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Case Series

Diarrhea as an Initial Presentation in Patients with Medullary Thyroid Cancer: Delaying the Diagnosis

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Chronic diarrhea · Medullary thyroid cancer

Abstract
Tumoral secretion of various molecular factors, such as calcitonin (Ct), can cause diarrhea in patients with medullary thyroid cancer (MTC). We report 3 patients (age 26–38 years, serum Ct levels ranging from 2,890 to 52,894 ng/L) with chronic diarrhea, and the diagnosis of MTC was delayed. Diarrheal symptoms improved after thyroid surgery. Two patients with elevated Ct had no diarrhea. The link between tumor humoral secretion and diarrhea is not well established in patients with MTC. Diarrhea is more common in patients with metastatic disease and improves after resection of the tumor. Diarrhea may result from elevated circulating levels of Ct or other substances, such as prostaglandins or serotonin. Other proposed mechanisms include decreased absorption in the colon secondary to gastrointestinal motor disturbances. In conclusion, MTC should be considered when evaluating chronic diarrhea.

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Introduction

Chronic diarrhea is a common presenting symptom among patients referred to gastroenterology (GI) clinics. When routine diagnostic tests do not reveal an etiology for diarrhea, other causes, such as pancreatic endocrine tumor syndromes, gastrinomas, vasoactive intestinal polypeptide-secreting tumors, glucagonomas, somatostatinomas, carcinoid syndrome, systemic mastocytosis, and medullary thyroid cancer (MTC), have to be considered [1, 2]. Because these disorders are an uncommon cause of chronic diarrhea (<1% of all cases), they are not often considered in a differential diagnosis, resulting in considerable delays in treatment. MTC comprises 3–10% of thyroid gland malignancies [3, 4]. Tumoral secretion of calcitonin (Ct), Ct-related peptides, or other molecular factors can cause diarrhea or facial flushing in MTC patients with advanced disease. Furthermore, diarrhea as an initial presentation of MTC is unusual. In patients with chronic diarrhea for whom routine clinical workups yield no diagnosis, the presence of a thyroid nodule should alert the physician to the possibility of MTC. Here, we present a case series of 3 patients with chronic diarrhea due to MTC for whom a timely cancer diagnosis was not made despite evaluation in a GI clinic.

Methods

We present 3 patients with chronic diarrhea, and in these patients, the diagnosis of MTC was delayed. Diarrheal symptoms improved after thyroid surgery. We also present 2 patients with advanced MTC and markedly increased level of serum Ct but with normal bowel movements. Additionally, we have reviewed the literature pertaining to manifestations of diarrhea in patients with MTC.

Case Reports

Case 1

A 26-year-old man presented to a GI clinic with a 6-month history of diarrhea. He reported watery bowel movements 10–14 times per day (Fig. 1). The patient was taking Imodium, which provided moderate relief. Vital signs and examination of heart, lungs, and abdomen were all normal. A detailed workup was performed, including serum vitamin B12, TTG IgA, thyroid function tests, red cell folate, serum IgA, anti-endomysial antibodies, and serum immunoglobulins, which were all normal. An evaluation for stool ova, parasites, bacterial infection, *Clostridium difficile*, *Giardia* antigen, and *Cryptosporidium* was also negative. A stool evaluation was normal. A colonoscopy included biopsies of the colon and terminal ileum, but did not reveal any abnormalities. Ultimately, the patient was prescribed Imodium and tincture of opium, which provided some symptom relief.

Six months later, the patient re-presented for follow-up. Since the patient had lost about 16 pounds (approximately 9.4% weight loss), a computerized axial scan of the abdomen and chest was performed to rule out a malignancy. Imaging revealed a large left-sided thyroid mass measuring 3.4 cm with extensive bilateral cervical lymphadenopathy extending into the superior mediastinum and multiple pulmonary metastases, suggesting a primary thyroid

malignancy with metastatic spread. Biopsy of the thyroid nodule confirmed MTC, approximately 18 months after initial evaluation by the gastroenterologist. The serum Ct level was 52,894 ng/L (reference <10), procalcitonin (ProCt) 16.8 ng/mL (reference <0.1), and carcinoembryonic antigen (CEA) 48.9 μg/L (reference <4.6) (Table 1). Serum levels of vasoactive intestinal peptide, somatostatin, glucagon, pancreatic polypeptide, neurotensin, and gastrin were normal. The patient underwent a thyroidectomy and left lymph node neck dissection. Pathology confirmed MTC. Six weeks postoperatively, serum Ct levels dropped to 36,202 ng/L. The patient displayed some improvements in the severity of diarrhea (Fig. 1). Two months later, serum Ct levels were 825 ng/L, and both computed tomography (CT) and positron emission tomography scans of the neck and chest revealed extensive cancer metastases. The patient was prescribed vandetanib. Three months later, vandetanib was discontinued because of a worsening of the prolonged QT interval. Six months later, the patient was enrolled in a clinical trial for nivolumab and ipilimumab combination treatment. Presently, the patient remains stable on this combination therapy.

Regarding the severity of diarrhea, the patient continued to have diarrhea several times per day during the entire course of his illness (Fig. 1). There were some correlations between the diarrhea episodes and serum Ct levels (Fig. 1). However, it should be noted that the patient was taking tincture of opium to control his diarrhea during these periods.

Case 2

A 27-year-old female was referred to a GI clinic for increased bowel movements (8–10 times/day) for 3 months (Fig. 2). A detailed stool examination was negative. Upper endoscopy and colonoscopy with biopsies of the duodenum and colon were normal. A detailed laboratory evaluation was normal, including serum levels of endomysial antibodies, IgA, and urine 5-hydroxyindoleacetic acid (5-HIAA). Additional tests evaluating serum levels of vasoactive intestinal peptide, somatostatin, glucagon, pancreatic polypeptide, neurotensin, and gastrin were normal. Evaluation of the stool for the presence of laxatives was negative. A CT scan and ultrasound of the abdomen and pelvis were normal.

A diagnosis of irritable bowel syndrome was made. One month after her initial visit to the GI clinic, an internist noted the presence of a left-sided thyroid nodule. A thyroid ultrasound revealed a hypoechoic solid nodule measuring 1.8 cm in the right thyroid lobe. Additionally, the left thyroid lobe displayed a 1.6-cm nodule with coarse calcification and increased vascularity. A biopsy of the left thyroid nodule suggested a diagnosis of MTC. Serum Ct levels were 2,890 ng/L, serum ProCt level 9.7 ng/mL, and serum CEA 60.2 μg/L (Table 1). The patient underwent total thyroidectomy and cervical lymph node dissection with histology confirming MTC. Two months later, serum Ct levels were 490 ng/L, and they remained between 212 and 546 ng/L for the next 9 months of observation. Similarly, serum ProCt levels at corresponding follow-up periods ranged from 2.18 to 5.6 pg/mL, and CEA levels ranged from 11.9 to 16.8 μg/L (Table 1). Six weeks after surgery, the patient noted an improvement in diarrhea with episodes ranging from 4 to 6 per day (Fig. 2) while taking a reduced dose of loperamide. She was able to discontinue the tincture of opium treatment. The patient is currently being followed without additional treatment. She has declined a genetic screening test for a *RET* mutation.

Case 3

A 38-year-old man was referred to the GI clinic with a 4-month history of diarrhea (10–12 episodes per day) without blood (Fig. 3). He was not taking any medications. The patient was treated with cholestyramine without benefit and was subsequently placed on loperamide with improvement. A 3-day stool collection showed 670 g per day (reference <200 g). The patient underwent detailed evaluation, including thyroid function tests, serum B12, blood cell folate, serum IgA and anti-endomysial antibodies, serum immunoglobulins, and 24-h urine 5-HIAA, in addition to a detailed hormone panel for gastrin, somatostatin, vasoactive intestinal polypeptide, pancreatic polypeptide, and neurophysin. All of these tests and a laxative screen were negative. Biopsies of the distal duodenum, terminal ileum, and colon obtained during an upper GI endoscopy and ileo-colonoscopy were negative.

Abdominal and pelvic CT scan showed no abnormalities. Tests for fat absorption were negative. The patient was treated with loperamide and tincture of opium with partial relief. Three months later, the patient was seen in the internal medicine clinic where a physical examination revealed a 4-cm left-sided thyroid nodule. A fine-needle biopsy of the thyroid nodule suggested MTC. Serum Ct levels were 4,088 ng/L, serum ProCt 23.1 ng/mL, and CEA 16.3 μg/L (Table 1). The patient underwent total thyroidectomy and cervical lymph node dissection with histology confirming MTC, with lymphovascular invasion and external capsular spread.

Three months later, serum Ct levels were normal, and they remained normal for another 6 months of follow-up.

MTC Patients without Gastrointestinal Manifestations

Case 1

A 43-year-old Caucasian male was referred for evaluation of a thyroid nodule. The patient denied any gastrointestinal symptoms, including diarrhea. A biopsy suggested a possible MTC. Serum Ct levels were 3,139 ng/L (Table 2). The patient underwent total thyroidectomy and bilateral cervical lymph node dissection with histology confirming MTC. A detailed hormone panel was negative, including gastrin, somatostatin, vasoactive intestinal polypeptide, pancreatic polypeptide, and neurophysin levels. Over the next 3 years, the patient's serum Ct levels rose to 48,052 ng/L. At this time, serum CEA levels were 682 μg/L.

A CT scan of the chest and abdomen revealed metastatic lesions in the cervical lymph nodes, liver, and lungs. The patient refused treatment with tyrosine kinase inhibitors or chemotherapy. He died 4 months later. From the time of initial diagnosis, the patient continued to have normal bowel movements until he died.

Case 2

A 64-year-old woman initially presented with a left thyroid nodule. She underwent a left thyroidectomy, and pathology confirmed a 1.8-cm MTC. Serum Ct levels were 953 ng/L. The patient subsequently underwent a complete thyroidectomy and left cervical lymph node dissection. Three years later, the patient presented with recurrent lymph node metastases in the left supraclavicular area, and serum Ct level increased to 2,389 ng/L. The patient underwent a left-sided radical lymph node dissection followed by radiotherapy. Skeletal survey and

chest/abdominal CT confirmed extensive metastases. Follow-up serum Ct level was 32,080 ng/L, ProCt 353 ng/mL, and CEA 102 μg/L. Six months later, the patient developed extensive pulmonary metastases and died. The patient reported normal bowel movements throughout the course of her illness.

Discussion

Diarrhea can be a presenting manifestation of several endocrine disorders, such as hyperthyroidism, carcinoid syndrome, tumors secreting vasoactive intestinal polypeptide (VIPomas), and MTC [1, 2]. There are also several nonendocrine causes of chronic diarrhea. Presentation of MTC with chronic diarrhea is usually seen in patients with metastatic disease. Earlier studies have reported that 28–29% of the patients with MTC may have symptoms of diarrhea [4]. The link between humoral secretion from a tumor and diarrhea is well established, and this symptom immediately improves after surgical resection of the tumor [5–7]. The improvement in diarrhea was likewise seen in our patients with MTC following surgical intervention. Although diarrhea is well known as a presenting symptom of MTC, our first patient experienced a considerable delay in the MTC diagnosis despite a detailed workup, thereby postponing appropriate surgical treatment. Similarly, for the other 2 patients, the primary care physician diagnosed MTC instead of the gastroenterologist.

Diarrhea accompanying MTC is typically considered the result of a secretory process triggered by elevated circulating Ct or other substances [5–10]. Several investigators have suggested that prostaglandins may play a role in causing diarrhea in patients with MTC. It has been shown that circulating prostaglandins cause diarrhea by acting on the gut musculature to increase motility. Alternatively, and more likely, prostaglandins may promote fluid secretion in the gut [9]. In contrast, several other investigators do not support a role for prostaglandins in causing diarrhea in patients with MTC. In 1969, Bernier et al. [6] suggested that prostaglandins may not play a role in causing diarrhea in patients with MTC. In 1974, Isaacs et al. [7] studied a patient with diarrhea and MTC and observed abnormalities in ileal transport of electrolytes, mucosal permeability, and ileal transit time, concluding that these factors may be collectively responsible for causing diarrhea. Furthermore, indomethacin, an inhibitor of prostaglandin synthesis, was ineffective in controlling diarrhea. These investigators, therefore, concluded that prostaglandins did not play a role in causing diarrhea. It has also been suggested that Ct was the major cause of diarrhea instead of prostaglandins. Our 3 patients with diarrhea presented with markedly elevated serum Ct, ProCt, and CEA levels. However, the 2 control patients with markedly elevated levels of serum Ct, ProCt, and CEA experienced no gastrointestinal symptoms. Hence, it is unlikely that the Ct, ProCt, and CEA were the sole causes of diarrhea. However, whether ProCt has any separate effects remains to be investigated. It is also unlikely that CEA has any role in causing diarrhea since several disorders associated with elevated CEA levels do not result in altered bowel function. These findings suggest that additional factors are involved in causing diarrhea in MTC patients. Ct injections in relatively large doses in experimental animals may cause diarrhea [9], and Ct infused in normal subjects has also been shown to induce net intestinal secretion in the jejunum [10]. However, patients with Paget's disease of the bone or hypercalcemia treated with pharmacologic doses of Ct do not develop diarrhea.

In summary, Ct-induced secretory diarrhea may be an important mechanism independent of cyclic adenosine monophosphate. Other potential mediators of diarrhea include prostaglandins, Ct-related peptides, serotonin, histaminase, kallikrein, dopa-decarboxylase, and possibly ProCt. Diarrhea may also be related to disordered intestinal motility, but secretory mechanisms mediated by elevated levels of prostaglandin are clearly important [4–10].

MTC-associated diarrhea is best managed by complete removal of the tumor, although this is not always possible. Treatment with tyrosine kinase inhibitors often does not result in complete remission, and tyrosine kinase inhibitors may also cause diarrhea [11]. Diarrhea is generally treated with antidiarrheal medications. The patients in this study displayed a good response to these medications and did not require any additional treatment. Interestingly, nutmeg, which is an inhibitor of prostaglandin synthesis, was effective in controlling diarrhea in 1 patient [8], although indomethacin, which is another inhibitor of prostaglandin synthesis, was not effective in a different study [7]. Smid and Dullaart [12] studied the effect of octreotide in 1 patient with MTC-associated diarrhea and concluded that there was a sustained improvement without a concomitant reduction in serum Ct levels. In contrast, Frank-Raue et al. [13] studied 7 patients with MTC and concluded that octreotide treatment was not effective for relieving diarrhea, nor did it slow or halt tumor growth. Alawneh et al. [14] administered glycopyrrolate in a patient with octreotide-resistant diarrhea due to MTC and noted improvement. Dadu et al. [15] recently studied the effect of calcium aluminosilicate antidiarrheal drug in 7 patients with metastatic MTC-associated diarrhea and concluded that 5 of the 7 patients responded to this treatment.

In conclusion, the molecular mechanisms causing diarrhea in patients with MTC are poorly understood. No recent studies have investigated the pathophysiological factors causing diarrhea in patients with MTC. MTC should be considered in the differential diagnosis for chronic diarrhea, especially in patients presenting in GI clinics. MTC should also be considered when other common causes of chronic diarrhea have been excluded, particularly if the patient has a family history of MTC and/or if the patient has a palpable thyroid nodule.

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Statement of Ethics

This article has been cleared by the institutional review board. The patients have given written informed consent to publish the case (including publication images).

Conflict of Interest Statement

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Disclaimer

The views expressed in this article are those of the author and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or US Government.

References

1 Jensen RT. Overview of chronic diarrhea caused by functional neuroendocrine neoplasms. Semin Gastrointest Dis. 1999 Oct;10(4):156–72.
2 Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer. 2000 Mar;88(5):1139–48.
3 Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, 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.
4 Williams ED. Diarrhoea and thyroid carcinoma. Proc R Soc Med. 1966 Jul;59(7):602–3.
5 Steinfeld CM, Moertel CG, Woolner LB. Diarrhea and medullary carcinoma of the thyroid. Cancer. 1973 May;31(5):1237–9.
6 Bernier JJ, Rambaud JC, Cattan D, Prost A. Diarrhoea associated with medullary carcinoma of the thyroid. Gut. 1969 Dec;10(12):980–5.
7 Isaacs P, Whittaker SM, Turnberg LA. Diarrhea associated with medullary carcinoma of the thyroid. Studies of intestinal function in a patient. Gastroenterology. 1974 Sep;67(3):521–6.
8 Barrowman JA, Bennett A, Hillenbrand P, Rolles K, Pollock DJ, Wright JT. Diarrhoeae in thyroid medullary carcinoma: role of prostaglandins and therapeutic effect of nutmeg. BMJ. 1975 Jul;3(5974):11–2.
9 Kisloff B, Moore EW. Effects of intravenous calcitonin on water, electrolyte, and calcium movement across in vivo rabbit jejunum and ileum. Gastroenterology. 1977 Mar;72(3):462–8.
10 Gray TK, Bieberdorf FA, Fordtran JS. Thyrocalcitonin and the jejunal absorption of calcium, water, and electrolytes in normal subjects. J Clin Invest. 1973 Dec;52(12):3084–8.
11 Tsang VH. Management of treatment-related toxicities in advanced medullary thyroid cancer. Curr Opin Oncol. 2019 May;31(3):236–42.
12 Smid WM, Dullaart RP. Octreotide for medullary thyroid carcinoma associated diarrhoea. Neth J Med. 1992 Jun;40(5-6):240–3.
13 Frank-Raue K, Ziegler R, Raue F. The use of octreotide in the treatment of medullary thyroid carcinoma. Horm Metab Res Suppl. 1993;27:44–7.
14 Alawneh A, Tuqan W, Innabi A, Abu-Sheikha A, Al-Arja G, Shehadeh I. Successful palliation of octreotide-resistant diarrhea using glycopyrrolate in a patient with medullary thyroid cancer: a case report. J Pain Symptom Manage. 2015 Sep;50(3):e4–6.

15 Dadu R, Hu MI, Cleeland C, Busaidy NL, Habra M, Waguespack SG, et al. Efficacy of the natural clay, calcium aluminosilicate anti-diarrheal, in reducing medullary thyroid cancer-related diarrhea and its effects on quality of life: a pilot study. Thyroid. 2015 Oct;25(10):1085–90.

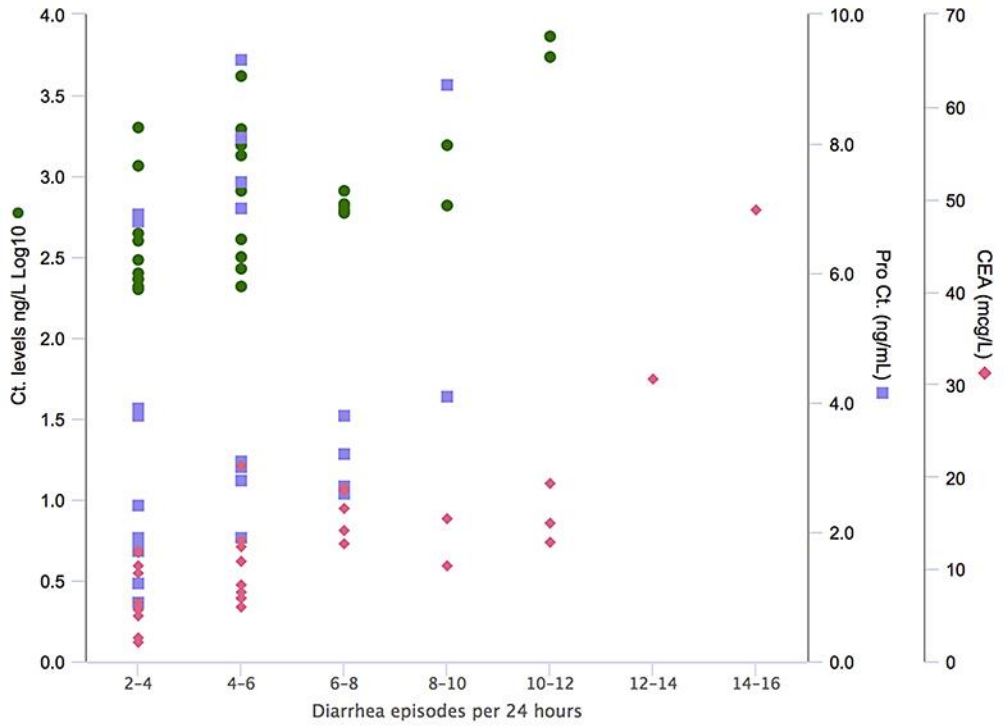

Fig. 1. Patient 1: correlation of serum Ct, ProCt, and CEA levels with episodes of diarrhea.

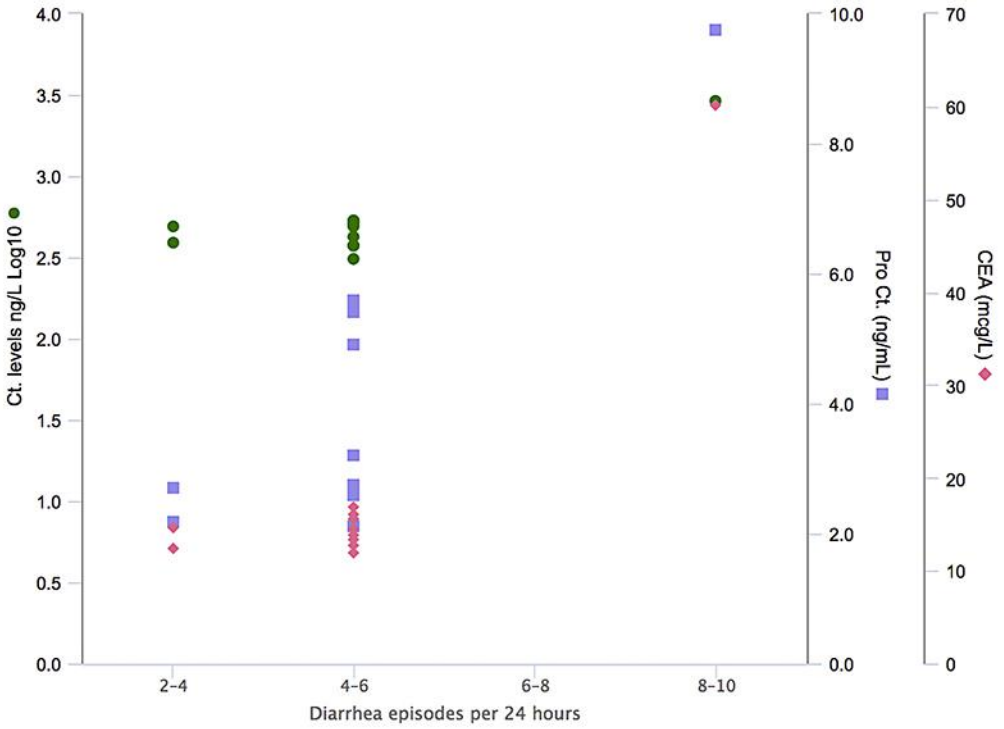

Fig. 2. Patient 2: correlation of serum Ct, ProCt, and CEA levels with episodes of diarrhea.

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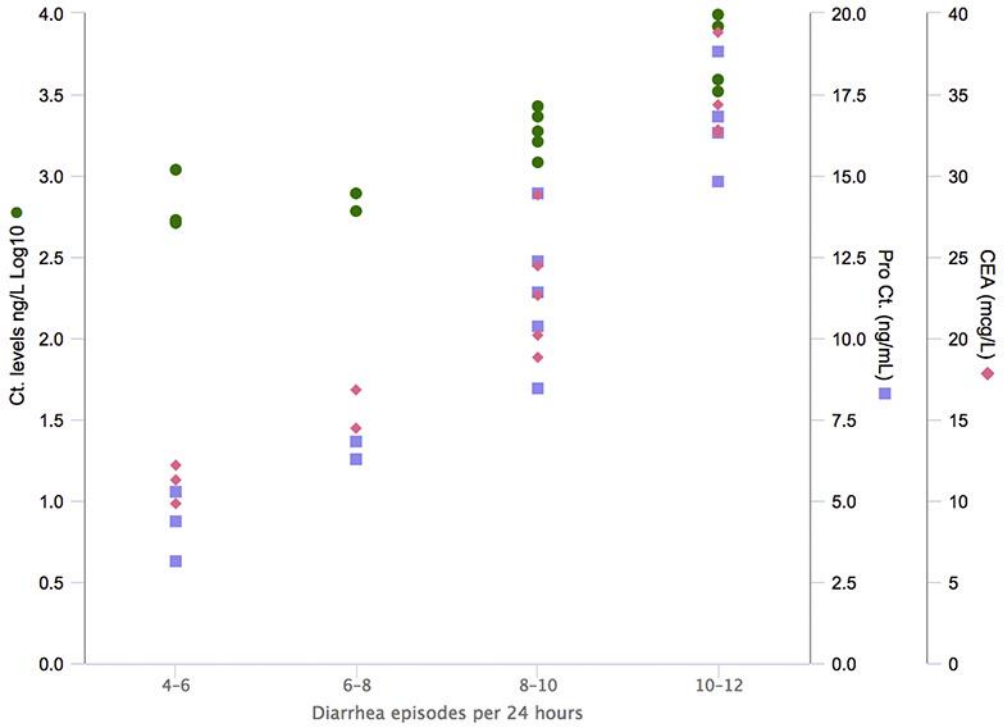

Fig. 3. Patient 3: correlation of serum Ct, ProCt, and CEA levels with episodes of diarrhea.

Table 1. Serum levels of calcitonin (Ct), procalcitonin (ProCt), and carcinoembryonic antigen (CEA) in patients with MTC and diarrhea

Laboratory value	Patient 1		Patient 2		Patient 3	
	pre-op	post-op	pre-op	post-op	pre-op	post-op
Ct, ng/L	52,894	825	2,890	490	4,088	8.2
ProCt, ng/mL	16.8	12.7	9.7	5.6	23.1	<0.1
CEA, µg/L	45.9	19.6	60.2	11.9	16.3	2.1

Reference values: Ct <10 ng/L, ProCt <0.1 ng/mL, CEA <4.6 µg/L.

Table 2. Serum levels of calcitonin (Ct), procalcitonin (ProCt), and carcinoembryonic antigen (CEA) in patients with MTC and normal bowel movements

Laboratory value	Patient 1	Patient 2
Ct, ng/L	3,139	953
ProCt, ng/mL	13.8	6.7
CEA, μg/L	16.4	12.9

Reference values: Ct <10 ng/L, ProCt <0.1 ng/mL, CEA <4.6 μg/L