

# Diarrhea as a form of presentation of medullary thyroid carcinoma

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## Abstract

A case is presented of a 57-year-old man consulting for chronic diarrhea. Based on subsequent findings (thyroid nodule and metastases), the possibility of metastatic medullary thyroid carcinoma (MTC) was raised. Thyroidectomy allowed diagnosing a multicentric left lobe MTC. MTC is a rare cause of diarrhea, but should be considered, especially in the presence of signs or symptoms of alarm or nonresponse to empirical therapy.

**Abbreviations:** CEA=carcinoembryonic antigen, CT=computed tomography, MEN 2=multiple endocrine neoplasia type 2 syndrome, MTC=medullary thyroid carcinoma, PTH=parathyroid hormone.

**Keywords:** cervical metastases, chronic diarrhea, metastatic medullary thyroid carcinoma

## Introduction

Medullary thyroid carcinoma (MTC) is a rare form of neuroendocrine tumor and accounts for 1% to 2% of thyroid cancer cases.<sup>1</sup> The vast majority of MTC are sporadic and only 25% of the cases are hereditary, as part of the of multiple endocrine neoplasia type 2 syndrome, MEN 2. Sporadic MTC occurs between the 5th and the 6th decade of life and usually presents itself as a solitary nodule. At the time of diagnosis, 70% of patients present with cervical metastases and 10% distant metastases. The tumor originates from the neuroendocrine C cells and secretes calcitonin and carcinoembryonic antigen (CEA), which are sensitive biomarkers of the neoplasia. In advanced stages of the disease, secretion of calcitonin and other active peptides by tumoral cells can cause systemic symptoms such as diarrhea or facial flushing.<sup>2</sup> The only potential curative treatment for MTC is surgical and consists of total thyroidectomy with cervical lymph node dissection of the central compartment and, in some cases, modified radical neck dissection.<sup>3</sup>

## Case

The patient was a 57-year-old man, smoker, with no previous history of systemic diseases and no chronic medication. He was

referred to gastroenterology consultation for chronic watery diarrhea (about 10 bowel movements per day) lasting more than 2 years, associated with marked weight loss (approximately 30 kg). He denied fever, blood loss, or associated abdominal pain. Initial laboratory evaluation including complete blood count, C-reactive protein, renal function, ionogram, glycemia, thyroid hormones, immunoglobulins, celiac serologies, and faecal elastase revealed no alterations. In addition, stool microbiological studies, imaging (computed tomography [CT] enterography) and endoscopic studies (including upper endoscopy, ileocolonoscopy, videocapsule endoscopy, and enteroscopy) were within normal range.

The patient went to the Emergency Department due to moderate hemoptysis and was admitted for study. Underwent fiberoptic bronchoscopy that revealed no significant alterations and performed selective embolization of hypertrophied and hypervascularized bronchial arteries with control of hemorrhage. The chest CT revealed multiple suspicious enlarged mediastinal lymph nodes, a left para-tracheal nodular lesion compatible with an adenopathy or a thyroid nodule, a nodular contrast filling defect in the apical region of the left ventricle, as well as several suspicious hepatic nodular lesions, the largest measuring 13 mm in segment VIII. An echocardiogram confirmed an apical nodular image suggestive of intracavitary thrombus in the left ventricle. Thyroid ultrasound revealed 2 suspicious nodules in the lower third of the left lobe with 3.5 and 1.3 cm, as well as suspicious homolateral jugular lymphadenopathy.

Based on the symptoms and subsequent findings (long-term diarrhea of unknown cause, thyroid nodule, and metastases) the possibility of metastatic MTC was raised and blood tests requested, which have indicated a marked elevation of serum calcitonin (15,971.0 pg/mL, normal < 8.5), elevation of the CEA (76.6 ng/mL; normal = 0–3), a slight elevation of PTH-i (68.1 pg/mL; normal = 10–65) with no other alterations, notably in calcemia, thyroid function, urinary catecholamines, or metanephrines. An ultrasound-guided biopsy of the thyroid nodule and one of the cervical lymphadenopathies were performed. Cytology of the nodule was compatible with MTC with calcitonin assay yielding 138,570 pg/mL. Bone scintigraphy was performed, revealing hypercaptation foci in the projection of the 1st right costal arch (anterior extremity), as well as in the

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vertebral column (right pedicle of D9, right articular apophysis of L2, spinous apophysis of L5 and coccyx) and basin (body of the right pubis), suggesting the existence of bone metastases that were subsequently confirmed in magnetic resonance imaging. An ultrasound-guided liver lesion biopsy was performed. The histological assessment was consistent with the diagnosis of MTC metastasis.

The patient underwent total thyroidectomy with left modified radical neck dissection. It was necessary to resect the sternothyroid muscle, recurrent and vagus nerves, and internal jugular vein due to invasion of these structures by the tumor and metastatic lymph nodes, which were also adherent to the esophagus and left carotid artery.

It was documented by indirect laryngoscopy, paralysis of the left hemilarynx in the median position, with anteriorization of the arytenoid and shortening of the vocal cord. The postoperative course was uneventful, without a new onset of dysphonia or hypoparathyroidism. The level of calcitonin at 24 h was 7873 pg/mL. Study of the RET gene mutation yielded negative results.

The pathological assessment of the surgical specimen diagnosed an MTC in the left lobe measuring 7.5 cm, intersected by the surgical margin, with extra-thyroid and vascular invasion. It was classified as pT3N1bM1R2. Metastases were identified in 18 of the 35 excised lymph nodes, the largest (4 cm) displaying signs of extra-nodal extension. Two papillary microcarcinomas of 0.3 and 0.4 cm in the left and right lobe, respectively—pT1a (m) N0R0—were also observed, both consisting of well delimited follicular variants without angio-invasion.

The group consultation of endocrine pathology decided for therapy with a tyrosine kinase inhibitor, Vandetanib. Six months after surgery the patient's diarrhea had subsided maintaining about 4 bowel movements per day.

## Discussion

This case describes the diagnostic approach of a patient with MTC with diarrhea and severe weight loss as the initial

presentation. MTC is a rare cause of diarrhea, but it is a diagnosis that must be considered after exclusion of the most common causes, especially in the presence of signs or symptoms of alarm or nonresponse to empirical therapy. Metastatic MTC is incurable and the treatment chosen should be individualized. Surgical treatment should take into consideration the extent of the disease and the patient's medical comorbidities while minimizing complications. Total thyroidectomy with clearance of cervical compartments provides loco-regional disease control and palliates symptoms of hormonal excess. Vandetanib, a tyrosine kinase inhibitor, is indicated in cases of aggressive and symptomatic locally advanced or metastatic MTC. It has been shown to prolong progression-free survival and reduce symptoms such as diarrhea. These benefits were observed both in patients with an RET mutation and those without.<sup>4,5</sup>

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None.

## Conflicts of interest

The authors declare no conflicts of interest.

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