Unique Case of a Large Indolent Medullary Thyroid Carcinoma: Time to Reconsider the Medullary Thyroid Adenoma Entity?

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What Is Known about This Topic?

- The most important clinical prognostic factors for medullary thyroid carcinoma are basal serum calcitonin (Ctn) at diagnosis and pathological stage.
- When the diameter of the primary cancer exceeds 2–4 cm, there is always central lymph node involvement.
- Distant metastases are to be expected when preoperative basal Ctn levels are higher than 500 pg/mL.

What Does This Case Report Add?

- We describe a case of medullary thyroid carcinoma 7 cm in largest diameter associated with high serum Ctn levels (>5,000 ng/L), but no locoregional or distant spread.
- Our case report presents many very peculiar pathological features. We speculate that our case may represent a borderline entity, between C-cell adenoma (never described in humans, only in animals) and carcinoma.

Keywords

Medullary thyroid cancer · Calcitonin · Carcinoembryonic antigen

Abstract

Background: Medullary thyroid carcinoma (MTC) is a rare neuroendocrine cancer originating from parafollicular, calci-

tonin (Ctn)-producing C-cells. Prognosis correlates with primary tumor stage and Ctn levels. **Patient:** We describe a case of MTC involving a mass 7 cm in its largest dimension, associated with high Ctn concentrations (>5,000 pg/mL), but normal carcinoembryonic antigen levels, and with no lymph nodes or distant metastases, in complete remission after thyroid surgery. The MTC had very peculiar histological features, with an expansive, noninfiltrating growth around the thy-

roid follicles, and no signs of invasion. These histopathological characteristics are reminiscent of the C-cell adenoma described in animals. The tumor also revealed an ossifying extracellular matrix unlike the classical amyloid. Despite the size of the tumor and the patient's high Ctn levels at diagnosis, the case described here reached complete remission after surgery. **Conclusions:** Further studies are needed to clarify the characteristics of MTC and better predict its behavior at diagnosis.

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Introduction

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine cancer originating from parafollicular, calcitonin (Ctn)-producing C-cells. It accounts for 5–10% of all thyroid carcinomas and is associated with a global 10-year survival rate of around 65–70% [1]. The most important clinical prognostic factors are basal serum Ctn at diagnosis and pathological stage [1]. High biomarker levels correlate with a large tumor burden. Most MTCs are asymptomatic, apart from the presence of a thyroid node. Symptoms such as diarrhea are sometimes reported, indicating advanced disease and possibly hepatic metastases.

Case Presentation

We report on a unique case of a 58-year-old woman with a large MTC, basal Ctn levels in excess of 5,000 pg/mL, and paraneoplastic diarrhea, but normal carcinoembryonic antigen (CEA) levels, and no lymph node involvement or distant metastases. The patient's clinical history included a normally functioning thyroid with a multinodular goiter, diagnosed 13 years earlier, and periodically followed up with thyroid ultrasound (US). Her serum Ctn was measured for the first time only shortly before she was admitted to our clinic, prompted by weight loss and gradually worsening diarrhea.

Thyroid US confirmed the presence of an enlarged right lobe that dislocated the trachea towards the left side. The whole lobe was replaced by a single nodule 7 cm in its largest diameter. No pathological lymph nodes were documented on US. Laboratory findings documented a normal thyroid function and a very high serum Ctn concentration: 5,300 pg/mL (normal value <10 pg/mL) on chemiluminescent immunometric assay (CLIA; DiaSorin, LI-AISON Calcitonin II-Gen, Stillwater, MN, USA). The patient's CEA levels were normal: 1.6 µg/L (normal range: 0–5 µg/L). Cancer antigen 15-3, vasoactive intestinal peptide, pancreatic polypeptide, 5-hydroxyindolacetic acid, gastrin, chromogranin A (CgA), neuron-specific enolase, urinary 24-h metanephrine, and normetanephrine levels were all negative. The node was cytologically benign (TIR 2, SIAPEC-SIE 2014).

Preoperative computed tomography of the abdomen and chest confirmed the large thyroid nodule and revealed a colliquated cen-

tral area. The examination was negative for other extrathyroid lesions, apart from a suspected breast nodule (measuring 15 mm in largest diameter). Then ^{68}Ga -DOTATOC-positron emission tomography (PET) revealed a marked uptake in the right thyroid lobe, particularly at its upper end, with a maximum standardized uptake value (SUV max) of 16. There was also a focal uptake coinciding with the mammary node (SUV max 3.8) (Fig. 1). ^{18}F -DO-PA-PET showed no pathological uptake, neither in the thyroid node. The patient underwent fine-needle aspiration biopsy of the mammary node, and cytology was suggestive of breast cancer cells. Ctn levels in the washout fluid from the fine-needle aspiration were 27 ng/L. We concluded with a diagnosis of MTC and simultaneous breast cancer. Before surgery, genetic testing showed no germline RET proto-oncogene mutations, thus confirming a sporadic MTC.

The patient underwent total thyroidectomy with nodal dissection of the central compartment, and right quadrantectomy with axillary dissection at the same time.

Breast cancer was confirmed histologically (stage T2 yN1a M0, G2; 8th edition American Joint Committee on Cancer [AJCC] TNM system, 2010). Thyroid histology documented MTC of the right lobe 7 cm in largest diameter, well-encapsulated, with no extrathyroid tissue invasion, a low mitotic rate (0–1/10 high-power fields), an expansive and noninfiltrating growth pattern, and evidence of vascular invasion. Some thyroid follicles were identified within the lesion, around which the tumor was growing, with no signs of invasion. In addition to staining positive for amyloid deposits, the tumor also revealed an ossifying extracellular matrix. No C-cell hyperplasia was documented. No lymph nodal metastases came to light (0/10 nodes analyzed). On immunohistochemical analysis, almost all neoplastic cells were found strongly positive for Ctn staining, whereas only a few cells were weakly positive for CEA. The cellular expression of Ki67 was <1%. Cells positive for thyroid transcriptional factor (TTF-1) were found in the thyroid follicles trapped within the lesion. CgA staining was completely negative (Fig. 2). TNM was pT3 N0 M0, stage II (8th edition AJCC TNM system, 2010). No sporadic RET or RAS mutations were found (the molecular methods used are described elsewhere) [2]. Three months after surgery, the patient's Ctn levels were very low (1.8 pg/mL), and she had completely recovered from diarrhea. Negative biochemical and radiological follow-up was confirmed up to 24 months after surgery. Western blot analysis was performed on the patient's MTC tissue to compare her phospho-ERK (pERK) and pAKT expression with that of normal thyroid, with MTC tissues from other patients carrying different somatic RET mutations or RET wild type, and with RET-mutated cell lines (Fig. 3).

Discussion

MTC usually presents as an ill-defined, nonencapsulated, hard, invasive mass. Cancer cells are immune-reactive for Ctn, CEA, CgA, and negative for thyroglobulin, and they usually exhibit positive staining for amyloid deposits. Regional metastases occur early in the course of the disease, while distant metastases to the liver, lung, or bone develop later [3].

Fig. 1. ^{68}Ga -DOTATOC PET/CT. Thyroid showed an abundant uptake in the right thyroid lobe, particularly towards the top, while the lower part carried a wide cold central area. The right upper part of the figure also shows a focal uptake coinciding with the mammary node.

Fig. 2. Histological and immunohistochemical features of the present case. **a** Thyroid follicles were documented within the lesion and the tumor grew with no sign of invasion. **b** On higher magnification, the neoplastic cells were arranged with a trabecular and solid pattern. **c** The tumor showed an ossifying extracellular ma-

trix, unlike classic MTC. On immunohistochemical analysis, all neoplastic cells stained strongly positive for calcitonin (**d**), while CgA staining was completely negative (**e**). **f** Only a few cells showed weak positivity for CEA (original magnification, $\times 10$ for **a** and **b**, $\times 5$ for **c**, and $\times 20$ for **d-f**).

Fig. 3. Western blot analysis (protein extraction from frozen tissues and cell lines). Representative Western blot (**a**) and quantitative Western blot (**b**) corresponding to band quantification of the downstream effectors (pERK and pAkt) of the main signaling pathway activated in MTC (MAPK and mTOR/Akt, respectively). 1: MTC from the patient described in the present case report; 2, 3: RET and RAS wild-type MTCs from patients cured after surgery;

4, 5: somatic RET-mutated (M918T) MTCs from patients with locally persistent disease after surgery; 6: somatic RET-mutated (C634Y) MTC with systemic spread; 7: MZ-CRC-1 RET M918T cell line; 8: TT RET C634W cell line. Our case showed an intermediate signaling activation pattern, between wild-type MTC and somatic RET-mutated MTC.

To our knowledge, this is the first report to describe an MTC 7 cm in largest diameter associated with high serum Ctn levels (>5,000 ng/L) and paraneoplastic diarrhea, but no locoregional or distant spread.

For the reasons explained below, we speculated that this was an “atypical” MTC. Indeed, several studies have demonstrated that, when the diameter of the primary cancer exceeds 2–4 cm, there is always central lymph node involvement [4, 5], and distant metastases are to be expected when preoperative basal Ctn levels are higher than 500 pg/mL [5].

The finding that our patient’s CEA levels were undetectable, in contrast with her large tumor mass, led us to suspect that her low CEA serum concentrations were false, due to a hook effect. The weak CEA staining on immunohistochemistry confirmed its low expression, however. The negative immunostaining for CgA was another peculiar feature of this case: CgA levels rise as the neoplastic mass increases in size, and CgA production and immunoreactivity are seen in 80–100% of cases [3].

At present, after 24 months of follow-up, the patient does not show any imaging or biochemical sign of relapse. However, it is known that in presence of an intrathyroidal

localization and when lymph node metastases are absent, the possibility to obtain the definitive cure of the disease with the surgical treatment is very high [6]. Moreover, regardless of tumor size, when tumor capsule is present and complete, in absence of infiltration, MTC have a significantly better outcome [7]. The absence of somatic RET mutation was another favorable prognostic factor in the case of sporadic MTC described here [8]. Thus, in this case, based on the characteristics of the MTC, that was intrathyroidal, without lymph node metastases, well-encapsulated without any sign of infiltration and negative for RET mutations, a cure was expected. On the other hand, up to 10% of MTC with undetectable postoperative CT level can recur several years after surgery [9], and our outcome is still too short to exclude this possibility.

However, as mentioned earlier, the tumor also had very peculiar histological and immunohistochemical features (an expansive, noninfiltrating growth, with thyroid follicles trapped inside the lesion; no reaction to CgA; and a positive immunoreactivity to TTF-1 only among the thyroid follicles trapped within the lesion) [10, 11], which bring to mind those reported in the literature, seen in horses with C-cell adenomas. In animals, C-cell adenoma

is described as a firm, well-encapsulated mass with an expansive growth pattern, compressing the normal thyroid gland, with a solid proliferation of clear cells containing variously sized follicles, a strong positive reaction to Ctn staining [11], and a negative reaction to CgA staining [10] on immunohistochemistry. The ossifying extracellular matrix seen in the cancer described here is also unusual in MTC. Ferreira et al. [12] recently wrote that expression of the glycoprotein osteopontin, an organic component of bone matrix, is a potential marker of a good prognosis in primary MTC lesions.

In conclusion, although there have been no descriptions of clinical and pathological features of “atypical” forms of MTC or medullary thyroid adenoma in humans, we speculate that our case may represent a borderline entity, between adenoma and carcinoma. Further molecular and histopathological investigations are needed to better define the behavior of MTC at the time of its diagnosis. It is well known that MTC can have a variable outcome, with some rapidly aggressive variants and others taking an indolent course, irrespective of tumor stage at diagnosis, and with or without distant metastases [13, 14].

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Statement of Ethics

Written consent to the publication of this case report was obtained from the patient.

Disclosure Statement

The authors declare no conflicts of interest.

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