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Neuroendocrine Tumor of Small Intestine, a Diagnostic Challenge

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Abstract

Incidence of neuroendocrine tumors (NET) has significantly increased in the past three decades. In the small intestine, NET are the most frequent tumors, even more frequent than adenocarcinomas. Due to atypical presentations and late symptoms, NET in the small intestine frequently represent a diagnostic challenge. It is important to take these tumors into consideration in differential diagnosis of gastrointestinal neoplasms. Surgeons, oncologists, endocrinologists, and gastroenterologists should understand the disease characteristics and management alternatives. This document aims to review the key points of NET and main diagnostic tools. We present the case of a 50-year-old male who presented lower gastrointestinal bleeding. Imaging and endoscopic studies showed no conclusive findings. A capsule endoscopy showed multiple ulcered lesions with neoplastic aspect in the distal jejune. Due to the multifocal nature of the lesions, clinicians suspected NET-associated digestive bleeding. The patient underwent exploratory laparoscopy with ileectomy and radical abdominal lymphadenectomy. Histopathologic examination confirmed the suspected diagnosis of NET. This case reflects the complexity of diagnostic approach and differential diagnoses for these tumors.

Keywords

Neuroendocrine Tumor, Carcinoid Tumor, Intestinal Cancer, Diagnostic Laparoscopy, Case Report

1. Introduction

Neuroendocrine tumors (NET) are malignant epithelial neoplasms that arise from enterochromaffin cells with neuroendocrine differentiation. These tumors may release vasoactive peptides, such as serotonin, tachykinins, and bradykinins.

The NET may present in different body areas, and they were once considered infrequent in the small intestine. In the past 35 years, however, small intestine NET incidence has increased from 300% - 500%, and they now represent 37% of small intestine tumors [1]. Such an increase is probably due to improved detection of new cases thanks to better imaging techniques and a higher frequency of endoscopic procedures [2].

Intestinal neuroendocrine tumors (iNET) may involve the jejunum, ileum, appendix, and proximal colon. Of all iNET, 89% are present in the ileum, commonly 100 cm from the ileocecal valve. Peculiarly, iNET present as multiple tumors in 30% - 56% of cases, and 50% of iNET have metastasis at diagnosis. Despite the more aggressive presentation, patients with metastatic iNET who receive timely surgical treatment have good long-term survival, reaching more than 50% at 5 years [2] [3].

Usually, diagnosis of NET is delayed due to their small size and unspecific symptoms. Manifestations include abdominal pain, gastrointestinal bleeding, and intestinal obstruction, as well as symptoms secondary to metastasis, carcinoid syndrome, or anemia [2] [4]. Variable presentation leads clinicians to initially consider other diagnoses.

Diagnostic aids, such as endoscopy, computed tomography (CT), magnetic resonance image, and capsule endoscopy, are essential in determining the NET location. Locating the tumor may be challenging even with those methods and may require exploratory surgery. Surgery may be curative, and liver metastasis resection may improve survival [5].

2. Case Presentation

A 50-year-old male patient came to the emergency room for consultation due to hematochezia in the previous four days. The melena was accompanied by non-irradiated, 6/10-intensity pain in the right hypochondrium. Systems review did not reveal constitutional symptoms, functional class deterioration, or bowel habit changes. Past medical and social history included overweightness and alcohol consumption every week. Family history included pancreatic cancer in his maternal grand-mother.

General examination showed vital signs within normal ranges, generalized pallor, and dry mouth. Deep palpation of the abdomen revealed pain in the left flank and left hypochondrium, with no masses or signs of peritoneal irritation. Due to lower digestive bleeding, the patient received intravenous hydration and proton-pump inhibitor.

Laboratory tests showed normocytic anemia with hemoglobin at 7.7 mg/dl (normal range: 13.5 - 18 mg/dl), mean corpuscular volume at 87.5 femtoliter (normal range: 79 - 101 ft), and hematocrit at 22.3% (normal range: 42% - 52%). An upper endoscopy revealed a 2-cm hiatal hernia, antral and corporal erythematous gastropathy, as well as urease-positive erythematous duodenitis. A colonoscopy reported abundant digested blood that impeded view of the mucous

layer. An ileocolonoscopy showed no lesions or active bleeding. Given the lack of conclusive findings, a capsule endoscopy was performed. This exam revealed multiple 1 - 1.5-cm large, ulcered masses with neoplastic aspect at the jejunum/proximal ileum (**Figure 1**). Secondary neoplastic involvement of the thorax was ruled-out. A CT enterography evidenced segmentary thickening of the small intestine walls with no enlarged lymph nodes. A retrograde enteroscopy attempted to obtain a sample for histopathological examination, but it was not possible to reach the lesions. Blood chromogranin level was 240.75 ng/l (reference value: <100 ng/l).

Differential diagnoses of the intestinal masses included NET, lymphoma, gastrointestinal sarcoma, and intestine adenocarcinoma. Due to the gastrointestinal bleeding at presentation, the patient underwent an exploratory laparoscopy. This procedure evidenced multiple nodules in an 80-cm segment of the proximal ileum. All the intestine was then explored with video-assisted manual palpation. It identified approximately 18 whitish lesions involving the serosa. These lesions were 3 - 20 mm in diameter and produced no apparent stenotic effect. The mesentery of the involved segment had multiple visible nodes as large as 2 cm (**Figures 2(a)-(c)**).

Histopathological examination of the surgically removed section revealed grade I, well-differentiated NET. The biggest lesion was 1.2 cm, extending from the muscularis propria to the subserosa, with vascular and perineural invasion. Surgical margins were free of tumoral involvement. The mitotic count showed <2 mitoses per 2 mm^2.

Of 22 removed nodes, 8 had tumoral involvement. Additional immunohistochemical studies found positive synaptophysin, chromogranin, the cytokeratin monoclonal antibodies AE1/AE3, and the CD56 antigen. There were tumoral cells in the blood vessels with positive D2-40, CD31, and CDX2. The PHH3 showed <2 mitoses per 2 mm^2 and the Ki67 proliferative index was <3%. With this information, the tumor was classified as a well-differentiated, stage III, jejunal NET, pT3N1M0.

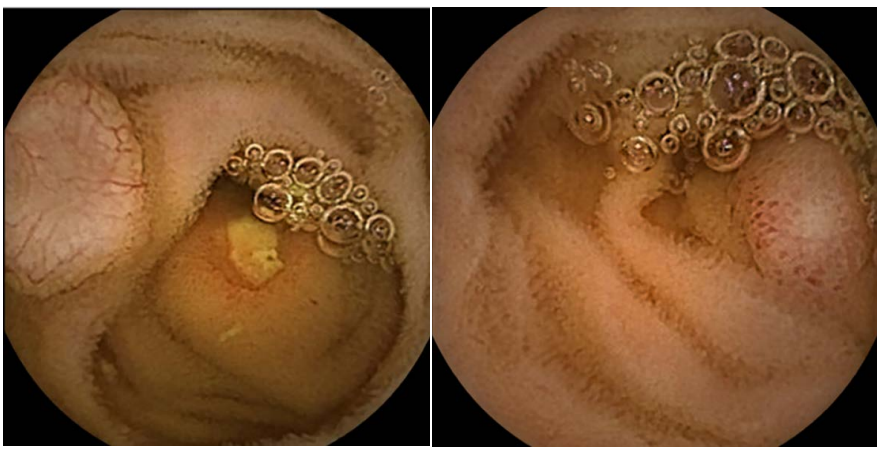
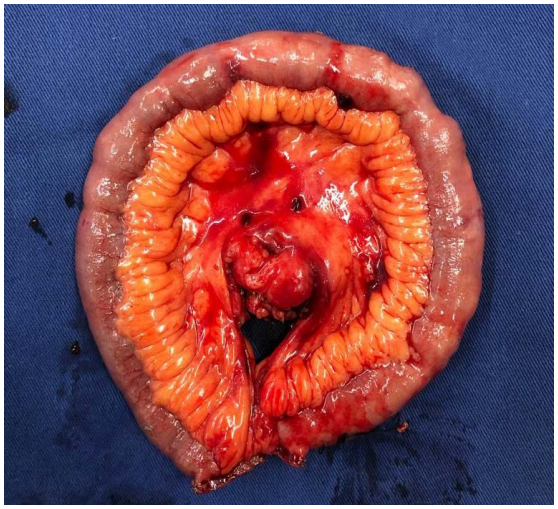
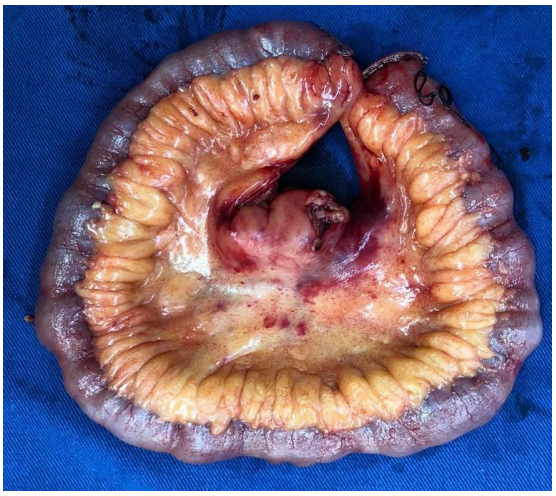


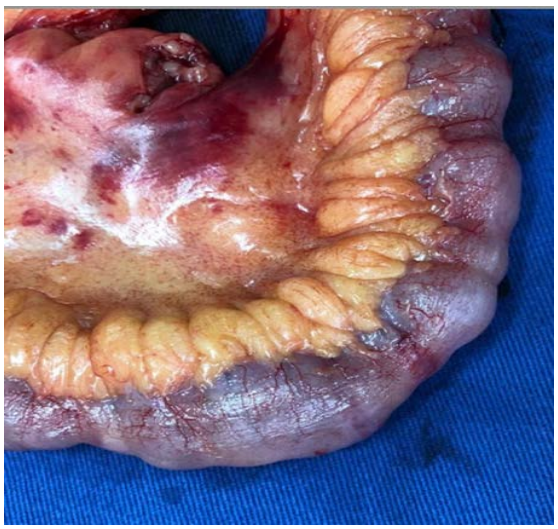
Figure 1. Capsule endoscopy imaging shows masses in jejunum/proximal ileum.



(a)



(b)



(c)

Figure 2. (a) Small intestine specimen; (b) Nodularity in small intestine; (c) Enlarged nodes in the mesentery root.

In the post-operative period, the patient had modulated pain with no emesis or respiratory distress. He progressively tolerated oral diet and, on the sixth post-operative day, was discharged from the hospital. At a 6-month follow-up, the patient had continued with adequate evolution.

3. Discussion

It appears that tumors in the small intestine present more frequently in association with 1) Genetic diseases, such as the familial adenomatous polyposis, and Peutz-Jeghers syndrome. 2) Intestinal inflammatory diseases, such as Crohn's disease and celiac disease. Primary tumors of the small intestine, such as adenocarcinomas, NET, leiomyosarcomas, and lymphomas may have an insidious presentation. Unspecific manifestations may include intestinal obstruction, jaundice, bleeding, or abdominal pain when they achieve local infiltration [6].

According to 2019 statistics of the United States National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program [7], less than 5% of gastrointestinal cancers are in the small intestine. Cancers of the small intestine are primarily small bowel adenocarcinoma accounting for 40% of cases and NET which account for another 40%. The remaining 20% is attributed to stromal tumors, sarcomas, and lymphomas [8]. Most of the NETs are in the gastrointestinal (GI) system (55%) or in the bronchopulmonary system (25%). In the GI tract the most common site is the small intestine (45%), rectum (20%), appendix (16%), colon (11%), and stomach (7%) [9]. These tumors can secrete a variety of hormones including serotonin, somatostatin, gastrin and substance P, also Carcinoid tumors exhibit immunoreactivity to chromogranin A [6] [10].

There are several nomenclatures and staging systems for NET, depending on the involved area. No system is standardized in the scientific community. The European Neuroendocrine Tumor Society (ENETS) recommends the World Health Organization (WHO) classification system. The North American Neuroendocrine Tumor Society (NANETS) proposes the American Joint Committee on Cancer (AJCC) staging system, adding basic pathological elements. These include proliferation rate, extension, and immunohistochemical markers [11]. **Table 1** and **Table 2** present NET nomenclature systems.

Table 1. Gastroenteropancreatic NET nomenclature system.

Grade	ENETS, 2010	WHO, 2010
Low grade	Grade 1 NET (G1)	G1 Neuroendocrine neoplasm
Intermediate grade	Grade 2 NET (G2)	G2 Neuroendocrine neoplasm
High grade	Grade 3 neuroendocrine carcinoma (G3), small-cell carcinoma Grade 3 neuroendocrine carcinoma (G3), neuroendocrine large-cell carcinoma	Grade 3 neuroendocrine carcinoma, small-cell carcinoma Grade 3 neuroendocrine carcinoma, neuroendocrine large-cell carcinoma

Kulke, M. H., Anthony, L. B., Bushnell, D. L., *et al.* & North American Neuroendocrine Tumor Society (NANETS), 2010 [13].

Table 2. Small intestine NET staging AJCC 2018.

Stage	Description
Primary tumor	
TX	Not classifiable.
T0	No evidence of primary tumor.
T1	Tumor invades lamina propria or submucosa and tumor size ≤ 1 cm.
T2	Tumor invades muscularis propria or tumor size > 1 cm.
T3	Tumor invades muscularis propria and subserosa, no invasion of serosa.
T4	Tumor invades visceral peritoneum (serosa) or invades other organs.
Lymph nodes	
NX	Regional lymph node involvement cannot be assessed.
N0	No regional lymph node involvement.
N1	Regional lymph node involvement <12 nodes.
N2	Large mesenteric tumor (>2 cm) and/or ≥ 12 nodal deposits (especially those encasing the superior mesenteric vessels).
Metastasis	
M0	No distant metastasis.
M1	Distant metastasis.
M1a	Metastasis confined to liver.
M1b	Metastasis in at least one extrahepatic site.
M1c	Hepatic and extrahepatic metastases.
Stage	
I	T1, N0, M0.
II	T2/T3, N0, M0.
III	T4, N0, M0.
	Any T, N1/N2, M0.
IV	Any T, any N, M1.
Tm	Multiple tumors.

Amin MB, Edge SB, Greene F, *et al.* (2017) AJCC Cancer Staging Manual (ed 8). New York, NY: Springer.

The iNET frequently arise in the distal ileum, less than 80 cm from the ileocecal valve. The majority of these are carcinoids of serotonin-producing enterochromaffin cells [12].

By the former ENETS classification, the clinical case presented in this paper was a low-grade, well-differentiated iNET. This type of NET may release hormones, such as serotonin, gastrin, and P-substance, as well as serum markers [12].

Chromogranin A (CgA) is present in endocrine, neuroendocrine, and immune cells. The CgA may be segmented in biologically active peptides, such as vasostatin and pancreastatin. Because of its sensitivity, the CgA is the most-used marker for NETs and is suitable for NET diagnosis and follow-up. A study published in Frontiers in Oncology retrospectively reviewed CgA levels in patients with grade 1 and grade 2 NET. The study showed that CgA levels had a diagnostic sensitivity of 73% for secreting tumors and 45% for non-secreting tumors ($p < 0.004$). The cutoff value in that study was 130 ng/ml [13]. The patient in this

clinical case presented elevated chromogranin.

As with this clinical case, 60% of NET do not present clinical manifestations. Conversely, as many as 21% of well-differentiated (G1) and 30% of moderately differentiated NET debut with metastasis and unknown primary location [14]. Like in this clinical case, where 18 lesions were macroscopically identified, multiple tumors present in 15.6% of cases of stage I-IIIA NET [15].

Imaging studies for iNET detection are anatomical and functional. Anatomical studies include CT scan which is useful for staging and operative planning. The sensitivity ranges from 7% to 38% but can be improved to 82% if there are mesenteric lymphadenopathy//fibrosis as evidence of small bowel primary tumor. CT enteroclysis has better sensitivity: 50% - 85% [16]. Abdominal CT may show mesenteric tumors with attachments to the bowel, lymphadenopathies, and liver metastases. The masses, however, may not be visible due to their extraluminal location. Occasionally, these anatomical imaging techniques provide little preoperative visualization. Such was the situation in the present clinical case.

Functional studies include ^{68}Ga-DOTATATE PET/CT scanning. The radiomarked somatostatin analogue is useful to identify the primary tumor. It is also valuable to detect metastases, mainly hepatic, that may be treated with somatostatin analogues, interventionist radiology, or surgery. Also, this scan has 92% sensitivity and 83% specificity for diagnosis of metastatic node disease [17]. This exam is very effective for identification of well-differentiated, less aggressive NET, due to higher cell-membrane expression of somatostatin receptors (SSTRs) by these tumors. Conversely, FDG PET/CT scan is best for poorly differentiated, more aggressive tumors, with worse prognosis and lower marker intake [18].

Surgery with curative or palliative intention is recommended as the first line of treatment for iNET. Results may be better with a laparotomy, since it allows exploration of all the small intestine by palpation, and it also guarantees appropriate node resection. This clinical case combined that approach with video-assistance, allowing proper exploration and tumor resection [4].

Surgery principles include 1) Complete resection of the primary tumor. Bidigital palpation is necessary to assess all the small intestine, given the high incidence of multifocal tumors. 2) Radical lymphadenectomy of mesenteric nodes. A minimum of 7 nodes includes those in group 1 (peri-intestinal nodes), group 2 (mesenteric nodes), and group 3 (mesenteric root nodes). 3) In case of metastatic liver disease, metastasis resection may be considered [4] [19].

Favorable oncological results in patients with NET depend on tumor location, extent of local/metastatic disease, tumor functional status, and viability of complete tumor resection [20]. Clinicians should recognize the particular manifestations of NET. Timely diagnosis and treatment prevent complications and improve the patient's quality of life.

The case in this paper posed a challenge for the treating medical team. The patient's symptoms were unspecific, and the tumor was hardly visible in routine imaging. Also, obtaining a sample for histopathological examination was not

possible on the first attempt. This case underscores the importance of surgical exploration for iNET diagnosis.

4. Conclusion

This clinical case highlights challenges in the diagnostic approach for iNET. This paper reminds healthcare professionals to more consciously consider this condition among differential diagnoses of small intestine tumors. In case of suspected NET of the small intestine, a diagnostic algorithm should include imaging and endoscopic studies aiming to define the lesions' locations and characteristics. Finally, surgical excision employing oncologic principles followed by a histopathological examination of the surgical specimen is paramount for accurate diagnosis and specific management.

Consent

Written informed consent was obtained from the patient for 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 journal.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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