be given a choice in decision making and newer drug therapies should always be considered.

Conclusion: Since gastric NETs are a rarer cause of abdominal pain, it can often be overlooked in favor of other, more common differentials. One should be aware of this disease and the newer diagnostic methods to have any sort of clinical suspicion when presented with such a scenario. The management of the condition although not been established, novel therapies should be considered if the tumor is not resectable.

1. Introduction

Gastric Neuroendocrine tumors (NETs) are rare neoplasms arising from the enterochromaffin cells in the gastric mucosa, comprising approximately 8 % of all gastrointestinal NETs [1,2]. The World Health Organisation classified these neuroendocrine tumors histologically into well differentiated low and intermediate grade (G1, G2), and poorly differentiated (G3). This classification (Table 1) is based on mitotic count and Ki67 index [3].

Gastric NETs are broadly divided into Type I, II, and III based on clinical characteristics, pathophysiology, and prognosis. While prognosis of Type I and II are good, type III is similar to gastric adenocarcinoma. Typically, elevated levels of gastrin are seen in Types I and II, although the mechanism of their hypergastrinemia is different. Type III is not known to produce hypergastrinemia or alterations in acid levels, but is sometimes associated with carcinoid syndrome [4,5].

Gastric NETs may be diagnosed incidentally, or as part of the work-up for non-specific abdominal pain, anemia, or upper gastrointestinal bleeding. Type III gastric NETs usually appear endoscopically as solitary lesions, often larger than 2 cm in size and are mostly located in the body or fundus. These tumors commonly present with lymph node involvement at diagnosis and may have already metastasized widely [5]. This

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Table 1
WHO histological grading [3].

	Grade 1	Grade 2	Grade 3
Tumor size (cm)	≤2	>2	Any
Mitoses/10 HPF	<2	2–20	>20
Ki 67 index (%)	<3	3–20	>20
Differentiation	Well	Well	Well/poorly

article was written according to the SCARE guidelines [6].

2. Case presentation

A 79-year-old lady presented with complaints of upper abdominal pain and loss of weight and appetite for the last 6 months. The pain was associated with nausea and occasional vomiting, relieved with oral analgesics. She reported reduced appetite with early satiety, which resulted in a weight loss of approximately 20 kg over the last 6 months. She denied fever, jaundice, melaena and alteration of bowel habits. She had an open cholecystectomy 20 years back. Family history was unremarkable for any familial syndromes.

On examination, she had pallor, epigastric tenderness, with the liver palpable up to 3 cm below the right costal margin. The investigations revealed moderate anemia, with elevated levels of liver enzymes and protein/albumin ratio. Infection markers for hepatitis were negative and renal function was preserved.

Abdominal ultrasonography revealed an enlarged liver with multiple heterogeneous space occupying lesions in the liver parenchyma. Triphasic contrast enhanced computed tomography revealed (Fig. 1) a mass in the stomach with evidence of metastasis to liver. Upper gastrointestinal endoscopy (Fig. 2) showed lobulo-proliferative mass in the proximal body along the greater curvature of the stomach. Few ulcers within friable erythematous mucosa seen. Overall this was suggesting malignant disease. Endoscopic biopsy revealed (Fig. 3) bits of gastric mucosa with normal gastric glands, underneath which there were nests and lobules of small monomorphic cells with rosette formation. Individual cells had scanty eosinophilic granular cytoplasm and stippled nuclear chromatin. Mitotic count was <2/10 hpf. Immunohistochemistry (Fig. 4) revealed that synaptophysin was positive, whereas cytokeratin and LCA (CD45) were negative suggestive of gastric well-differentiated neuroendocrine tumor. At the time of diagnosis the patient had a limited performance status (WHO grade 3). She was started on Imatinib therapy. However, she developed gram negative sepsis and succumbed to the illness after 2 months.

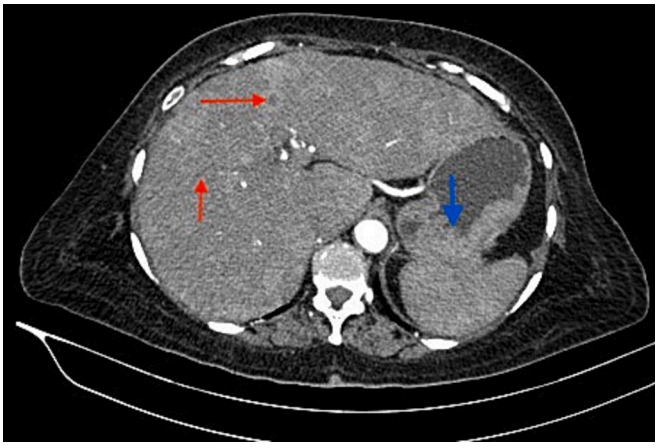

Fig. 1. Triphasic contrast enhanced computed tomography showing a gastric lesion (blue arow) with evidence of metastasis to liver (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

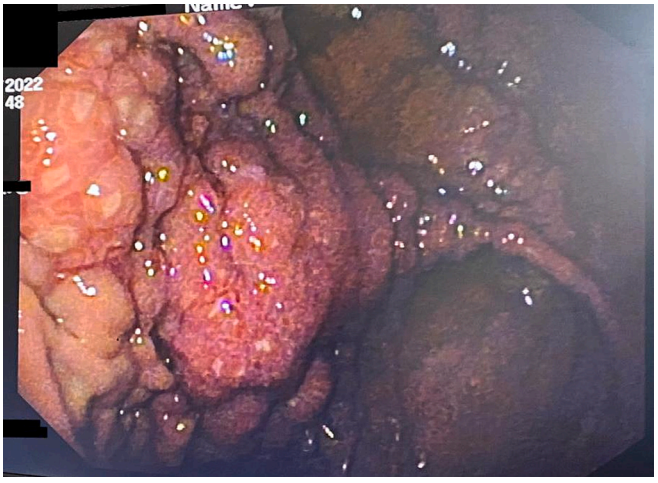

Fig. 2. Endoscopic image showing lobulo-proliferative mass in the proximal body along the greater curvature of the stomach.

3. Discussion

The patient's presentation aligns with the non-specific nature of Gastric NETs and enabled detection of metastatic disease prior to endoscopic visualization. The Immunohistochemistry with synaptophysin, chromogranin A, and cytokeratin aides in the confirmation of NETs. G3 subtypes are highly aggressive and needs to be distinguished from other NETs. Above case provides us with an example of advanced disease with evidence of metastasis at first presentation. The slow and indolent course of Gastric NETs often poses a significant challenge to the diagnosis and management.

Type III Gastric NETs should be managed aggressively, akin to that of gastric adenocarcinomas. Partial gastrectomy and lymph node dissection should be done, however selected lesions (<1–2 cm) can be treated endoscopically with Endoscopic mucosal resection (EMR) or Endoscopic submucosal dissection [4]. Metastatic liver disease from gastric NETs however, is managed using multiple treatment modalities and should be individualized and undertaken as part of a multidisciplinary team approach [4].

Novel approaches to management of metastatic disease include the addition of growth factor receptor targeted therapies like bevacizumab, imatinib or targeted radiotherapy [7,8]. The choice of Imatinib therapy for this patient was based on the fact that it shows dose and time dependent cytotoxic effect, with ability for in-vitro growth inhibitory activity for NETs [8]. Although synthetic somatostatin analogues (SSAs) can be given and are known to be successful for metastatic disease, with absence of carcinoid symptoms, it did not warrant therapy [9]. Aggressive surgical resection of liver metastasis showed a 5-year survival rate of 80 % when compared to 30 % when left untreated. Surgery however, is contraindicated in diffuse bilobar involvement [8,10].

4. Conclusion

Gastric NETs are an uncommon cause of abdominal pain, and are easy to miss if not clinically suspected. Thorough investigation and subtyping is necessary for choosing appropriate mode of management. Multiple lines of therapy have been proposed, albeit only few seem to be effective for metastatic disease, with enrollment in clinical trials encouraged.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this

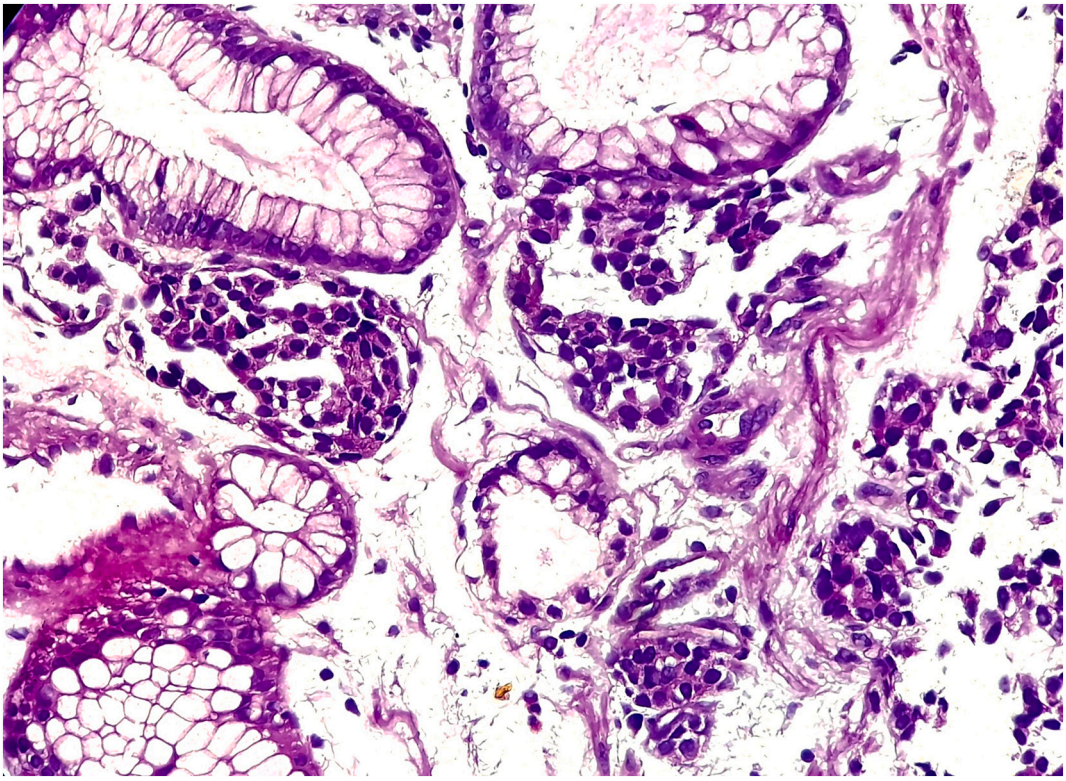

Fig. 3. Histopathology image showing nests and lobules of small monomorphic cells with rosette formation. Individual cells with scanty eosinophilic granular cytoplasm and stippled nuclear chromatin.

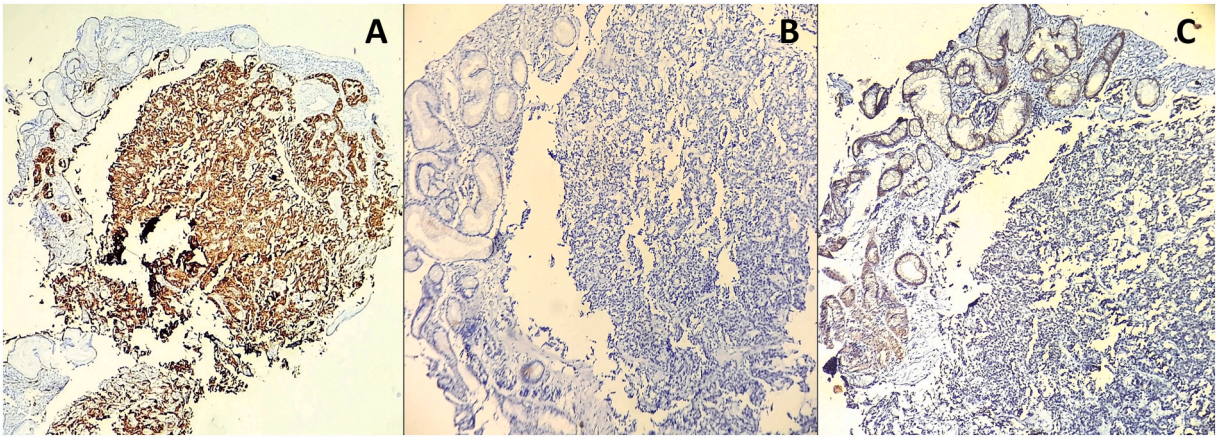

Fig. 4. Immunohistochemistry showing synaptophysin positive (A), cytokeratin (B) and LCA (C) negative suggestive of gastric well-differentiated neuroendocrine tumor.

journal on request.

Ethical approval

Not required in our institution to publish anonymous case reports.

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Author contribution

Lakshmi Deepak Bethineedi: Acquisition of the data, drafting the manuscript, final approval of the version to be submitted.

Roger B Rathna: Acquisition of the data, drafting the manuscript, final approval of the version to be submitted.

Jyotirmoy Biswas: Drafting the manuscript, final approval of the version to be submitted.

Arkadeep Dhali: Conception, design of the study, acquisition of the data, drafting the manuscript, final approval of the version to be submitted.

Sukanta Ray: Conception, design of the study, acquisition of the data, drafting the manuscript, final approval of the version to be submitted.

Gopal Krishna Dhali: Acquisition of the data, final approval of the version to be submitted.

Guarantor

Prof. Gopal Krishna Dhali will act as guarantor of the article.

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Provenance and peer review

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Declaration of competing interest

None.

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