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CASE REPORT

An Unusual Case of Medullary Thyroid Carcinoma and A Revision of Current Literature

Claudia Cipri[1*], Fabio Vescini[1], Francesca Torresan[2], Gianmaria Pennelli[3], Maria Rosa Pelizzo[2], Vincenzo Triggiani[4], Edoardo Guastamacchia[4] and Franco Grimaldi[1]

[1]*Endocrinology and Metabolism Unit, University-Hospital "Santa Maria della Misericordia", Udine;* [2]*II General Surgery, Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova;* [3]*II Pathology Unit, University of Padova, Padova;* [4]*Interdisciplinary Department of Medicine-Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases. University of Bari "Aldo Moro", School of Medicine, Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy*

Abstract: ***Background:*** Medullary thyroid cancer (MTC) accounts for 5% of all thyroid cancers and occurs either sporadically or in a hereditary pattern. Routine calcitonin (CT) measurement is suggested for MTC screening in patients with nodular thyroid disease.

Patient Findings: A 45 years-old woman incidentally discovered, with neck ultrasound, the presence of thyroid micronodules. Fine-needle aspiration (FNA) on thyroid prevailing nodule did not demonstrate cellular atypia.

During follow-up, FNA was repeated on the previously analyzed nodule suspicious for Hürthle cell nodule suspicious for follicular neoplasm and on another hypoechoic right nodule which showed cellular atypia. CT was <2 pg/ml (normal values <18.2 pg/ml), anti-thyroid antibodies were positive and the patient showed a normal thyroid function.

The patient also was diagnosed with primary hyperparathyroidism with an enlarged parathyroid gland behind the right thyroid lobe. Therefore, she underwent total thyroidectomy and a selective parathyroidectomy was performed.

Histology showed an encapsulated microMTC (pT1aNxMx) associated with diffuse C-cell hyperplasia and lymphocytic thyroiditis. The neoplasm was positive for calcitonin and chromogranin A and negative for thyroglobulin. A right parathyroid adenoma was also diagnosed. One month after surgery basal and stimulated CT were <2 ng/ml. Genetic analysis did not reveal mutation of RET proto-oncogene. Twelve months after surgery, neck ultrasonography, chest and abdomen computed tomography did not demonstrated residual/recurrent disease with undetectable serum CT.

Conclusion: In the literature, few MTC cases with normal serum CT have been reported. Although MTC without elevated plasma CT is extremely rare, normal or low CT levels, do not entirely exclude this diagnosis.

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1. INTRODUCTION

Among all thyroid cancers, medullary carcinoma (MTC) has a presentation rate around 5% and it occurs either sporadically (75% of cases) or in a hereditary pattern: familial MTC (FMTC), multiple endocrine neoplasia (MEN) type 2A and type 2B [1, 2]. The MTC rises from C-cells developing, in the beginning, as primary C-cell hyperplasia (CCH); it may evolve to early invasive medullary microcarcinoma and eventually to an invasive macroscopic form [3]. The tumor marker is calcitonin (32-aminoacid polypeptidic hormone), therefore in patients with nodular thyroid disease, routine calcitonin measurement has been suggested [4-7]. Based on these facts, it is very unlikely to find normal calcitonin levels in patients with MTC. Here we describe the case of a woman with normal serum calcitonin levels, whose thyroid was discovered, after surgery, to harbour a medullary cancer.

2. PATIENT

The patient is a 45 years-old woman, who, during investigations for other diseases and in the absence of symptoms, had a neck ultrasound which incidentally revealed the presence of thyroid micronodules. Fine-needle aspiration (FNA)

*Address correspondence to this author at the Endocrinology and Metabolism Unit, University-Hospital "Santa Maria della Misericordia", Udine; E-mail: claudia.cipri@asuiud.sanita.fvg.it

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on thyroid prevailing nodule (middle third of the right lobe, hypoechoic with hyperechoic spots, diameters 7x8x9 mm) did not demonstrate cellular atypia.

During follow-up, the patient repeated the neck ultrasound that confirmed the presence of thyroid micronodules. Due to enlargement of the previously analyzed nodule, fine-needle aspiration was repeated (nodule n°1); FNA was also performed on another hypoechoic right nodule (nodule n°2), already present in the former ultrasound, which showed a longest diameter enlarged (10 mm).

The cytology of n°1 pointed to a Hürthle cell nodule, suspicious for follicular neoplasm, while n°2 showed cellular atypia.

The patient was, therefore, referred to surgery for right lobectomy and isthmusectomy.

The pre-surgery basal serum calcitonin (CT) was lower than 2 pg/ml (normal values < 18.2 pg/ml). Anti-thyroid antibodies were positive (AbTG = 126 UI/ml, with normal values <60 UI/mL, and AbTPO = 7.3 UI/ml with normal values <50 UI/mL) and TSH and free thyroxine were within the normal range (TSH = 2.5 mUI/L with normal values 0.27-4.20 mUI/L; fT4 = 18.01 pmol/l with normal values 12-22 pmol/l).

At the same time, the patient was also diagnosed with primary hyperparathyroidism due both to high calcium (5.2 mEq/l with normal values 4.2-5.1 mEq/l) and PTH values (93 pg/ml with normal values 15-65 pg/ml); moreover neck ultrasound detected an enlarged parathyroid gland, located behind the lower pole of the right thyroid lobe. At this point a selective right low parathyroidectomy was suggested as well.

The surgeon's final decision was to perform a total thyroidectomy associated with selective right inferior parathyroidectomy.

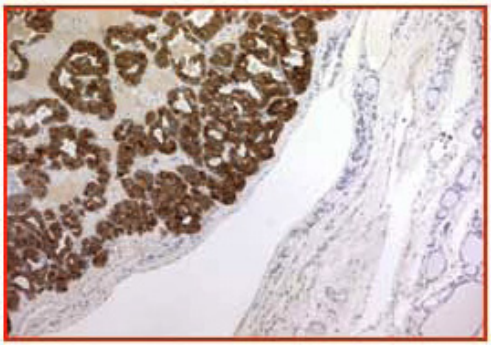
Histological examination showed a micro-encapsulated medullary thyroid carcinoma (pT1a Nx Mx) associated with diffuse CCH and lymphocytic thyroiditis. The neoplasm showed positive staining for calcitonin and chromogranin A, while it resulted negative for thyroglobulin (Figs. **1** and **2**). A right parathyroid adenoma was also diagnosed. One month after surgery serum calcium and phosphate were normal and basal serum CT was < 2 ng/ml. Carcinoembryonic antigen (CEA) levels and 24-hour urine metanephrines resulted within the normal range as well. Genetic analysis did not reveal mutation of RET proto-oncogene.

The provocative test with intravenous calcium performed after surgery did not rise CT values that remained always undetectable.

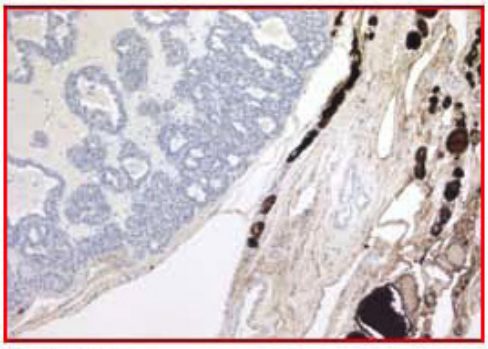
Twelve months after surgery, the patient underwent neck ultrasonography, chest and abdomen computed tomography with no evidence of residual/recurrent disease. Serum levels of CT and CEA still remained below normal thresholds.

3. DISCUSSION AND REVIEW OF LITERATURE

Serum calcitonin is a specific marker for MTC useful both at the time of diagnosis and during the follow-up. It is also correlated with tumor burden and prognosis [8-10].

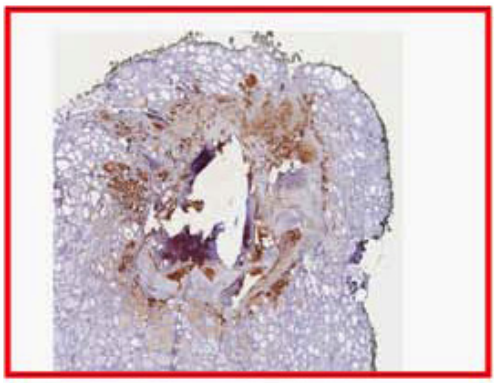


(A)

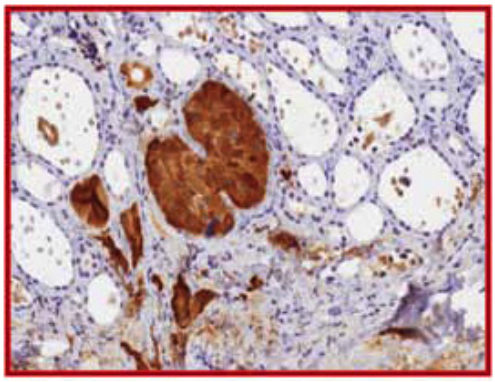


(B)

Fig. (1). epithelial cells with an organoid and trabecular pattern with positive immunohystochemical staining for chromogranin A (**A**), and negative for thyroglobulin (**B**).



(A)



(B)

Fig. (2). epithelial cells with an organoid and trabecular pattern with positive immunohystochemical staining for calcitonin (**A**-**B**).

As in our case, incidentally discovered MTCs are described after thyroidectomy performed for other indications. Literature data showed that about 1-2% of thyroid nodules with indeterminate cytology, become medullary carcinomas at histological examination [11]. Also, in some patients operated for cytology consistent with thyroid cancer, histology revealed medullary thyroid cancer.

MTC is incidentally discovered also in patients who undergo total thyroidectomy for known differentiated thyroid cancer (DTC). Up to 3% of MTC patients have also papillary (PTC) or follicular thyroid carcinoma (FTC) on surgical pathology, (U.S. Surveillance, Epidemiology and End Results (SEER) database (1973–2002)) [12]. A higher prevalence of mixed MTC and PTC in thyroidectomy specimens was seen in a retrospective study of 196 consecutive cases of MTC; of these, 27 (13.8%) were found to have coincidental microscopic PTC. No association was found between the presence of microscopic PTC and overall outcome of MTC [13, 14].

The peculiarity of the present case is the absence of detectable serum calcitonin before surgery. In the literature, so far, twelve papers describing this particular condition have been published. Nine of these are case reports [15-23] (Table **1**) and the remaining four papers are reviews of thyroid surgical series where non secretory medullary thyroid cancers were found [5, 24-26]. Overall, 19 patients were described, 11 females and 6 males (gender not reported in 2 cases). The average age was 50 years old, (16–73 years), with a mean cancer size of 26 mm (range 0.5–80 mm). Of these, four patients died within 36 months from diagnosis. Final histological diagnosis was of micro-MTC in 2 patients, well differentiated MTC in 10, while the 6 remaining had poorly-differentiated MTC. In 15 cases immunohistochemical analysis was performed with positive results.

Overall, the clinical presentation and outcome of this small series are similar to those reported for MTC patients.

Such as reported in literature, some explanations for these findings have been given, such as the possibility of calcitonin assay interferences, or the ‘‘hook effect’’. Serum calcitonin can be measured by different immunoassay methodologies, like enzyme-linked immunosorbent assays (ELISA), radioimmunoassay (RIA), immunoradiometric assays (IRMA) and immunofluorometric assays (IFMA). The hook effect occurs when the serum antigen level is extremely high during the one-step IRMA where the signal antibodies, bound to the noncaptured antigens, are washed out during the measurement, inducing the loss of signal. To prevent the “hook effect”, successive dilutions of the same sample of serum can be done [27]. In our case, the hook effect was excluded by performing 1:10 and 1:100 dilutions of patient’s serum.

Another possible explanation for the normal serum calcitonin levels could be that the calcitonin antibodies used during immunohistochemistry (IMHC) staining, cannot recognize the calcitonin molecule due to aberrant post-translational modifications. For all the reported cases, IMHC staining was performed with the same calcitonin antibodies used for serum calcitonin assay and the tumors showed a strongly positive staining, thus excluding major abnormalities in calcitonin protein. Therefore, it seems that for unknown reasons these cells retain the ability to synthesize but not to secrete the calcitonin molecule. Theoretically, there are two potential mechanisms for impaired calcitonin secretion in our case, such reported in literature: some abnormality in the secretion of calcitonin occurs in the dedifferentiation process of the parafollicular cell towards MTC cell or there is a preneoplastic impairment in calcitonin secretion of the parafollicular cells. However, the exact mechanism remains uncertain [20] and we have no evidence to confirm this, although we believe that this theory may be the most plausible explanation in our case.

CONCLUSION

Although medullary carcinoma without elevated plasma calcitonin is extremely rare, we decided to describe the present case in order to emphasize that normal or low levels of

Table 1. Medullary Thyroid Cancer and Normal pre-surgery Serum Calcitonin, Case Report.

Sex/Age	Tumor Size	TNM Stage	RET Mutation	Familial History	Immunohistochemistry					References
					CT	CEA	SPH	CGA	TG	
F/39	2,6 cm	II	-	-	+	NA	NA	+	NA	2014 [20]
F/16	3 cm	II	-	-	+	+	NA	+	NA	2011 [21]
F/43	4,5 cm	III	-	-	+	+	-	+	-	2008 [22]
M/44	1.7 cm	III	-	-	+	+	+	+	-	2008 [19]
M/48	5 cm	IV	NA	-	+	+	+	+	-	2007 [17]
F/73	NA	IV	NA	-	+	+	NA	NA	NA	2006 [14]
F/50	2 cm	II	-	-	+	+	NA	+	-	2004 [16]
F/30	4.5 cm	III	-	-	+	+	+	-	-	2000 [18]
F/65	NA	IV	NA	-	+	NA	NA	NA	NA	1997 [15]

CT: calcitonin; CEA: carcinoembryonic antigen; SPH: synaptophysin; CGA: chromogranin A; TG: thyroglobulin.

calcitonin, especially when a thyroid neoplasm is suspected, do not entirely exclude this diagnosis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The research was performed in human in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/

CONSENT FOR PUBLICATON

A written informed consent was obtained from the patient prior to the publication of the study.

CONFLICT OF INTEREST

Authors declare no conflict of interest, financial or otherwise.

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Declared none.

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