

## Clinical note

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

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## ARTICLE INFO

## Article history:

Received 12 May 2015

Accepted 19 May 2015

Available online 26 September 2015

## Keywords:

Medullary thyroid cancer

MTC

Large tumor masses

Serum markers

Serum calcitonin and CEA

## ABSTRACT

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 worst 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

## RESUMEN

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 tumorales 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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## Palabras clave:

Cáncer medular de tiroides

MTC

Enormes masas tumorales

Marcadores séricos

Suero Ct y CEA

## 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.<sup>1</sup>

We report on three cases of MTC, two of them sporadic and one MEN II A, in which very advanced metastatic disease corresponded unpredictably 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.

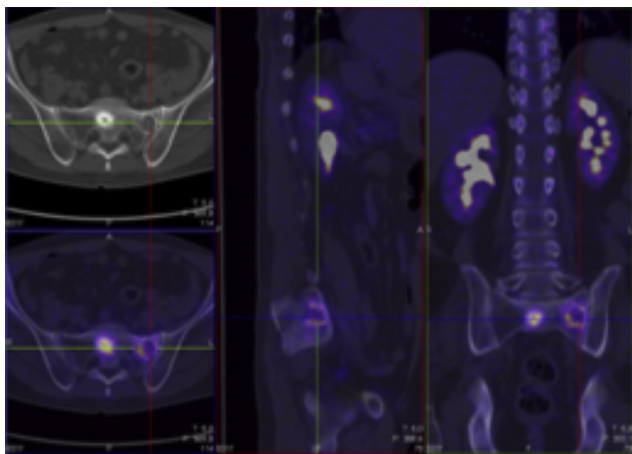
### Case 1

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  $\mu\text{mol}$ ) and computed tomography demonstrated a large para-aortic mass suggestive of paraganglioma. <sup>18</sup>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  $\mu\text{g/L}$ ). Genetic analysis revealed the RET mutation C620R.

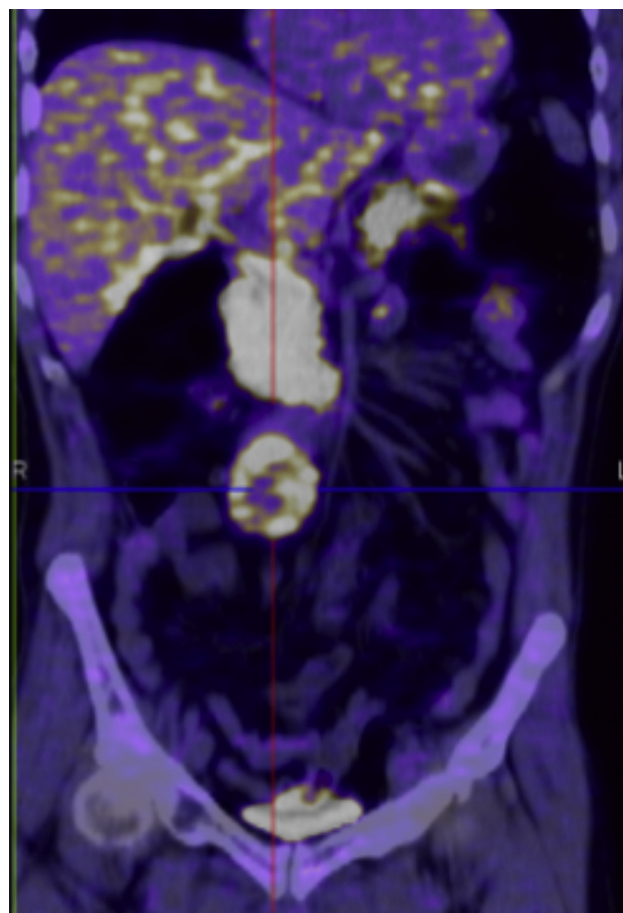
The patient underwent total thyroidectomy and selective left lateral cervical lymph node dissection (Fig. 3), with laparoscopic resection of the para-aortic paraganglioma (Fig. 1) at the same time.

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 (585 ng/L) and a <sup>68</sup>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.



**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.

Follow-up at two years reports that the patient is alive with disease (Ct = 447 ng/L; CEA = 102  $\mu\text{g/L}$ ).

### 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 oncogene mutations was negative and computed tomography identified no distant metastases.

Forty-eight hours after surgery, serum Ct had dropped to undetectable values.

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