

“Atypical” non-secretory medullary thyroid carcinoma: case report and review of the literature

Abstract

Medullary Thyroid Carcinoma (MTC) is an uncommon neuroendocrine malignancy of the thyroid. It is aggressive, with a 10 - year survival rate about 70%. Early diagnosis is highly important, mostly because radical surgical excision is the only mean of cure since MTC exhibits poor response to chemotherapy and radiation therapy. In the majority of cases the diagnosis is secured based on the level of serum calcitonin.

We present 71 year old female patient with histologically proven medullary thyroid carcinoma and almost undetectable preoperative serum calcitonin (serum calcitonin was 0.94 pg/ml -reference rate <4.6 pg/ml). To this date only a few cases of non - secreting MTC have been described, cases presenting some similarities but many differences as well. Are these “atypical” non - secreting MTC a new subgroup? The only certainty is that the diagnosis and follow up of such patients is challenging.

Keywords: medullary thyroid carcinoma, calcitonin, atypical, non- secreting, procalcitonin

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Argyro Panagiotakou, Dimitrios Ioannidis, Dimitrios Lilis, Georgios Karageorgos
Sismanoglio-Amalia Fleming General Hospital, Amalia Fleming
Department of Endocrinology and Metabolism, Greece

Correspondence: Argyro Panagiotakou, Sismanoglio-Amalia Fleming General Hospital, Amalia Fleming Department of Endocrinology and Metabolism, Athens, Greece,
Email arpanagiotakou@gmail.com

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Introduction

Medullary thyroid carcinoma (MTC) is a rare malignancy of the parafollicular cells of the thyroid. It accounts for about 3 - 10 % of all thyroid cancer.^{1,2} Although MTC is considered a well differentiated tumour, it is quite aggressive.³ In fact it is the second most aggressive thyroid cancer after anaplastic carcinoma,⁴ with a mortality rate that ranges between 13, 4 - 38%.²⁻⁵ Its poor prognosis relies not only on its aggressive nature but also on its limited response to chemotherapy and radiation.⁶ Currently the only possible mean of care for MTC is surgical excision.⁷ Almost 37% of patients have lymph node metastases at the time of diagnosis regardless if they have large palpable tumours or small micro carcinomas.⁸ Preoperative diagnosis is crucial in order to plan the extent of surgery.

Parafollicular carcinoma cells retain their ability to express, synthesize and secrete calcitonin,⁴ making serum calcitonin an important tool not only for the diagnosis but also for the follow up and prognostication of patients with MTC.^{8,9} The routine measurement of serum calcitonin has been an area of great dispute, mostly when it comes to cost-effectiveness because of the low prevalence of MTC and the unnecessary thyroidectomies resulting from false positive results.^{2,4} There are a number of other causes besides MTC for hypercalcitonemia,^{2,4} making the false positive results of serum calcitonin a true diagnostic challenge. However false negative results are very rare.⁴ In fact in the past 20 years there have been some reports of medullary thyroid cancer patients without elevated and in some cases even undetected serum calcitonin (Table 1).

The main question is, does negative calcitonin MTC really exist or is it a glitch of the laboratory tests. If there is in fact such a subgroup of “atypical” non-secretory MTC, does it behave differently than the classical MTC? We have encountered such a case in our department, a female patient with histologic proven MTC and very low preoperative serum calcitonin.



Figure 1 Ultra sound of the left thyroid lobe, the suspicious nodule is marked with crosses.

Case report

The patient was a 71 year old female with a history of autoimmune “Hashimoto” thyroiditis and hypothyroidism treated with 100mcg of L-Thyroxine per day. The rest of her personal as well as family history did not exhibit anything remarkable. The patient’s thyroid ultrasound showed a small heterogeneous thyroid gland consistent with chronic thyroiditis, and revealed a hypoechoic nodule on the upper left lobe 0.83 X 0.86 cm long with partially calcified capsule, irregular borders and vascularisation (Figure 1). The fine needle aspiration cytology of the nodule was inconclusive (the result came back as undiagnostic/undetermined). Since the patient had no family history suspicious for MTC and her serum calcitonin was 0.94 pg/ml (reference rate <4.6 pg/ml), there was no further investigation towards the diagnosis of

MTC. She was advised for follow up and a new FNA of the suspicious nodule in six months. The patient however decided not to repeat the FNA, but instead to have a thyroidectomy. The pathology report came back as medullary thyroid carcinoma.

The histology report showed a vascularized tumor 7mm, partially encapsulated. The tumor cells were mostly spindle-shaped, arranged in trabecules infiltrating the surrounding gland, they exhibit deep stippled chromatin nucleus, sometimes multinucleated with rare mitotic figures. The immunohistochemistry showed diffuse staining for Chromogranin A, TTF1 and weak focal staining for Calcitonin. The tumor was completely negative for thyroglobulin, CK7, CK19, CK20 and CEA. The non-neoplastic gland showed lymphocytic infiltration and destruction consistent with Hashimoto's thyroiditis.

After the thyroidectomy the patient had a new ultra sound of the cervical area, a computer tomography scan of the thorax and abdominal, a new measurement of serum calcitonin, CEA and PTH, and a RET

oncogene mutation analysis. The calcitonin and CEA as expected were low (calcitonin 0.5pg/ml, CEA 3.8 ng/ml) and PTH was within normal range (PTH 32.2 pg/ml). The cervical ultra sound and the CT of the abdominal were negative but the CT of the thorax showed a small lesion of 5mm. In any other case an undetectable postoperative serum calcitonin would corroborate this thoracic finding as a benign nodule.⁹ Since in this case serum calcitonin was of no use, to clarify the nature of the nodule, the patient had a fluorine-18, 2-deoxy-2-D-glucose positron emission tomography/ computer tomography ([18F] FDG-PET/CT). The results exonerated the thoracic nodule. The RET oncogene analysis reveal a double mutation in exon 11 (G691S) and in exon 15 (S904S).

In regards to her follow up, she will have a cervical ultra sound, an X- ray or a CT of the thorax, measurement of serum calcitonin, CEA, and PTH, as well as 24-hour urinary collection for evaluation of catecholamines and metanephrines every six months for five years and then annually.

Table 1 Negative Calcitonin Medullary Thyroid Carcinoma Cases Published

Author	Journal/Year	Type of article	Cases
Iglesias et al. ¹⁹	Med Clin/ 1997	Case Report	1
Niccoli et al. ²⁰	JCEM/ 1997	Original Article (to evaluate calcitonin routine measurement in diagnosing MTC)	2
Redding et al. ²¹	Thyroid/ 2000	Case Report	1
Bockhorn et al. ¹⁵	Thyroid/ 2004	Case Report	1
Bugalho et al. ²²	J of Surgical Oncology/ 2005	Original Article (to compare FNA with calcitonin measurement in preoperative diagnosis of MTC)	1
Sand et al. ³	W J Surgical Oncology/ 2006	Case Report	1
Dora et al. ¹³	Thyroid/ 2008	Case Report	1
Giovanella et al. ¹⁹	Int J Biol Markers/ 2008	Case Report	1
Alapat et al. ¹⁴	Endocrine/ 2011	Case Report	1
Chambon et al. ²³	JCEM/ 2011	Case Report	2
Pirich et al. ²⁴	The Central European Journal of Medicine/ 2012	Original Article (to evaluate Pg stimulation test in early manifestation of familial MTC)	1
Frank- Raue et al. ¹⁰	Thyroid/ 2013	Original Article (to evaluate the prevalence and clinical spectrum of non-secretory MTC)	7
Pina et al. ⁴	Clinic Endocr/ 2013	Original Article (to compare basal calcitonin to Pg stimulation test in diagnosing MTC)	2
Solymosi et al. ²⁵	Int J of Endocrinology/ 2013	Original Article (preoperative diagnosis of MTC in iodine-deficient region)	1
Ferreira et al. ²⁶	Port Endocrinol Diab Metab/2014	Case Report	1
Brutsaert et al. ⁷	JCEM/ 2015	Case Report	1
Total Cases of Negative Calcitonin Mtc			25

Discussion

Atypical medullary thyroid carcinomas have been reported in the past, Schmid et al.,¹¹ described cases of MTC showing diffuse immunoreactivity for Chromogranin A, but weak and focal staining for Calcitonin and complete lack for CEA. However, in these cases serum calcitonin was not evaluated. Ever since, some case reports have been published (Table 1) regarding "atypical" negative calcitonin MTC, but only recently Frank - Raue et al.,¹⁰ described non-secretory MTC cases as a "subgroup" within 839 MTC patients, with a prevalence of 0.83%. In the total, 25 cases of such "atypical" non-secretory MTC have been described so far. Could all of these cases be laboratory errors? Serum calcitonin is difficult to handle, it exhibits pulsatile secretion and if left in room temperature it quickly degrades by serum proteases.¹² In addition cases of "hook effect" leading to false negative results have been described.^{9,13} All of the authors that encountered such cases of negative calcitonin MTC, just like us, consider this and after careful and thorough evaluation of the laboratory results, excluded laboratory errors.

Why these "atypical" MTC lose their ability to secrete calcitonin? Do all of these cases share the same features? In some cases the carcinoma exhibits diffuse staining for calcitonin,^{3,13,14} in other cases weak or focal.^{3,10,15} In some cases are micro MTC¹⁶ in other metastatic.³ One could say that not all could be explained by the same theory. If we could divide these negative calcitonin MTC into two categories, one were cancer cells show diffuse staining for calcitonin and another with weak and focal immunoreactivity, we could say that in the first category MTC maintain its ability to produce calcitonin but lose its ability to secrete it, whereas in the second category cancer cells cannot produce calcitonin. In regards to the first type of negative calcitonin MTC, one could hypothesize that there might be a defect in the secretory mechanism, or that the tumor preferential secrete precursor peptides and aberrant forms of calcitonin instead of the mature molecule,⁶ or that a mutation in the calcitonin/CGRP gene is responsible for the normal or reduced serum calcitonin.⁴ When it comes to the second category, we already know that in progressive disease calcitonin levels may decrease due to dedifferentiation,^{9,15} we could consider that tumor cells with weak calcitonin expression indicate a loss of function and there for dedifferentiation and more aggressive nature.^{7,14}

The past few years the role of pro-calcitonin have been investigated.^{12,16} Pro-calcitonin has the same sensitivity and specificity as calcitonin but it is a much more stable and easier to handle molecule than calcitonin.^{7,16} Could pro-calcitonin help us when it comes to patients with negative MTC? Brutsaert⁷ has evaluated serum pro-calcitonin in a negative MTC patient with diffuse immunoreactivity for calcitonin, preoperatively it was elevated (0, 21 ng/ml), whereas after thyroidectomy it decreased (<0, 1ng/ml). This rise of serum pro-calcitonin that Brutsaert measured is supportive of the theory of a tumor preferentially secreting precursor molecules than mature calcitonin. So perhaps serum pro-calcitonin can help us in some cases of non-secreting MTC. Some of the authors suggest that no matter the reason, negative calcitonin MTC have poorer prognosis than classical MTC.^{4,7}

On the other hand, Frank-Raue et al.,¹⁰ states that the prognosis of such cases is not different substantially from secretory sporadic MTC. Unfortunately the small number of non-secretory MTC does not allow us to evaluate the nature and behaviour of such tumours. The follow up of these patients is more difficult, since serum calcitonin is of no

use. Most authors suggest a neck ultra sound, an x-ray or CT of the thorax, an ultra sound or MRI of the liver, and measurements of serum calcitonin and CEA,^{10,15} upon follow up, and if needed [18F] FDG-PET/CT.^{15,17} Of course if a RET mutation is discovered the follow up must include evaluation of PTH and catecholamines/ metanephrines.

Conclusion

Although we cannot right now explain the molecular mechanism for the lack of elevated serum calcitonin, "atypical" non-secretory calcitonin medullary thyroid carcinomas are a fact. If we consider that 10-15% of MTC are diagnosed after thyroidectomy,¹ and there have been some reports for grossly metastatic MTC with limited rise on serum calcitonin,¹⁸ this subgroup of "atypical" non-secretory MTC might actually be underestimated. How these tumors will behave, it's difficult to establish a pattern with such a small number of patients. Close monitoring of these patients will help us understand the true nature of this rare form of medullary thyroid carcinoma.

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Conflicts of interest

The author declares there is no conflict of interest.

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