

**Case report****Rare presentation of occult medullary carcinoma of the thyroid as a mediastinal mass**

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**ABSTRACT**

**OBJECTIVE:** To describe a rare case of occult (<1cm in diameter) medullary thyroid carcinoma (MTC) in a 45-year-old woman, presenting as an asymptomatic mediastinal mass. **DESIGN:** The diagnostic methodology included laboratory measurements of relevant biochemical and hormonal parameters including calcitonin (CT), carcinoembryonic antigen (CEA) and chromogranin A, and imaging techniques including ultrasound (U/S), computed tomography (C/T), magnetic resonance imaging (MRI) and radio labeled somatostatin analog (<sup>111</sup>In-DTPA-octreotide). **RESULTS:** Chest CT revealed a mediastinal mass measuring 5cm in diameter abutting the right thyroid lobe. CEA was elevated and an association with thyroid malignancies was considered. CT was found to be markedly elevated, pointing to the diagnosis of MTC metastatic to the mediastinum. The patient underwent total thyroidectomy, lymph node dissection and removal of the mediastinal mass. Histological examination revealed MTC of the right thyroid lobe measuring 0.5 cm, metastatic to regional and superior mediastinal lymph nodes. **CONCLUSIONS:** Occult MTC can infrequently present as an asymptomatic mediastinal mass. Elevated serum CT and CEA along with imaging techniques leads to the correct diagnosis and surgical management of the disease.

**Key words:** Medullary thyroid carcinoma, Lymph node metastases, Carcinoembryonic antigen

**INTRODUCTION**

MTC is a relatively uncommon thyroid tumor which

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Received 03-05-11, Revised 01-08-11, Accepted 10-09-11

derives from the parafollicular or C cells of the gland that synthesize and secrete the calcitropic hormone calcitonin (CT). Carcinomas of this type account for 5-10% of all thyroid malignancies. MTC may occur sporadically or may be inherited. Germline mutations of the RET oncogene lead to the manifestation of either familial medullary thyroid carcinoma (FMTC) or to the multiple endocrine neoplasia syndromes types IIa and IIb.<sup>1</sup>

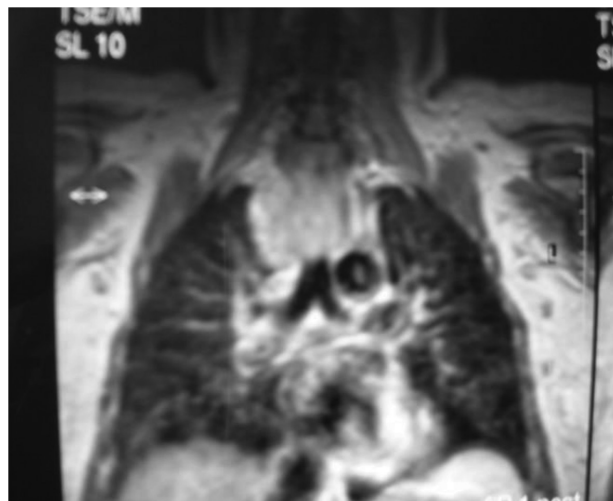
Metastatic dissemination to both the central and lateral cervical lymph node compartments, including the mediastinum, is a common occurrence in patients with clinically apparent MTC.<sup>2,3</sup> The central compartment lymph nodes tend to be affected more frequently. In this report we describe a rare patient with occult MTC who presented with an asymptomatic mediastinal mass and elevation of carcinoembryonic antigen (CEA).

### CASE PRESENTATION

A 45-year-old woman from Bulgaria, living in Greece for the last 5 years, presented with an elevated CEA detected a year prior to her admission to our Department on a routine measurement done by her gynecologist. She had a history of hysterectomy due to uterine leiomyoma two years prior to admission. Further tests were carried out to ascertain the cause of the elevated CEA, including a CT of the chest. A mediastinal mass 5 cm in diameter was found, abutting the lower margin of the right thyroid lobe. She was referred to the Endocrinology Department of our hospital for further diagnostic and therapeutic management. Hematologic workup, gastrointestinal endoscopic studies and magnetic resonance imaging (MRI) imaging of the abdomen conducted elsewhere on an outpatient basis had failed to identify the cause of the mediastinal mass. The patient was completely asymptomatic. She had a medical history of renal colic for 10 years prior to admission. The family history was negative for thyroid diseases or other endocrinopathies. The physical examination was unremarkable. There was no goiter or palpable thyroid nodules and no enlargement of regional or distant lymph nodes.

Ultrasound examination of the neck revealed a thyroid gland of normal size with inhomogeneous echo pattern and several small nodules of 0.5-0.6 cm in diameter in both lobes. A few small jugular lymph nodes less than 1 cm were observed. MRI examination of the chest confirmed the presence of a large mediastinal mass contiguous to the lower margin of the right thyroid lobe that displaced the trachea to the left (Figure 1).

Because of the unusual clinical presentation, rare causes of CEA elevation associated with mediastinal masses and thyroid malignancies were considered



**Figure 1.** MRI of the thorax showing the large mediastinal mass in touch with the lower margin of the right lobe of the thyroid and displacing the trachea to the left.

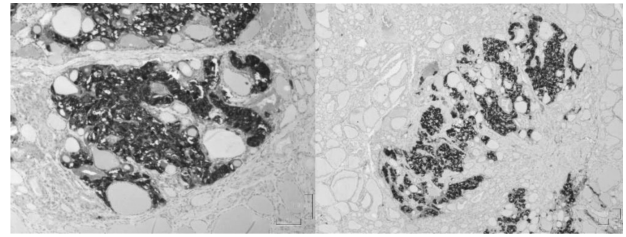
and in this context CT was measured as well as CEA as tumor markers (Table 1). A CT of 603 pg/ml was found. Therefore, the combination of a markedly elevated CT well above 100 pg/ml, an elevated CEA and a mediastinal mass pointed to the diagnosis of MTC metastatic to the mediastinum. Other causes of elevated CT were also considered (Table 1) but were thought less likely on the basis of previous reports.<sup>4,5</sup> Based on the findings of these studies, the lack of clinical symptoms and signs and the lack of imaging findings of a neuroendocrine tumor elsewhere, no

**Table 1.** Differential Diagnosis of Hypercalcitoninemia (modified from S. Toledo et al 2009)

Physiologic conditions	
Drugs	
Non-thyroid pathologies	Hypergastrinemias Hypercalcemias Renal insufficiency Neuroendocrine tumors: pheochromocytoma paraganglioma enteropancreatic endocrine tumors VIPoma, insulinoma, carcinoids small cell pulmonary tumor
Thyroid pathologies	Thyroid carcinomas: follicular carcinoma papillary carcinoma Chronic autoimmune thyroiditis

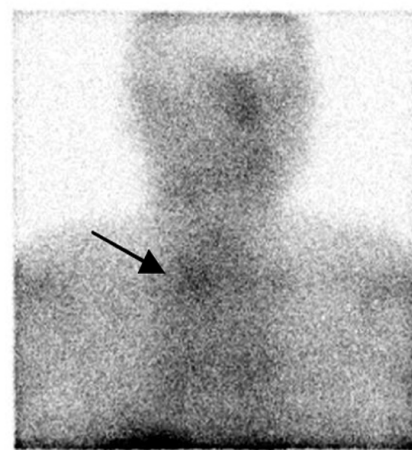
stimulatory tests such as pentagastrin or calcium infusion were deemed necessary. The patient was further investigated for pheochromocytoma preoperatively in order to exclude MEN 2 syndrome. The values of urinary catecholamines, metanephrines and VMA were within normal limits. The possibility of primary hyperparathyroidism was also considered based on the patient's clinical history of renal colics. The laboratory tests showed an elevated PTH without hypercalcemia but a low-normal plasma 25-OH-D (Table 2). Thus, a diagnosis of secondary hyperparathyroidism was made. The PTH levels were corrected to normal with vitamin D replacement.

The patient underwent resection of the mediastinal mass, total thyroidectomy and dissection of the central compartment lymph nodes. Fourteen cervical lymph nodes and the mediastinal mass were examined histologically and immunohistochemically. Histopathology confirmed the preoperative diagnosis of MTC with metastases to cervical and mediastinal lymph nodes. The thyroid tumor measured 0.5 cm in diameter, was located in the right thyroid lobe and consisted of a homogeneous amyloid-rich cell population. Metastases to 9 of 14 resected cervical lymph nodes and to a block of superior mediastinal lymph nodes were also found. The malignant cell population immunophenotype was CK7 (+), CK18 (+), CEA (+), Calcitonin (+), Chromogranin (+), TTF-1 (+), Thyroglobulin (-) and EMA (-) (Figure 2). The patient recovered uneventfully. Three months after surgery, CT and CEA were measured and a CT scan of the neck, chest and upper abdomen was performed. The CT and CEA levels were 318 pg/ml and 24.18 ng/ml, respectively, indicating the presence of residual disease. The CT scan of the neck, chest and upper abdomen showed a small jugular lymph



**Figure 2.** Histological examination showing typical morphology of medullary carcinoma. Immunohistochemistry with the alkaline phosphatase method was positive for (a) calcitonin (original X 100) and (b) chromogranin (original X40).

node in the right posterior cervical triangle (level V), measuring 1.15 cm in diameter with characteristics suspicious for metastasis. This finding was further investigated with  $^{111}\text{In}$  DTPA octreotide scintigraphy which showed a high concentration of the radiolabeled somatostatin analogue anterolaterally, in the lower right neck, indicating the presence of residual tumor (Figure 3). A second operation with cervical lymph node dissection (levels II, III, IV and V) on the right side of the neck was performed. Fifty-one lymph nodes were removed. Histological examination revealed metastatic dissemination of MTC to 3 of 51 lymph nodes. Following reoperation, calcitonin dropped to undetectable levels to this date. Genotype screening did not reveal mutations associated with familial forms of MTC. The study of family members revealed normal calcitonin levels.



**Figure 3.** Post-operative Octreoscan, showing uptake by metastatic lymph node.

**Table 2.** Summary of pertinent hormone and marker blood values

	Measured Values	Normal Values
TSH	1.0918 $\mu\text{IU/ml}$	0.25-3.43 $\mu\text{IU/ml}$
FT3	2.24 pg/ml	1.71-5.53 pg/ml
FT4	0.98 ng/dl	0.7-1.94 ng/dl
Tg	23 ng/ml	1.6-55 ng/ml
Calcitonin	603 pg/ml	<11.5 pg/ml
CEA	40.73 ng/ml	0-5 ng/ml

## DISCUSSION

Medullary thyroid carcinoma is a thyroid tumor deriving from parafollicular C cells. MTC may be sporadic or hereditary. Hereditary MTC accounts for 25% of all cases and is transmitted as an autosomal dominant trait either alone as FMTC or as part of multiple endocrine neoplasia (MEN) type 2A or 2B. The pathogenetic mechanism has been associated with germline gain-of-function mutations of the RET proto-oncogene (RET), mainly in exons 10–15.<sup>6</sup> The biological behavior of medullary thyroid carcinoma is much less favorable than other well-differentiated thyroid carcinomas. A 10-year survival of about 50% of medullary thyroid carcinoma patients is reported in several series. Early diagnosis may result in higher probability of cure and long-term survival.<sup>7,8</sup>

Calcitonin is the most reliable tumor marker because it is highly specific and sensitive.<sup>9</sup> A variety of diseases, other than MTC, including nodular thyroid disease, autoimmune thyroiditis and neuroendocrine tumors, may also cause elevation of CT<sup>4,10,11</sup> (Table 1) but levels of CT above 100 pg/ml are reported to be invariably associated with MTC. Stimulatory tests with pentagastrin and calcium infusion can be utilized in suspicious cases with borderline serum levels of CT.<sup>12</sup> Routine measurement of calcitonin in all patients with thyroid nodules remains controversial and does not appear to be cost-effective.<sup>4,13,14</sup> Other proteins, including CEA, may also be synthesized and released by the malignant C cell and may be associated with dedifferentiation of the tumor and aggressive disease.<sup>15,16</sup> Serum CEA, a glycoprotein involved in cell adhesion, is usually elevated when MTC is diffuse and distant metastases are present, but not in preclinical MTC.<sup>17</sup> CEA is a tumor marker in colorectal carcinoma, gastric carcinoma, pancreatic carcinoma, lung carcinoma and breast carcinoma.<sup>18-20</sup> MTC is more often located at the junction of the upper third and the lower two-thirds of the thyroid lobes. Metastatic dissemination to both central and lateral cervical lymph nodes occurs frequently. Cervical lymph node metastases are found in 20-30% of patients with MTC <1 cm in diameter,<sup>21,22</sup> in 50% of patients with a tumor 1-4cm in diameter and in up to 90% of patients with a tumor >4cm in diameter.<sup>23,24</sup> Metastases outside the neck may occur in the liver, lungs, bones and, less frequently, brain and skin.

A combination of imaging techniques (neck ultrasonography, chest spiral CT, liver MRI with standardized procedures and both bone scintigraphy and axial bone MRI) is used to determine the disease extent and lymph node metastases. These imaging modalities detect 98% of neck recurrences, 100% of mediastinal lymph node, lung and liver metastases and 94% of bone metastases.<sup>25</sup> Radioisotope techniques using radiotracers like MIBG, radiolabeled analogues of somatostatin (111In DTPA octreotide) and FDG PET have low prognostic value but may be helpful in certain patients.<sup>25</sup>

Total thyroidectomy and bilateral modified radical neck dissection after exclusion of a coexisting pheochromocytoma is the treatment of choice for all patients with MTC. Biochemical cure is achieved in about 80% of cases. However, 20% of patients will relapse or harbor residual disease.<sup>26,27</sup>

In our case, the removal of the mediastinal mass proved laborious and time-consuming because the tumor was fragile, bled easily and was close to major vascular structures of the mediastinum. Following the removal of the mediastinal tumor, the intraoperative condition of the patient dictated a conservative approach to the removal of the primary thyroid tumor and neck lymph node metastases. As a result, total thyroidectomy with central neck compartment dissection was carried out instead of bilateral modified radical neck dissection.

To our knowledge this is the first case of an occult medullary microcarcinoma presenting as an asymptomatic mediastinal mass with concomitant elevation of CT and CEA. A high index of suspicion is required for diagnosis and early intervention, since the outcome of the disease depends on tumor burden at diagnosis.

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