An Unusual Cause of Chronic Diarrhea in a Young Patient – Diagnostic Challenge

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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 consistent with increased frequency for more than four 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].

Objective

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 particular in a young healthy patient.

Case report

We present a 42 years old man referred to the gastroenterology clinic for more than six months of persistent diarrhea. He reported about 8 to 10 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 negative for fecal leukocyte, 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 but had an increase in creatinine to 1.37 and GFR greater than 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. 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 have 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, positive for Ki-67 in 5% of nuclei, and negative for p40 and p16 (Figure 1). The final pathology was determined as an atypical carcinoid tumor. 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). Focal area of increased uptake in left ischium/acetabulum (SUV 2.9) (Figure 2).

Further workup included a serotonin level of 83 (56-244 ng/mL), chromogranin A 392 (less than 311 NG/mL), and a 24-hour urinary 5-HIAA of 3.6 (less than 6.0 mg/24h). 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 the metastatic neuroendocrine disease. Since his clinical presentation was atypical for carcinoid syndrome, we further investigated with a CEA 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 scans. 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. His diarrhea and diaphoresis significantly improved in one week after starting therapy.

Discussion

Medullary thyroid cancers (MTC) originate from the parafollicular cells, also called the C- cells of the thyroid gland. MTC consists of approximately 1 to 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 neoplasms (MEN) syndromes [7]. MTC associated with MEN syndromes 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 to 10% of patients will have metastatic disease at the time of presentation, commonly involving the liver, lung, bone, skin, and brain [11]. Rarely did 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 carcinoembryonic antigen (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 Computed Tomography (CT) is helpful in staging the disease. Gallium 68 Dotatate PET/CT can identify smaller lesions and 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 and immunohistochemical expression of 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 to 60 % of MTCs harbor a somatic RET mutation,

particularly the M918T mutation, and it's 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 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 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). Phase 3 trials are ongoing for selpercatinib and pralsetinib in advanced medullary thyroid cancer patients.

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. It is important for providers to 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.

Consent

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

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.

Keywords

Diarrhea, medullary thyroid cancer, RET mutation, MEN syndrome

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None

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.

Author contributions

Aswanth Reddy contributed to the preparation of the manuscript, writing the initial draft, and finalizing the final draft. The author has given final approval for the version to be published. The author agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part are appropriately investigated and resolved.

Nkolika Nwankwo contributed to the preparation of the manuscript, writing the initial draft, and finalizing the final draft. The author has given final approval for the version to be published. The author agrees to be

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References

1. Schiller LR, Pardi DS, Sellin JH. Chronic Diarrhea: Diagnosis and Management. Clin Gastroenterol Hepatol. 2017 Feb;15(2):182-193.e3.

2. Burgers K, Lindberg B, Bevis ZJ. Chronic Diarrhea in Adults: Evaluation and Differential Diagnosis. Am Fam Physician. 2020 Apr 15;101(8):472-480.

3. Gómez-Escudero O, Remes-Troche JM. Approach to the adult patient with chronic diarrhea: A literature review. Rev Gastroenterol Mex (Engl Ed). 2021 Oct-Dec;86(4):387-402.

4. Camilleri M, Sellin JH, Barrett KE. Pathophysiology, Evaluation, and Management of Chronic Watery Diarrhea. Gastroenterology. 2017 Feb;152(3):515-532.e2.

5. Thielman NM, Guerrant RL. Clinical practice. Acute infectious diarrhea. N Engl J Med. 2004 Jan 1;350(1):38-47.

6. Wells SA Jr, Asa SL, Dralle H et al. American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015 Jun;25(6):567-610.

7. Roy M, Chen H, Sippel RS. Current understanding and management of medullary thyroid cancer. Oncologist. 2013;18(10):1093-100.

8. Chen H, Sippel RS, O'Dorisio MS et al. North American Neuroendocrine Tumor Society (NANETS). The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. Pancreas. 2010 Aug;39(6):775-83.

9. Thomas CM, Asa SL, Ezzat S et al. Diagnosis and pathologic characteristics of medullary thyroid carcinoma-review of current guidelines. Curr Oncol. 2019 Oct;26(5):338-344.

10. Pellegriti G, Leboulleux S, Baudin E et al. Long-term outcome of medullary thyroid carcinoma in patients with normal postoperative medical imaging. Br J Cancer. 2003 May 19;88(10):1537-42.

11. Pacini F, Castagna MG, Brilli L et al. ESMO Guidelines Working Group. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010 May;21 Suppl 5:v214-9.

12. Pusztaszeri MP, Bongiovanni M, Faquin WC. Update on the cytologic and molecular features of medullary thyroid carcinoma. Adv Anat Pathol. 2014 Jan;21(1):26-35.

13. Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab. 2005 Apr;90(4):2029-34.

14. Tran K, Khan S, Taghizadehasl M et al. Gallium-68 Dotatate PET/CT is superior to other imaging modalities in the detection of medullary carcinoma of the thyroid in the presence of high serum calcitonin. Hell J Nucl Med. 2015 Jan-Apr;18(1):19-24.

15. Ciampi R, Romei C, Ramone T et al. Genetic Landscape of Somatic Mutations in a Large Cohort of Sporadic Medullary Thyroid Carcinomas Studied by Next-Generation Targeted Sequencing. iScience. 2019 Oct 25;20:324-336.

16. Wells SA Jr, Robinson BG, Gagel RF et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012 Jan 10;30(2):134-41. Erratum in: J Clin Oncol. 2013 Aug 20;31(24):3049.

17. Elisei R, Schlumberger MJ, Müller SP et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013 Oct 10;31(29):3639-46. Sep 3. Erratum in: J Clin Oncol. 2014 Jun 10;32(17):1864.

18. Schlumberger M, Jarzab B, Cabanillas ME et al. A Phase II Trial of the Multitargeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer. Clin Cancer Res. 2016 Jan 1;22(1):44-53.

19. Wirth LJ, Sherman E, Robinson B et al. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. N Engl J Med. 2020 Aug 27;383(9):825-835.

20. Subbiah V, Hu MI, Wirth LJ et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. Lancet Diabetes Endocrinol. 2021 Aug;9(8):491-501. doi: 10.1016/S2213-8587(21)00120-0. Epub 2021 Jun 9. Erratum in: Lancet Diabetes Endocrinol. 2021 Oct;9(10):e4.

21.Pais MC, Maia T, Peixoto A et al. Diarrhea as a form of presentation of medullary thyroid carcinoma. Porto Biomed J. 2018 Jul 3;3(3):e18.

Figure legends

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

Figure 2. Positron emission tomography showing FDG avid left lower neck, bilateral supraclavicular, and upper mediastinal lymph nodes.

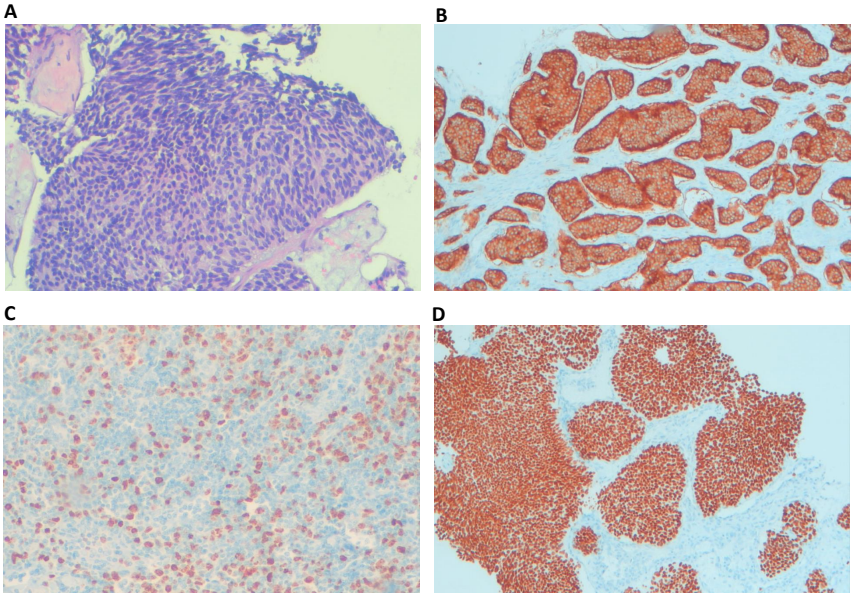

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FIgure 2. PET scan.docx available at https://authorea.com/users/601093/articles/632430-an-unusual-cause-of-chronic-diarrhea-in-a-young-patient-diagnostic-challenge