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CASE REPORT | PATHOLOGY

A Case of Profound Secretory Diarrhea Revealing 2 Primary Neuroendocrine Tumors

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ABSTRACT

Neuroendocrine tumors (NETs) are unusual neoplasms with a diverse spectrum of clinical presentations. There is a lack of literature on cases of 2 primary histologically distinct NETs. We report a case of a 40-year-old man who presented with chronic diarrhea. A colonoscopy was performed which discovered a rectal polyp, with pathology showing a well-differentiated NET. A subsequent somatostatin scan revealed a pancreatic tail mass. Biopsy showed a histologically distinct well-differentiated vasoactive intestinal peptide-producing NET. Given that pancreatic and rectal NETs come from different embryonic origins, the diagnosis of 2 primary NETs presents a unique case.

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous category of neoplasms arising from secretory cells of the neuroendocrine system. They are characterized by an indolent growth rate and the ability to produce various peptide hormones.[1] They are increasingly recognized neoplasms with a rising incidence, partially because of expanding awareness and diagnostic techniques.[2] NETs are classified based on their origin from the embryonic divisions of the alimentary tract. Midgut or hindgut NETs typically originate from enterochromaffin cells of the gut, whereas pancreatic NETs are foregut tumors that specifically arise from the islet cells of Langerhans.[1] According to the most recent WHO classification, NETs are classified into well- or poorly differentiated which relate to low and high grade, respectively.[3] Differentiation refers to the extent that the neoplastic cells resemble their non-neoplastic counterparts, and grade refers to tumor aggressiveness or proliferation. Metastatic potential is estimated using grade, tumor size, and extent of invasion.[3,4] Systems of grading rely on a proliferative rate based on the Ki67 staining index or mitotic rate, and this can provide significant prognostic information.[5] NETs can be classified as functioning or nonfunctioning based on the presence of excess hormone production from the tumor.[3] Approximately two-thirds of all NETs arise from the gastrointestinal system.[2,5,6] Approximately 12%–34% of all NETs originate in the pancreas and 13%–26% in the rectum.[1,2,7,8] A fraction of NETs produce hormonal peptides that cause distinct syndromes, yet are usually clinically silent until late in the disease course.[2] Vasoactive intestinal peptide (VIP)-secreting NETs represent 0.8% of all NETs and can produce a syndrome consisting of watery diarrhea and electrolyte derangements. They are a rare etiology of chronic secretory diarrhea with an incidence of 1/10 million per year.[2,9]

CASE REPORT

A 40-year-old Hispanic man with poorly established medical care presented with complaints of a 1-year history of progressively worsening diarrhea. He reported 10 voluminous, watery bowel movements per day, including nocturnal episodes. He also endorsed diffuse myalgias, nausea, and vomiting. On presentation, he was afebrile with a blood pressure of 104/65 mm Hg and a heart rate of 85 bpm. The physical examination was notable for dry mucous membranes without flushing, and a soft, nondistended abdomen with mild, diffuse tenderness to palpation with normoactive bowel sounds. Laboratory results revealed white blood cell 11,900/μL,

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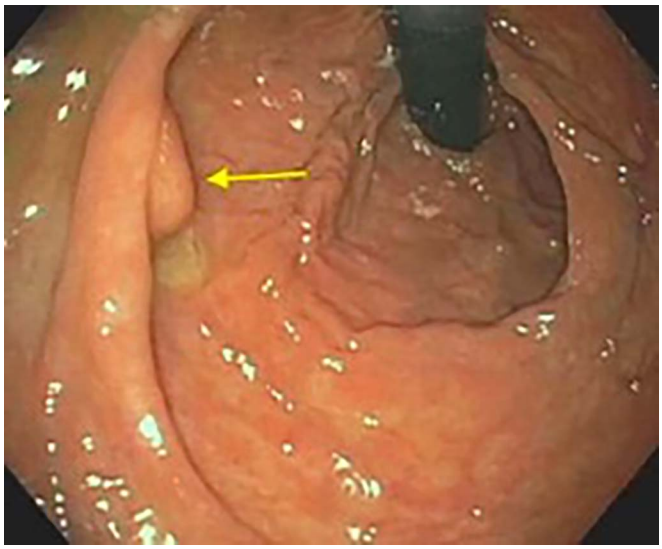

Figure 1. Retroflexion view during colonoscopy revealing an 8-mm semipedunculated polyp (yellow arrow) in the rectum, 5 cm from the rectal verge.

hemoglobin 12.6 g/dL, creatinine 3.58 mg/dL, potassium 1.7 mmol/L, magnesium 2.4 mg/dL, and phosphorus 0.9 mg/dL. He was treated with electrolyte and fluid resuscitation. Infectious work-up was negative for *Clostridioides difficile* toxin A/B, *Giardia*, *Cryptosporidium*, *Entamoeba*, *Salmonella*, *Shigella*, *Campylobacter*, Shiga toxin, *Cytomegalovirus*, and herpes simplex virus polymerase chain reaction. Human immunodeficiency virus serology was discovered to be positive with a CD4+ cell count of 568 cells/mm^3. Stool studies showed a secretory diarrhea pattern, and inflammatory markers were normal. Colonoscopy revealed an 8-mm rectal polyp which was resected with a hot snare (Figure 1).

Pathology was consistent with a low-grade (<2 mitoses/10 hpf, <3% Ki67 index), well-differentiated NET with invasion into the submucosa that stained positive for synaptophysin and negative for chromogranin A (Figure 2). Urinary 5-hydroxyindoleacetic acid and serum chromogranin A were both within normal limits. Rectal endoscopic ultrasound was performed to assess the level of invasion which demonstrated an intramural subepithelial lesion and was staged T3N0 (Figure 3). Colorectal surgery was consulted who resected the lesion; yet, diarrhea and electrolyte derangements persisted. Somatostatin receptor scintigraphy was performed revealing a significant focus of uptake in the left upper abdomen and none within the rectum. An abdominal computed tomography scan revealed a 4.5 × 4.6 × 4.6-cm mass in the tail of the pancreas without evident metastases (Figure 4). Thoracic computed tomography showed no evidence of lung lesions. Serum VIP levels were elevated above 800 pg/mL. He underwent endoscopic ultrasound–guided fine-needle aspiration of the pancreatic tumor, which resulted in a low-grade (<2 mitoses/10 hpf, <3% Ki67 index), well-differentiated NET that stained positive for synaptophysin and positive for chromogranin A (Figure 2). The patient underwent distal pancreatectomy with splenectomy and was started on pancrealipase and octreotide with drastic improvement in diarrhea.

DISCUSSION

The incidence of well-differentiated NETs has been rising in the United States,[2] partially because of improved diagnostic techniques and clinical awareness. With the implementation of screening colonoscopy, the number of patients diagnosed with rectal NETs has been rising in comparison with other NETs.[3] Rectal NETs are most often nonfunctioning and have a metastatic potential of 2% if their size is less than 1 cm.[4] Pancreatic NETs are rare and only account for 1%–2% of pancreatic neoplasms. This type of neoplasm grows slowly but shows a high degree of malignancy.[8] NETs can be classified as functioning or nonfunctioning.[10] Given the high levels of VIP and persistence of symptoms present after his rectal tumor was resected, our patient's pancreatic tumor was classified as functioning, while his rectal one was not. The profuse, watery diarrhea and severe electrolyte disturbances caused by VIP-secreting NETs (VIPomas) can be life-threatening. Fortunately, his diarrhea resolved after the resection of his pancreatic tumor. In our case, the detection of his rectal tumor was incidental because it was not suspected to be related to his presenting symptoms.

Regardless of the primary site, NETs are characterized by a strong propensity to metastasize to the liver.[7] Documented case reports of coincident rectal and pancreatic NETs are few and represent metastatic disease through hematogenous spread through the liver, most commonly confirmed by identical histopathology and staining.[9,11] It is generally accepted that rectal NETs stain negative for chromogranin A and positive for synaptophysin, whereas pancreatic NETs stain positive for both, which is consistent with our case.[12,13] It is further supported by normal levels for chromogranin A, which is typically elevated in metastatic disease.[7] Differences in histopathological architecture and stains, lack of invasion around the rectal polyp, low Ki67 mitotic rate, divergent morphological appearance on biopsy, and lack of liver lesions also support that we encountered a rare case of a primary rectal NET and pancreatic NET simultaneously in the same patient, without evidence of metastasis. The sequence of procedures, in this case, led to the diagnosis of 2 primary NETs. Given that primary pancreatic and rectal NETs have a different embryologic origin (foregut and midgut), this case demonstrates an extremely rare case of 2 primary NETs with low metastatic potential. The goal of this case report is to increase awareness of the possibility of concomitant NETs. Given the rare and indolent nature of NETs, they commonly present as a diagnostic challenge.

DISCLOSURES

Author contributions: AA Thompson wrote the manuscript, reviewed the literature, revised the manuscript for intellectual content, approved the final manuscript, and is the article

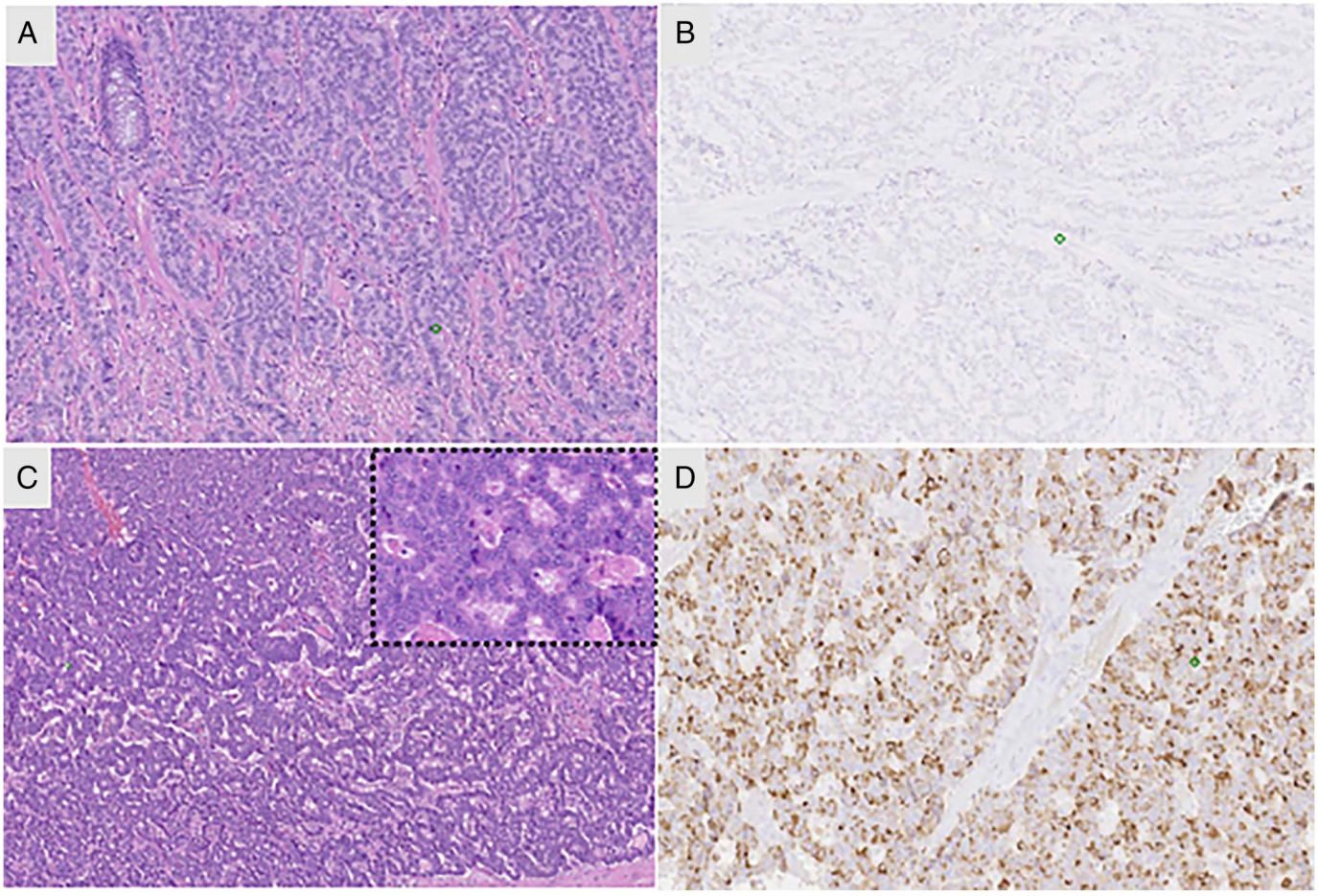

Figure 2. Pathologic findings in the rectum showing (A) cells arranged in trabeculae type architecture with the appearance of cords (hematoxylin and eosin stain, 10× magnification). (B) The rectal tumor cells were negative for chromogranin A (10× magnification). Pathologic finding in the pancreas showing (C) an organoid/nested appearance (hematoxylin and eosin stain, 10× magnification), inset showing cells with round nuclei and eosinophilic cytoplasm (hematoxylin and eosin stain, 40× magnification). (D) The pancreatic tumor cells were positive for chromogranin A (10× magnification).

guarantor. FK Suhail edited the manuscript and reviewed the literature. K. Mirchia edited the manuscript and provided the images. SR Rawlins revised the manuscript for intellectual content and approved the final manuscript.

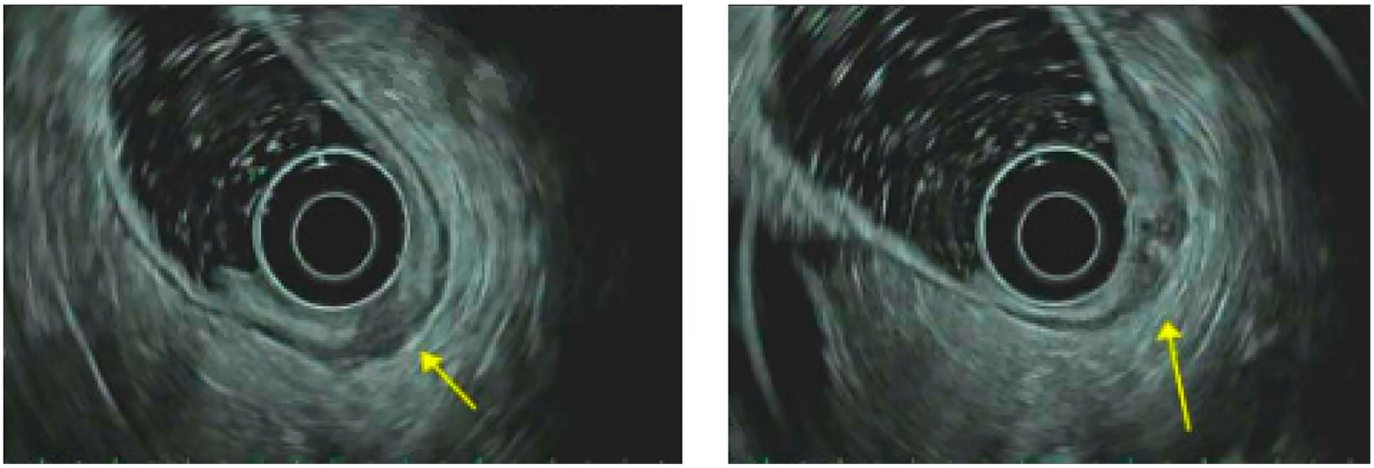

Figure 3. Rectal endoscopic ultrasound of the subepithelial rectal lesion located in the posterior rectal wall, 5 cm from the rectal verge. The lesion was hypoechoic, noncircumferential with irregular endoscopic borders and was noted to be invading the muscularis propria (left, yellow arrow) and perirectal fat (right, yellow arrow), measuring 4 mm in thickness.

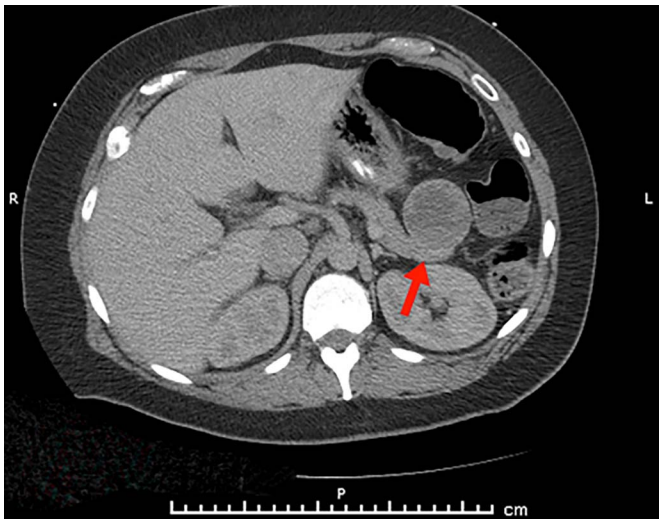

Figure 4. Abdominal noncontrast computed tomography highlighting a 4.5 × 4.6 × 4.6-cm well-circumscribed, heterogeneous pancreatic tail mass (red arrow).

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Informed consent was obtained for this case report.

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