

Clinical Case Seminar

A1(1-6)

To screen or not to screen for medullary thyroid cancer? This is (yet) the question. An illustrative case.

¹Rosaria M. Ruggeri, ²Luca Giovanella, ³Francesco Trimarchi, ⁴Alfredo Campennì

¹Department of Clinical and Experimental Medicine, University of Messina; ²Department of Nuclear Medicine and Thyroid Centre, Oncology Institute of Southern Switzerland, Bellinzona, 6500, Switzerland; ³Accademia Peloritana dei Pericolanti, at the University of Messina; ⁴Department of Biomedical and Dental Sciences, and Morpho-Functional Images, Unit of Nuclear Medicine, University of Messina, Messina, Italy

Abstract

Medullary thyroid cancer (MTC) is a rare disease, often displaying an aggressive behavior and a poor prognosis. Serum calcitonin represents the most sensitive marker of MTC and its routine measurement in patients with thyroid nodules allows early detection of occult MTC and appropriate surgical cure. Here we report on a 55-yr-old woman with a long-standing goiter, autonomously functioning thyroid nodules and subclinical thyrotoxicosis, who was diagnosed with MTC at an early stage by means of calcitonin screening. This rare case highlights the importance of performing routine calcitonin measurement in thyroid nodules.

KeyWords: medullary thyroid cancer; calcitonin-thyroid nodules

Introducing Member: Rosaria M. Ruggeri

Corresponding Author: Rosaria M. Ruggeri - rmruggeri@unime.it

Introduction

Medullary thyroid cancer (MTC) is an uncommon malignancy arising from parafollicular C cells, accounting for about 5-10% of thyroid malignancy (1). MTC presents in sporadic (75-80%) and familial forms (20-25%, multiple endocrine neoplasia, MEN2A and MEN 2B, or familial MTC), the latter being secondary to germline mutations in the RET proto-oncogene (2). Compared to well-differentiated thyroid cancers (DTC) arising from the follicular epithelium, MTC has a more aggressive behaviour and a lower rate of cure once the disease spreads beyond the thyroid (1,2). It has been estimated a 10-year survival rate of about 50%, mostly depending on the stage of the tumour at diagnosis (2). Therefore, early diagnosis of MTC is paramount, but it still represents a challenge in clinical practice (2).

The main clinical manifestation of MTC is a thyroid nodule, either single or in the context of a multinodular goitre (1,2). However, neither neck ultrasonography (US) nor fine needle aspiration biopsy (FNAB) achieve as high diagnostic reliability in MTC as they have in DTC (3,4). Calcitonin (Ctn) secreted by parafollicular C cells represents a highly sensitive marker of MTC and

the measurement of serum Ctn levels allows early diagnosis and curative surgery in most patients (5). However, there is no consensus on cost-effectiveness of routine Ctn screening in patients with thyroid nodules (6-8).

Herein we present a 55-year-old woman with MTC detected at an early stage by means of Ctn screening during the diagnostic work-up of a long-standing multinodular goiter.

Case Report

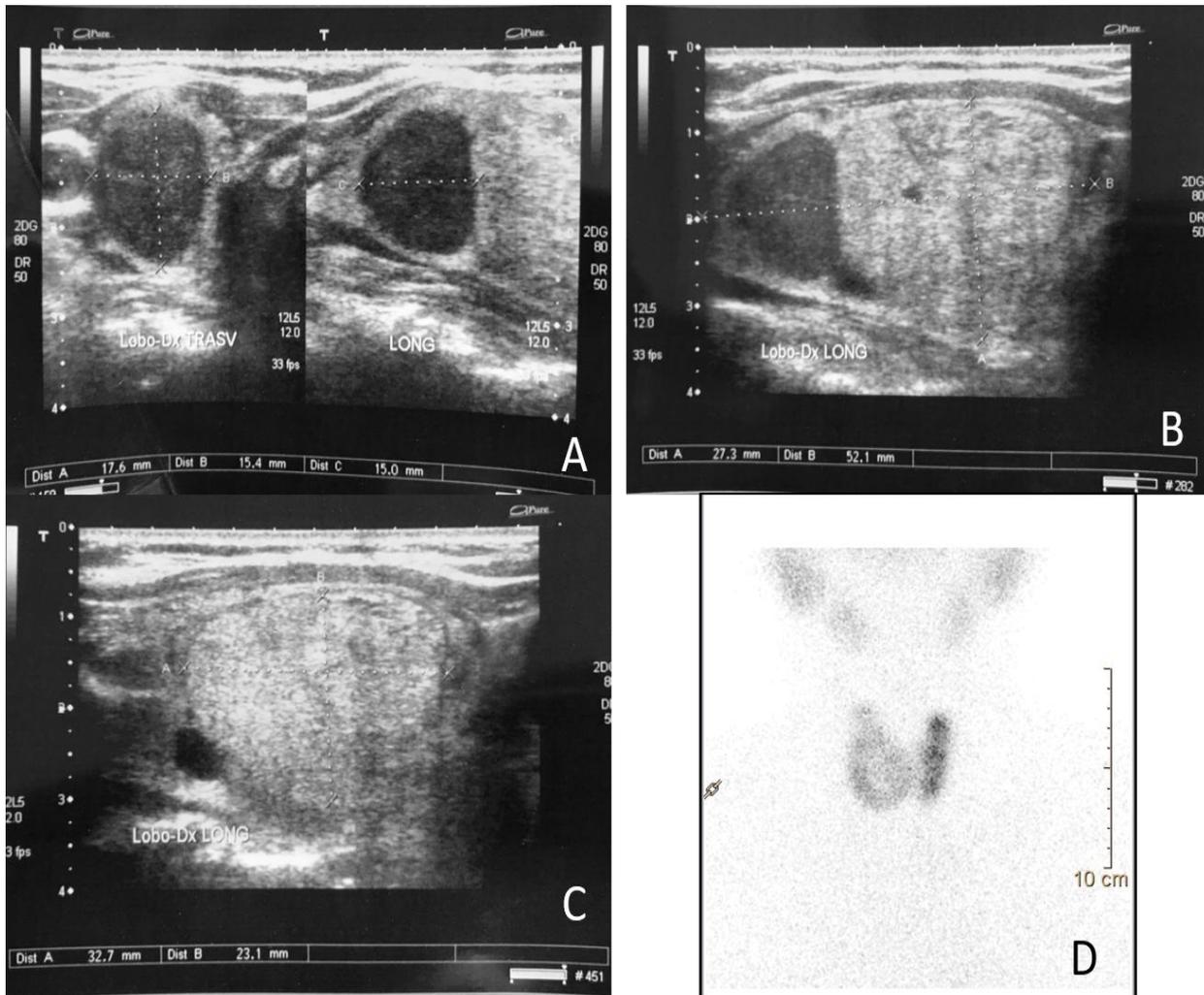
A 55-year-old female patient was referred to our Endocrine Unit in 2016, because of recurrent atrial fibrillation (AF) and subclinical thyrotoxicosis. There was no family history of thyroid cancer. The patient had a long-standing multinodular goiter and was not taking any medications. Starting from 2014 she had suffered from recurrent AFs and serum TSH values had been found to be low or frankly suppressed, with free thyroid hormones levels within the normal range (subclinical thyrotoxicosis). A painless mass in the right anterior side of the neck had appeared about one year earlier. Physical examination demonstrated an enlarged thyroid lobe with a palpable, nodular lesion in its lower part, moving with deglutition. Neck US demonstrated a 33-mm isoechoic nodule, with regular margins, a peripheral halo and colliquative areas, in the lower portion of the right thyroid lobe, corresponding to the palpable mass.

Also, a hypoechoic nodule, with regular margins, measuring 15x14x17 mm, was described in the upper portion of the right lobe, along with three sub-centimetric, isoechoic nodules in the left lobe (Figure 1, panels A-C). Thyroid scintigraphy revealed an avid uptake of the tracer in the right lower lobe and in the left-sided nodules, with no uptake by the extra nodular tissue, consistently with autonomously functioning thyroid nodules (AFTNs) (Figure 1, panel D).

US-guided FNAB of the right-upper "cold" nodule was performed, but cytological examination was inconclusive (TIR1). Hormonal profile confirmed suppressed serum TSH, with normal values of free triiodothyronine (FT3) and free thyroxine (FT4) (Table 1).

Serum Ctn measurement was performed to screen for medullary thyroid cancer and was found to be high (Table 1). The patient refused to undergo intravenous calcium stimulation test, that could have been useful in distinguishing between MTC and a non-thyroidal malignancy secreting Ctn (i.e. an enteric or pulmonary neuroendocrine tumor). Since serum Ctn was greater than 500 pg/mL, pre-operative systemic imaging (total-body contrast-enhanced computed tomography, TCT) was performed, in addition to neck US; no regional or distant metastases were detected.

Figure 1. Thyroid ultrasonography and scintigraphy of our patient: illustrative images.



The presence of a pheochromocytoma and/or primary hyperparathyroidism (pHPTH) was also excluded (Table 1). The patient underwent total thyroidectomy and central and lateral compartment neck lymph node dissections. At pathology, the right-upper nodule was confirmed as an MTC, without vascular or capsular invasion (pT1aN0M0). All the excised lymph nodes (n=14) were negative. After surgery, serum Ctn dropped to 0.7 pg/ml and CEA to 0.5 ng/dl, and so they remained during the follow-up. No genetic alterations of the RET gene were found by sequencing of germline DNA from the patient. At the last control in our hospital, two years after surgery, the patient had no clinical, biochemical and instrumental evidence of recurrent or residual MTC.

Table 1. Main biochemical data of our patient at time of MTC diagnosis.

Analyte (unit of measure)	Patient's value*	Normal range
Calcitonin ng/ml	1764	0-6.4
CEAng/ml	5.5	0-5.0
Chromogranin A ng/ml	19.2	<101.9
TSH μIU/ml	0.08	0.27-4.20
FT3 pg/ml	2.15	2-4.4
FT4 pmol/L	18.7	12-22
TPO-Ab	NEG	<10
Tg-Ab	NEG	<100
PTH pg/ml	29.90	8-76
Calcium mg/dl	9.3	8.2-10.4
Urinary epinefrine μg/24h	9.5	1.7-22.4
Urinary normetanephrineμg/24h	17.7	12.1-85.5
Urinary metanephrineμg/24h	125	10-275

**Patient's values typed in bold are altered.*

Discussion

The unusual case of this 55-yr-old woman demonstrates the importance of routine measurement of Ctn to detect occult MTC in patients harboring thyroid nodules. In our patient, there were no clues to suspect malignancy preoperatively. She had no family history of thyroid cancer or personal risk factors, except for the multinodular goiter, which represents itself a modifiable risk factor. The clinical presentation was mainly characterized by the presence of recurrent AF, subclinical thyrotoxicosis and AFTNs in the context of a longstanding multinodular goiter, a quite common and reassuring clinical picture. To the best of our knowledge, this is the second report of such an association of MTC and AFTNs with subclinical thyrotoxicosis. Prior of us, Pacini et al. reported an unique case of unsuspected MTC in a patient harboring an AFTN in the same lobe, among a large unselected series of patients with nodular thyroid disease (9). In our patient, US did not reveal features of suspected malignancy: the nodule was hypoechoic, but its margins were regular and there were no other US signs of malignancy (taller than wide shape, microcalcifications, intra-nodular vascularity, ...) or lymph nodal involvement.

The present case emphasizes how US, that represent the main tool for evaluation and risk stratification of thyroid nodules, is often unable to suspect/diagnose MTC preoperatively. Despite hypoechoic lesions have a higher risk of being malignant, hypoechogenicity alone is inaccurate in predicting malignancy. Moreover, most of studies evaluating US criteria of malignancy concern papillary thyroid carcinoma (PTC), that represents the most common histotype of thyroid cancer,

while only few studies are available on US criteria for possibly malignant MTC. From these studies it emerges that a not negligible proportion of MTC do not fit the “classic” US criteria of malignancy: at least, one out of four MTC nodules appears not suspicious on US (i.e., iso-echoid nodule, mixed or spongiform aspect, regular margins, no microcalcifications) (2,3). Trimboli and co-workers showed low frequency of US features associated to PTC when analysed in MTC. Furthermore, the presence of one US risk feature (as in our patient) was almost equal in MTC (58.3%) and benign lesions (55.5%), while it was significantly ($p < 0.001$) more frequent in PTC (3). Moreover, even when the suspicious nodule is submitted to FNAB, cytology has several pitfalls for MTC and is often non diagnostic (as in our case), with a reported sensitivity of no more than 63% (3,4).

Serum Ctn measurement represents the most sensitive tool for pre-operative diagnosis of MTC, much more sensitive than cytology (5, 9). Given the above discussed diagnostic limits of US, it is quite hard to propose serum Ctn measurement in selected patients; it should be rather performed in all patients with thyroid nodules. Indeed, routine measurement of Ctn in thyroid nodules allows pre-operative detection of MTC at an early stage and appropriate surgical approach, including total thyroidectomy and lymph node dissection, with a favourable impact on tumour outcome and prognosis (2,5, 9). However, the cost-effectiveness of a universal screening approach is still a matter of debate, due to the very low prevalence of MTC (0.3-1.4%) among patients with thyroid nodules (6). Moreover, false-positive Ctn results exist and non MTC-related causes of high Ctn should be recognized and excluded: chronic renal failure, heterophilic antibodies, HPTH, autoimmune thyroiditis, mastocytosis, and various non-thyroid tumors, including small cell and large cell lung cancers, prostate cancer, enteric and pulmonary neuroendocrine tumors (5, 8). Thus, evaluating the cost-benefit ratio, a universal screening for Ctn definitively improves the preoperative diagnosis of often unsuspected MTC and the initial surgical approach, achieving a high rate of definite cure. On the other hand, a larger number of subjects with abnormal serum Ctn levels who have no MTC would undergo unnecessary surgery, with its possible complications and the need of life-long L-thyroxine therapy. Also, the low specificity of assays for measuring Ctn should be taken into account: a negative test does not rule out disease (5, 8). For these reasons, recent ATA guidelines (6) do not recommend either for or against routine measurement of Ctn, while the AACE/AME/ETA guidelines (7) suggests Ctn in the routine workup of thyroid nodules. The ATA guidelines for MTC management (8) recommend “that physicians decide whether the technique is useful in the management of patients in their clinic (Recommendation 20)”.

Although anecdotal, the present case highlights the importance of considering MTC in the

differential diagnosis of thyroid nodules by means of Ctn screening.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

References

1. Griebeler, M.L., Gharib, H., Thompson, G.B. (2013). Medullary thyroid carcinoma. *EndocrPract.*19:703-711. doi: 10.4158/EP12430.
2. Trimboli, P., Giovanella, L., Crescenzi, A., Romanelli, F., Valabrega, S., Spriano, G., Cremonini, N., Guglielmi, R., Papini, E.(2014). Medullary thyroid cancer diagnosis: an appraisal. *Head Neck.* 36:1216-1223.
3. Trimboli, P., Nasrollah, N., Amendola, S., Rossi, F., Ramacciato, F., Romanelli F, et al.(2012). Should we use ultrasound features associated with papillary thyroid cancer in diagnosing medullary thyroid cancer? *Endocrine J.* 59: 503-508.
4. Dyhdalo, K.S., Chute, D.J. (2018) Barriers to the recognition of medullary thyroid carcinoma on FNA: Implications relevant to the new American Thyroid Association guidelines. *Cancer Cytopathol.* doi: 10.1002/cncy.21990.
5. Elisei R. (2008) Routine serum calcitonin measurement in the evaluation of thyroid nodules. *Best Pract Res ClinEndocrinolMetab.*22:941-953. doi: 10.1016/j.beem.2008.09.008.
6. Haugen, B.H., Alexander, E.K., Bible, K.C., Doherty, G.M., Mandel, S.J., Nikiforov, Y.E., et al. (2016) 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid.* 26: 1–133. doi: 10.1089/thy.2015.0020
7. Gharib, H., Papini, E., Paschke, R., Duick, D.S., Valcavi, R., Hegedus, L., et al. (2010) American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. *J Endocrinol Invest.*33:51–56.
8. Wells, S.A. Jr, Asa, S.L., Dralle, H., Elisei, R., Evans, D.B., Gagel, R.F., et al. (2015). Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma: The American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. *Thyroid.* 25: 567–610. doi: 10.1089/thy.2014.0335.
9. Pacini, F., Fontanelli, M., Fugazzola, L., Elisei, R., Romei, C., Di Coscio, G., Miccoli, P., Pinchera, A. (1994) Routine measurement of serum calcitonin in nodular thyroid diseases allows the preoperative diagnosis of unsuspected sporadic medullary thyroid carcinoma. *J ClinEndocrinolMetab.* 78:826-829.



©2018 by the Author(s); licensee Accademia Peloritana dei Pericolanti (Messina, Italy). This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>).

Communicated and received June 26 2018, revised August 7, 2018, published on line December 18, 2018