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CASE REPORT

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An unusual cause of chronic diarrhea in a Middle-Aged adult: A diagnostic challenge

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Key Clinical Message

Diarrhea is a common symptom in medical practice that often gets overlooked. This article is intended to increase the awareness of physicians and other providers on a subtle but important cause of chronic diarrhea.

KEYWORDS

chronic diarrhea, medullary thyroid cancer, MEN syndrome, *RET* mutation

1 | INTRODUCTION

Diarrhea is one of the most common gastrointestinal problems with significant healthcare utilization, and chronic diarrhea affects about 5% of the population at any given time.[1] Chronic diarrhea is considered a decrease in stool consistency with increased frequency for more than 4 weeks.[2] Diarrhea is frequently a symptom of an underlying disorder and can be caused by various factors, including viral, bacterial, or parasitic infections, food allergies, inflammatory bowel disease, or medication side effects.[3] The pathophysiology causing diarrhea is the disruption of the normal absorption and secretion of fluids and electrolytes in the small intestine and colon which leads to an increase in the amount of water in the stool and a decrease in the consistency.[4] A thorough medical history, physical examination, and laboratory tests, including stool cultures, are essential for diagnosing the exact etiology. Treatment typically involves addressing the underlying cause and supportive measures such as rehydration, electrolyte replacement, and anti-diarrheal medications.[5]

2 | CASE REPORT

We present a 42 years old Caucasian man residing in the United States who was referred to the gastroenterology clinic for more than 6 months of persistent diarrhea. He reported about eight to ten loose bowel movements a day but no reported weight loss with diarrhea. He reported no constitutional symptoms and took no prescription medications. He had tried loperamide over the counter without

any benefit. Initial workup was negative for fecal leukocytes, ova/parasites, clostridium difficile, escherichia coli, shiga toxin, campylobacter, giardia, cryptosporidium, and stool culture. Stool pancreatic elastase and fecal calprotectin were in the reference range.

Additional blood analysis noted no abnormality in complete blood count or thyroid function test but increased creatinine to 1.37 with normal glomerular filtration rate (>60 mL/min/1.73 sq meter). Endoscopic gastroduodenoscopy showed prepyloric erosions and grade B erosive esophagitis. A stomach biopsy was negative for helicobacter pylori, and a small bowel biopsy was negative for celiac sprue. Colonoscopy revealed no abnormal findings, and random biopsies revealed no evidence of microscopic colitis. Without any identifiable cause, the patient was advised to continue loperamide as needed. Three months later, he noticed a small swelling in his left neck, and computerized tomography (CT) of his neck confirmed bilateral cervical adenopathy extending through the thoracic inlet into the upper mediastinum. A core needle biopsy of the neck lymph node revealed infiltrating nests of malignant cells. The individual tumor cells had enlarged nuclei with a surrounding moderate cytoplasm. Individual cell necrosis was present, along with mitotic figures. The tumor cells were positive for synaptophysin, chromogranin, and TTF1(thyroid transcription factor 1), positive for Ki-67 in 5% of nuclei (Figure 1), and negative for p40 and p16. The final pathology was determined as an atypical carcinoid tumor (neuroendocrine tumor displaying 2–10 mitoses per 2 mm^2 or foci of necrosis). Positron emission tomography (PET) showed bilateral uptake in supraclavicular lymph nodes with a standard value unit (SUV) uptake of 2.9. Additional findings included bilateral upper neck lymph nodes (SUV of 2.2), bilateral lower-level neck lymph nodes (SUV of 3), bilateral upper mediastinal adenopathy (4.2 SUV), and pre-tracheal adenopathy (3.4 SUV) (Figure 2). A focal area of increased uptake in left ischium/acetabulum (SUV 2.9) is consistent with metastatic bone involvement.

Further workup included a serotonin level of 83 (56–244 ng/mL), chromogranin A of 392 (less than 311 NG/mL), and a 24-hour urinary 5-Hydroxyindoleacetic Acid

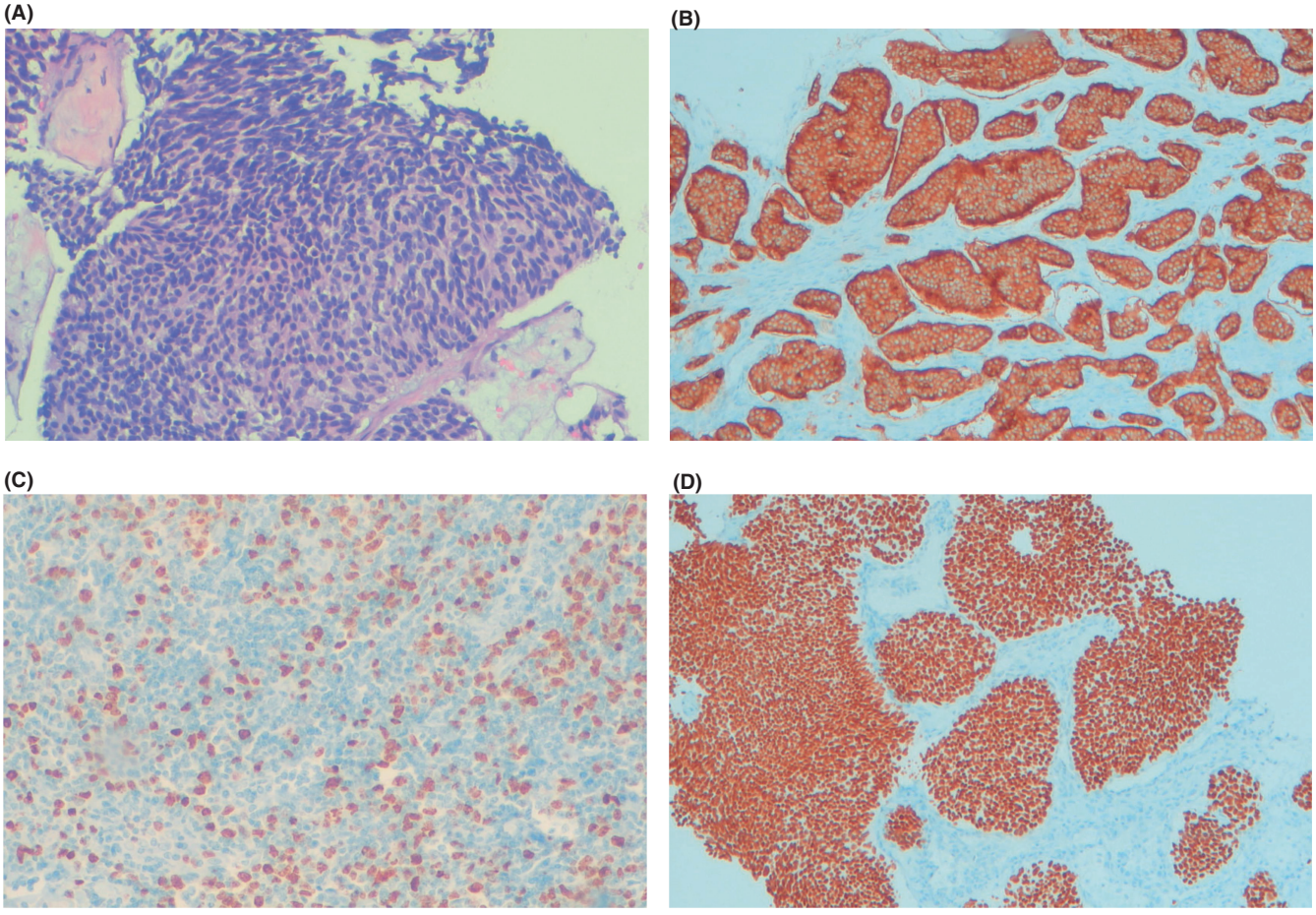

FIGURE 1 (A) Sheets of tumor cells seen with hematoxylin and eosin staining under 10x magnification. (B) Cytoplasmic tumor cell staining with synaptophysin under 10×magnification. (C) Ki-67 staining was noted in approximately 5% of tumor cells under 5×magnification. (D) Intense nuclear TTF1 staining was noted in the tumor cells under 5×magnification.

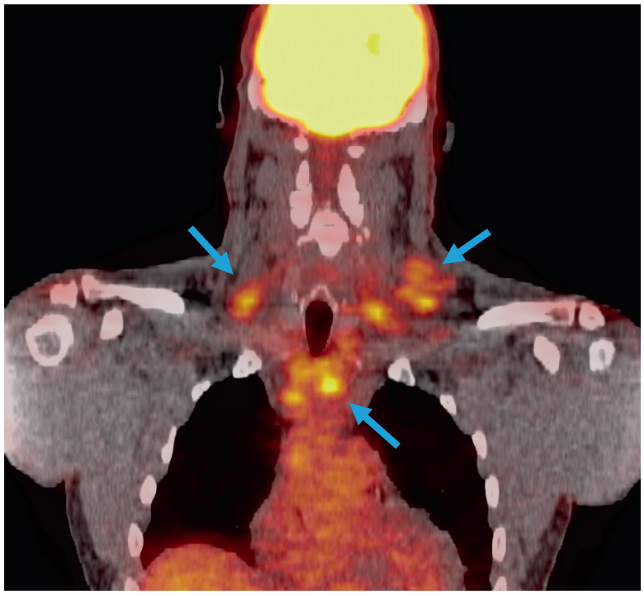

FIGURE 2 Positron emission tomography showing FDG avid (blue arrows) left lower neck, bilateral supraclavicular, and upper mediastinal lymph nodes.

of 3.6 (less than 6.0 mg/24 h). Serum cortisol, gastrin, plasma metanephrines, and vasoactive intestinal peptide levels were within the reference range. He started subcutaneous octreotide injection but noted no change in his diarrhea; rather started noticing frequent night sweats and weight loss. Follow-up Gallium 68 Dotatate PET scan showed persistent multiple dotatate avid bilateral cervical nodes, upper mediastinal conglomerate nodes at bilateral paratracheal/thoracic inlet regions, and several osseous lesions consistent with metastatic neuroendocrine cancer. Since his clinical presentation was atypical for carcinoid syndrome, we further investigated with a CEA (Carcinoembryonic antigen) level and calcitonin. Both CEA and calcitonin were elevated to 236 (<2.5 ng/mL) and 6400 (<10 pg/mL), respectively, raising the concern for medullary thyroid cancer, although no evidence of thyroid nodule was noted in the PET scan. Ultrasound thyroid revealed a suspicious small left thyroid nodule and bilateral cervical lymph nodes. A repeat biopsy of the left lymph node and immunohistochemical analysis confirmed patchy positivity of calcitonin in the tumor cells, thereby confirming metastatic medullary thyroid carcinoma. He was seen at a tertiary care cancer clinic and eventually was enrolled in a clinical trial to receive a *RET*-directed targeted therapy upon detection of *RET* (rearranged during transfection) *M918T* mutation in the tumor specimen. His diarrhea and diaphoresis significantly improved in 1 week after starting therapy. Genetic testing did not reveal a germline mutation in the *RET* gene, concluding a sporadic medullary thyroid cancer diagnosis.

3 | DISCUSSION

Medullary thyroid cancers (MTC) originate from the parafollicular cells, also called the C-cells of the thyroid gland. MTC consists of approximately 1%–2% of thyroid cancers in the United States, with the incidence of sporadic medullary thyroid cancer peaking in the fifth or sixth decade of life.[6] About 80% of these cancers are sporadic, with the remaining 20% hereditary. Hereditary MTC can be isolated or part of the multiple endocrine neoplasia (MEN) syndromes.[7] MTC associated with MEN syndrome peaks around the second or third decade of life. C-cells of the thyroid gland secrete calcitonin; therefore, elevated serum calcitonin is a good indicator for MTC with high sensitivity and specificity.[8] Other markers which can aid in diagnosis include CEA and chromogranin A. There are rare cases of serum calcitonin-negative MTC. MTC often involves the upper portions of both thyroid lobes because the C-cells are predominantly found in the upper lobe of the thyroid gland.[9]

Patients with MTC predominantly present with a thyroid nodule in the upper portion of the thyroid gland; about 70% will have cervical lymphadenopathy, and patients with T4 tumors and node-positive disease after surgery predict a higher chance of recurrence.[10] About 5%–10% of patients will have metastatic disease at the time of presentation, commonly involving the liver, lung, bone, skin, and brain.[11] Rarely patients present with diarrhea and flushing from very high calcitonin levels, and our patient presented only with isolated diarrhea.

Fine needle aspiration of the thyroid nodule is an accurate method for diagnosis, but sometimes the diagnosis can be challenging due to the morphological heterogeneity of this tumor,[12] especially when the tissue sample is obtained outside the thyroid gland, like in our case. Although calcitonin levels have high sensitivity, routine calcitonin screening is controversial due to the risk of false positivity but can add value in patients with multinodular goiter.[13] Other markers, such as CEA and chromogranin, should be cautiously evaluated as they may be elevated in other malignancies. Postoperative calcitonin and CEA doubling time provide a sensitive marker for disease progression.

Neck ultrasound or neck CT is helpful in staging the disease. Gallium 68 Dotatate PET/CT can identify smaller lesions and is helpful in patients with high calcitonin levels,[14] like our patient, as we identified new bone lesions in the PET/CT. The pathological analysis is the gold standard for diagnosis with positive immunohistochemical expression (calcitonin, chromogranin, synaptophysin, CEA, and TTF1).[15] The positivity in chromogranin and synaptophysin can lead to an alternative

diagnosis, especially in diseases outside the thyroid, as seen in our patient. Approximately 50%–60% of MTCs harbor a somatic *RET* mutation, particularly the *M918T* mutation, and it is associated with an aggressive clinical course.[15] In patients with germline *RET* mutation, it is recommended to screen for hyperparathyroidism and pheochromocytoma.

For locally advanced and metastatic MTC, chemotherapy and radiation have been largely ineffective. There is no role for radioactive iodine treatment or thyroid-stimulating hormone suppression. Tyrosine kinase inhibitors (TKI) like vandetanib have some promising outcomes in progression-free survival compared to placebo.[16] Other multikinase TKIs which has shown responses include cabozantinib and lenvatinib.[17,18] Selpercatinib is an ATP-competitive, highly selective, small-molecule *RET* kinase inhibitor studied in *RET*-mutated MTC. A phase 2 trial studied selpercatinib in patients previously treated with cabozantinib or vandetanib.[19] The results showed an objective response rate of 69%, with 9% having a complete response and 60% of patients with a partial response, which led to the FDA (Food and Drug Administration) approval for this drug. Pralsetinib was studied in a phase 1/2 Arrow trial and eventually was FDA-approved in patients with *RET* mutant MTC patients. Efficacy for advanced or metastatic *RET*-mutant MTC was evaluated in 55 patients who received prior cabozantinib or vandetanib. The ORR was 60% in all patients and 66% in patients with *RET*-mutant MTC who did not receive prior cabozantinib or vandetanib (29 patients).[20] Phase 3 trials are ongoing for selpercatinib and pralsetinib in advanced medullary thyroid cancer patients.

4 | CONCLUSION

Medullary thyroid cancer can present with various symptoms. Diarrhea is a rare symptom of MTC which, when present, could be due to increased secretion of calcitonin and other active peptides by tumor cells.[21] Our patient presented with diarrhea as the primary chief complaint prompting extensive workup, which was negative. Healthcare providers must have malignancies like MTC at the back of their minds while evaluating patients with chronic diarrhea. Early diagnosis of MTC can lead to more effective individualized treatments.

AUTHOR CONTRIBUTIONS

Aswanth Reddy: Writing – original draft; writing – review and editing. **Nkolika Nwankwo:** Writing – original draft. **Arjun Sekar:** Writing – original draft. **Aswini Kumar:** Writing – original draft.

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None.

CONFLICT OF INTEREST STATEMENT

I, Aswanth Reddy, corresponding author, certify that the authors have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Aswanth Reddy, upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent.

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