Clinical note

Mild to moderate increase of serum calcitonin levels only in presence of large medullary thyroid cancer deposits

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A B S T R A C T

Many open questions remain to be elucidated about the diagnosis, treatment and prognosis of medullary thyroid cancer (MTC). The most intriguing concerns the outcome of MTC patients after surgery. Great importance is usually given to serum calcitonin (Ct) and carcinoembryonic (CEA) levels. It is commonly believed that the higher are the levels of these tumor markers and their kinetics (double time and velocity of markers levels) the worse is the prognosis. However, this is not the rule, as there are huge MTC metastatic deposits characterized by low serum Ct and CEA levels, and this condition is not closely related to the outcome of the disease during post-surgical follow-up. A series is reported here of patients who have these characteristics, as well as a description of their prognosis and clinical outcome.

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Niveles séricos moderadamente elevados de calcitonina en presencia de grandes lesiones de cáncer medular de tiroides

R E S U M E N

Numerosas preguntas están pendientes de responder sobre el diagnóstico, tratamiento y pronóstico del cáncer medular de tiroides (MTC). El problema más intrigante se refiere a la evolución de los pacientes después de la cirugía. Por lo general, una gran importancia se le da a la calcitonina sérica (Ct) y los niveles de antígeno carcinoembrionario (CEA). Está ampliamente aceptado que cuanto mayor sean los niveles de estos marcadores tumoriales y su cinética (tiempo de duplicación de los niveles), peor será el pronóstico. Sin embargo esta no es una regla: pueden existir grandes depósitos metastásicos de MTC que se acompañan de niveles bajos de Ct y CEA, y esta condición no está estrechamente relacionada con la evolución de la enfermedad durante de seguimiento postoperatorio. Presentamos una serie de pacientes con estas características y describimos su pronóstico y evolución clínica.

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Introduction

The treatment of hereditary and sporadic medullary thyroid carcinoma (MTC) is challenging. Despite recent advances and the current stratification of hereditary MTC in different risk classes, its biological aggressiveness remains unpredictable. This is true not only for patients with sporadic MTC, but even among hereditary MTC family members sharing the same genetic mutation

In many cases, despite efforts to ensure complete tumor surgical resection, results are invalidated due to existing metastases at the time of initial diagnosis.

Early diagnosis is only feasible in asymptomatic carriers of RET gene mutations. The potential surgical management of such patients is controversial. Many open questions remain to be without answer as: should these patients always undergo surgery, or should they only be followed up, despite the gene mutation? If surgery is selected, when should it be performed?

On the other hand, some sporadic MTCs take the form of a solitary, perhaps large thyroid nodule with no metastases, and could consequently be cured with relatively limited surgery.

Hence the persistence of differing opinions on the appropriate preoperative staging, extent of thyroidectomy and level of lymph node dissection, even for patients whose serum basal calcitonin (Ct)

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levels are commonly considered to be indicative of tumor deposits, and who therefore presumably have disseminated disease.\(^3\)

We report on three cases of MTC, two of them sporadic and one MEN II A, in which very advanced metastatic disease corresponded unpredictable with moderate increased only of serum Ct levels and no unequivocal changes in their serum CEA values.

Calcitonin is a qualitatively reliable marker for the diagnosis and follow-up of MTC, but its serum levels seem to depend more on the secretory ability of the cancer cells than on their mass. We therefore surmise that serum Ct levels alone are not enough for disease staging purposes, but should always be supported by imaging data. Any discrepancy emerging between Ct levels and the disease stage identified on imaging suggests a lesser degree of tumor differentiation and a consequently worse prognosis, potentially limiting an effective local resection.

**Case 1**

A 49-year-old man presented with weight loss. Ultrasound (US) of the neck revealed a nodule in the left thyroid lobe and cytology suggested a follicular tumor. MTC was subsequently established based on the patient’s high serum Ct levels (572 pg/mL). 24-h urinary metanephrines were higher than normal (5.90 μmol) and computed tomography demonstrated a large para-aortic mass suggestive of paraganglioma. \(^{18}\)F-DOPA-PET revealed sacral and L4 bone metastases (Fig. 1) and right mesogastrium uptake consistent with the paraganglioma (Fig. 2). This bone uptake was first interpreted as a bone metastasis from the paraganglioma, since the basal serum Ct level was higher than normal but not pathognomonic for disseminated disease, but the patient’s preoperative CEA levels were high (143.5 μg/L). Genetic analysis revealed the RET mutation C620R.

The patient underwent total thyroidectomy and selective left lateral cervical lymph node dissection (Fig. 3), with laparoscopic resection of the para-aortic paraganglioma (Fig. 1) at the same time.

Histology confirmed bilateral, multifocal MTC with lymph node metastases and vascular invasion, stage IVA (pTNM = T3mN1b). The paraganglioma was cystic and encapsulated, with no evidence of necrosis.

After 48 h, basal Ct levels remained high (385 ng/L) and a \(^{68}\)Ga-DOTANOC-PET confirmed bone uptake (not shown), although radio-peptide therapy was not performed because of patient refusal. Cytology on the aspirate from the lesion involving lumbar-4 confirmed the presence of bone invasion from MTC.

**Case 2**

A 73-year-old man presented with a history of right lateral cervical lymphadenopathy described as reactive, discovered 10 years earlier, with enlargement over a one month period.

US showed a globular, irregular right lateral cervical lymph node suspected of malignancy, plus a solid, hypo-echoic 23 mm nodule in the right thyroid lobe. FNAC of the thyroid nodule and lymph node suggested MTC with lateral cervical lymph node metastases as proven at thyroidectomy and central and right lateral cervical lymph node dissection (Fig. 4).

Thyroid function tests showed normal serum levels of TSH and anti-thyroid antibody. Basal serum Ct level was 154 ng/L, and CEA was within the normal range (2.7 ng/mL).

The patient’s only mildly increased Ct and normal CEA levels, despite the evidence of wide metastatic MTC, prompted measuring Ct level from the lateral cervical lymph node aspirate, which was >200,000 ng/mL. A stimulated calcitonin test using calcium gluconate revealed a peak Ct of 467 ng/mL. Screening for RET onco-gene mutations was negative and computed tomography identified no distant metastases.

Follow-up at two years reports that the patient is alive with disease (Ct = 447 ng/L; CEA = 102 μg/L).

**Fig. 1.** (Patient n. 1). Bone metastasis in the left sacrum. Left down: upper, axial CT image. Right down: axial fused DOPA-PET/CT images. Right: coronal fused DOPA-PET/CT images.

**Fig. 2.** (Patient n. 1). Paraganglioma in the right mesogastrium showed at FDG PET/CT. Anterior abdominal pelvic region.
Histology confirmed MTC with vascular invasion, recurrent, with lateral cervical lymph node metastases (pTNM = T3N1b, stage IVA), and a concomitant papillary microcarcinoma (0.2 cm).

At two years follow-up, the patient is alive without disease (undetectable serum Ct and CEA levels).

Case 3

A 71-year-old woman, who had been treated with $^{131}$I in the past for autoimmune hyperthyroidism, was assessed for dysphagia. US revealed a 2 cm hypervascularized nodule in the right thyroid lobe, with apparent central and ipsilateral lateral cervical lymph nodes. The computed tomography confirmed the presence of lateral cervical node disease while no distant metastases were detected. FNAC of the thyroid nodule indicated follicular thyroid cancer (THY3). Laboratory tests identified high serum Ct (460 ng/L), and CEA within normal range (2.2 μg/L). Genetic analysis was negative for RET mutations. TSH was within the expected range for a patient on $L$-thyroxine replacement therapy. The patient underwent total thyroidectomy with central and ipsilateral lateral cervical lymph node dissection. Histology confirmed MTC with amyloid stroma and lymph node metastases (stage IVA, pTNM = T4a N1b). After 48 h, the patient’s serum calcitonin level remained relatively high (51 ng/L). A subsequent $^{18}$F-DOPA-PET was negative, but FDG-PET revealed recurrent disease in the paratracheal mediastinum and bilateral retroclavicular lymph nodes (Fig. 5). The patient underwent resurgery, after which her serum Ct dropped to 7.9 ng/L.

The patient is alive without evidence for disease at one year.

Discussion

These three cases suggest some practical considerations.

Preoperative cytological diagnosis of MTC

MTC is rarely diagnosed by FNAB on a thyroid nodule (the most common presenting clinical sign of MTC), because the cytological specimens are often inadequate for diagnostic purposes (THY I), or only indicate a generic follicular neoplasm (THY III). To avoid any ambiguity, many clinicians suggest to routinely measure Ct on fluid collected by FNA instead of the traditional microscopic cytology only. This type of procedure is useful for suspect extrathyroid nodes or relapsing disease, but is only of academic interest in the thyroid, given the diagnostic reliability demonstrated by high serum Ct levels. High Ct levels may prompt the review of previously-obtained cytological smears, and an initial indeterminate diagnosis may be revised as a result. Serum Ct elevation supports the diagnosis of MTC, however occasionally increased Ct may be associated with micro-occult MTC or parafollicular C-cell hyperplasia located together with other benign or malignant thyroid conditions.

The take-home message is that Ct levels should generally be tested in all patients with thyroid conditions, whatever their clinical or cytological diagnosis. Establishing a diagnosis of MTC without the support of a preoperative Ct assay, or with normal Ct levels may be questionable. These situations testify to the importance of identifying appropriate cutoffs for basal and stimulated serum Ct levels.

**Basal and stimulated Ct: discriminant values**

There is still some controversy over the best Ct cut-off for diagnosing MTC, but basal levels higher than 20 ng/L and stimulated levels over 100 ng/L are generally considered sufficient for this purpose. Confounding results may arise from testing errors or inadequate stimulation requiring calcium or pentagastrin. The pentagastrin test or calcium test are reserved for levels only slightly above normal ( < 20 ng/L), and is particularly useful for monitoring.
asymptomatic carriers (with a normal Ct) of low-risk RET mutations (accordingly to the American Thyroid Association (ATA) risk levels).\(^3\)

The value of testing serum Ct levels during the follow-up of operated patients is undeniable. In our experience, testing Ct 48 h after surgery has proven to be a strongly predictor of late surgical outcome. We have rarely seen Ct levels that were still high 2 days after surgery and subsequently return to normal, and we have never seen MTC recur in patients whose Ct levels were normal after 48 h.\(^4\)

**CEA**

Occasionally high CEA levels remain unexplained elevated for long periods of time. As some practitioners may be unaware that CEA may be expressed by MTC, elevated CEA may prompt repeated and often aggressive investigations instead of a straightforward serum Ct measurement. In fact, serum Ct should be included among the markers of unknown neoplasia. When serum levels of Ct and CEA diverge, this is generally considered a marker of a less differentiated disease, and consequently of a worse prognosis.

**Preoperative genetic test**

Genetic testing for all patients with mildly elevated serum Ct levels, including those with no family history of MTC remains debatable. Routine genetic testing is not justifiable in cases with borderline Ct levels unresponsive to stimulation. As a precautionary measure, urinary metanephrine levels should always be assayed in patients referred for surgery. On the other hand, genetic testing can be postponed and only scheduled in cases of histologically documented MTC or C-cell hyperplasia.

**Prophylactic or early thyroid surgery**

Which asymptomatic gene mutation carriers without US abnormalities and with normal basal Ct unresponsive to stimulation should undergo prophylactic surgery, and which patients risk nothing if surgery is delayed until there is US evidence of thyroid micronodularity or responsive Ct remains a matter of debate (ATA risk levels).\(^5\)

The main advantage of prophylactic surgery is that total thyroidectomy is an adequate treatment because it removes all the
C-cells and no further follow-up is necessary. Not all authors would consider the procedure justifiable for patients with low-grade RET mutations, however. Such patients should be monitored until there is evidence of disease, given the variable clinical expression of MTC and the risk of surgical complications. On the other hand, once a malignant change has been documented, early surgery (even if it is effective) cannot guarantee long-term cure, so patients will periodically need oncologic check-ups. Central node neck dissection is also an integral part of the surgical procedure, though the risk of side effects (hypoparathyroidism and laryngeal nerve injury) is higher than in the case of prophylactic total thyroidectomy alone using the minimally invasive technique.

**Surgery for clinical manifest MTC**

Preoperatively, patient assessment should focus on discovering hereditary, typically multifocal, MEN II MTC, and any associated parathyroid or adrenal disorders. Particular attention is paid to pheochromocytoma, a hazardous component of the MEN II syndrome that is potentially fatal if it goes unrecognized and untreated prior to surgery. Staging for MTC and MEN II, including genetic profiling is therefore essential. In the hereditary form, every C cell retains its malignant potential so there is no alternative to surgery, which necessarily means total, absolutely radical thyroidectomy. (16) Near- or sub-total thyroidectomy does not invalidate the criterion of total excision for sporadic, monofocal, intrathyroid MTC, but there is no way to support this option “a priori”. In the past, before routine Ct assay became part of the preoperative work-up for patients with thyroid disease, some sub-total thyroidectomies induced a stable postoperative normalization of Ct levels, thus providing proof of the surgical procedure’s efficacy and avoiding the need for subsequent completion thyroidectomy. Due to the lack of indicators of the biological aggressiveness of MTC, it is impossible to modulate its treatment in the thyroid and lymph nodes. In the case of prophylactic surgery, the risk stratification used for the purpose of timing surgery may also be considered as a criterion for nodal dissection. In sporadic MTC (which has yet to be divided into risk categories), serum Ct levels have been chosen as an arbitrary parameter for decisions regarding preventive dissection, since they appear to reflect tumor deposits and extrathyroid diffusion.4-6

The case series reported here demonstrates that moderately higher than normal Ct values may be associated with distant dissemination, upon which prophylactic neck node dissection can have no impact. Many surgeons prefer total thyroidectomy with central node compartment dissection to avoid having to return to the central surgical field in situations requiring completion thyroidectomy.

**Persistent MTC and persistent hypercalcitoninemia after surgery**

The distinction between occult disease identifiable only from laboratory tests and clinically manifest disease is by no means gratuitous in terms of the subsequent therapeutic options. Resurgery may be useful, but is only justified when there is evidence of the initial treatment having been incomplete. Completion surgery is sometimes done for palliative purposes, to reduce the mass and control diarrhea (a sign of the advanced form of MTC). In many cases, however, patients may have only a modest, stable hypercalcitoninemia with no morphological evidence of disease, in which case there may be inadequate indication to attempt completion surgery. It is important not to forget the need for a thorough restaging – with US, Ct, 18F-FDG and 18F-DOPA PET (21,22), and perhaps bone scintigraphy – before ruling out any completion surgery and opting for a ‘wait-and-see’ approach for as long as the markers remain stable; or, in the event of progression, enrolling patients in experimental pharmacological protocols with tyrosine kinase inhibitors.5

The conclusion that we can apparently draw is that preoperative Ct levels do not always reflect the actual stage of a patient’s disease. These levels correlate more with the tumor mass, the more the C cells preserve their secretory capacity, and consequently with the cancer’s degree of differentiation. This means that finding moderately increased Ct levels does not entitle us to assume that they support an “early” diagnosis, or that we can do without preoperative staging: the discrepancy suggests a worse prognosis.

**Conflict of interest**

The authors declare no conflict of interest.

**References**