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Beyond the Recommendations of the Clinical Guidelines for Medullary Thyroid Cancer – A Case Report

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Medullary thyroid cancer (MTC) is a rare disease from parafollicular C cells. Calcitonin has been suggested as a screening; its levels are proportional to the tumor size and predictive of metastatic disease. We present a case where an early action was taken with lower cut-off points. Male patient, 49 years old. Thyroid ultrasound (US) with a suspicious nodule. Fine Needle Aspiration Biopsy (FNAB) suggests MTC, with pre-operative serum calcitonin (CTN) of 591 pg/mL. Total thyroidectomy with central and bilateral dissection was performed. Biopsy: MTC in left nodule of 26 mm without lymph nodes (LN) metastases. Follow-up with undetectable CTN for six years. After that, CT was 4.7 pg/mL, and carcinoembryonic antigen (CEA) was 1.2 ng/mL. Neck US showed bilateral LN. FNAB of LN does not show recurrence. A progressive rise of markers with doubling time of CTN and CEA was 16 and 51.3 months, respectively. CTN raised until 112 pg/mL. Given the lack of cervical compromise, a neck and lung CT, liver MRI, and bone scintigraphy were ordered despite CTN levels < 150 pg/mL. MRI showed hypervascular hepatic lesions, contrasted with gadoxetic acid. PET Ga68-DOTATATE showed lesions with overexpression of somatostatin receptors in the liver. Surgery was done, and a biopsy confirmed metastases. ***Conclusions:*** *The clinical guidelines may allow the management of cases; however, they should be used considering each case context. In our patient, if the guidelines had been strictly followed, it would not have been possible to detect liver metastases to achieve a surgical resection with curative intent.*

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Key words: *Calcitonin; Clinical Protocols; Thyroid Neoplasms.*

Más allá de las recomendaciones de las guías clínicas de cáncer medular de tiroides – a propósito de un caso

Paciente masculino, 49 años. Ecografía tiroidea con nódulo sospechoso. Biopsia por aspiración con aguja fina (PAAF) sugiere cáncer medular de tiroides (CMT), calcitonina sérica preoperatoria (CTN) de 591 pg/mL. Se realizó tiroidectomía total con disección central y bilateral. Biopsia: CMT en nódulo tiroideo izquierdo de 2,6 cm sin metástasis en 29 ganglios linfáticos (GL). En el seguimiento, CTN sérica indetectable durante 6 años. Posteriormente CTN sérica de 4,7 pg/mL y antígeno carcinoembrionario (CEA) de 1,2 ng/mL. Ecografía cervical de control mostró GL subcentimétricos bilaterales en grupo IV. PAAF de GL sin evidencia de malignidad, con niveles de CTN indetectables en la muestra. El doblaje de CTN y CEA fue 16 y 51,3 meses respectivamente. Dado ausencia de compromiso cervical, se solicitó TC de cuello y tórax, RM hepática y gammagrafía ósea, a pesar de no presentar niveles de CTN > 150

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pg/mL. La RM mostró 3 lesiones hepáticas hipervasculares; se complementa con un PET Ga-DOTATATE que mostró 2 lesiones focales con sobreexposición de receptores de somatostatina en el parénquima hepático, con SUVmáx de 6,8 y 7,3. Se realiza cirugía extirpando 5 lesiones; la biopsia confirmó metástasis de CMT. Conclusiones: Las guías clínicas pueden dar orientaciones generales y permitir el manejo de casos basados en la evidencia; sin embargo, siempre deben usarse considerando el contexto de cada caso en particular. Si se hubieran seguido estrictamente las pautas, no habría sido posible detectar las metástasis hepáticas dentro de la ventana de oportunidad para lograr una resección quirúrgica con intención curativa.

Palabras clave: *Calcitonina; Neoplasias de la Tiroides; Protocolos Clínicos*

Medullary thyroid cancer (MTC) originates from parafollicular C* cells. It is a rare disease; according to the Surveillance, Epidemiology, and End Results (SEER) database program (1975 to 2016), it represents 1.6% of all thyroid cancers in all races[1,2]. It is characterized by a mean survival of 8.6 years and 10-year survival rates that range between 69 and 89%[3]. Most tumors are sporadic (75% to 80% of cases), but can also occur as part of the familial multiple endocrine neoplasia (MEN) 2A and 2B syndromes in 20% to 25% of cases[4]. A distinctive feature of this tumor is the ability to synthesize and secrete calcitonin, a 32-amino acid polypeptide hormone, which is considered a highly sensitive and specific tumor marker. Patients with MTC have elevated serum calcitonin, and routine calcitonin measurement has been suggested for screening for MTC in patients with nodular thyroid disease. Furthermore, serum calcitonin levels are directly proportional to the tumor size and are predictive of metastatic disease[5].

The strategy of using this biomarker to define treatment and follow-up is delimited by the current guidelines where standardized elevation parameters have been created that allow guiding the study of recurrence or possible metastases through the calculating of the doubling of CTN and CEA as predictors of recurrence[4,6]. We present a clinical case, with the prior written informed consent of the subject, where an early action was taken with lower cut-off points than usual, finding results that were critical for the treatment that influenced the ensuing evolution of the patient.

Clinical Case

Male patient; 49 years old, with a fine needle aspiration biopsy (FNAB) suggestive of MTC, with preoperative serum calcitonin (CTN) of 591 pg/mL. A total thyroidectomy was performed with central and bilateral dissection. The biopsy resulted in an MTC of the left thyroid lobe of 2.6 cm, without the involvement of the 29 nodes examined. A genetic blood study shows no germline mutation of the RET proto-oncogene. During the following, he presented non-detectable CTN for six years but began a progressive elevation after that time: CTN was 4.7 pg/mL and CEA 1.2 ng/mL. The adjunct table shows the evolution of the biomarkers. Given the rise in these parameters, a

Table 1. Evolution of tumor markers

	Mar 2015	Oct 2015	Jul 2016	Nov 2016	Aug 2017	Jun 2018	Nov 2019	Mar 2020	Jun 2020	**Sept 2020**	**Jul 2021**	**Dec 2021**
CTN pg/mL < 2	7,3	16,1	17,9	20,7	35,2	42,5	80,7	111	105	**9,9**	**14,3**	**21**
CEA ng/mL < 0,1	1,2	0,7	1,6	1,8	1,8	1,8	2,4	2,9	3,1	**1,9**	**2,3**	**1,9**

In bold the values after total thyroidectomy + lymph node dissection.

cervical ultrasound was performed, which showed subcentimeter nodes in the right and left group IV. During evolution, they do not increase in size, and 3 FNAB were performed at different times, which did not show elements of malignancy, along with undetectable levels of CTN in the sample.

After 5 years of follow up CTN and CEA doubling time were 16 and 51.3 months, respectively (Table 1). Given the absence of cervical involvement and breaking the recommendations of the MTC ATA 2015[4], a neck and lung Computer Tomography scan (CT), liver magnetic resonance imaging (MRI) and bone scintigraphy were requested, despite not presenting CTN levels > 150 pg/mL. Liver MRI shows three hypervascular liver lesions, which it is suggested to contrast with liver-specific medium (gadoxetic acid) to improve the characterization of the lesions. It demonstrated the presence of 5 focal lesions, the largest of 10mm, without contrast medium retention, suggesting metastases. It is complemented with PET 68Ga-DOTATATE (Image 2a-b) showing two foci of overexpression of somatostatin receptors in the liver parenchyma, which correlate with known lesions, with SUVmax of 6.8 and 7.3. In a multidisciplinary evaluation, it was decided to perform surgical management, being operated and removing five lesions whose biopsies confirmed MTC metastases, with an immunohistochemical (IHC), which was intensely positive for calcitonin, TTF-1 and synaptophysin. Ki-67 was 2% in tumor cells. In the one-year follow-up, the patient presented an abdominal MRI with no evidence of recurrence and a CTN of 9.9 pg/mL.

Discussion

In the diagnosis and during the follow-up of patients with MTC, CTN is the most sensitive and specific marker. Compared with FNAB performed at diagnosis, it has higher sensitivity and specificity (100 and 95%, respectively)[7]. Values between 20 and 50 pg/mL were associated with lymph node metastases in the ipsilateral central and lateral compartment; between 50 and 200 pg/mL in the contralateral central compartment; over 200 pg/mL in the contralateral lateral compartment; abo-

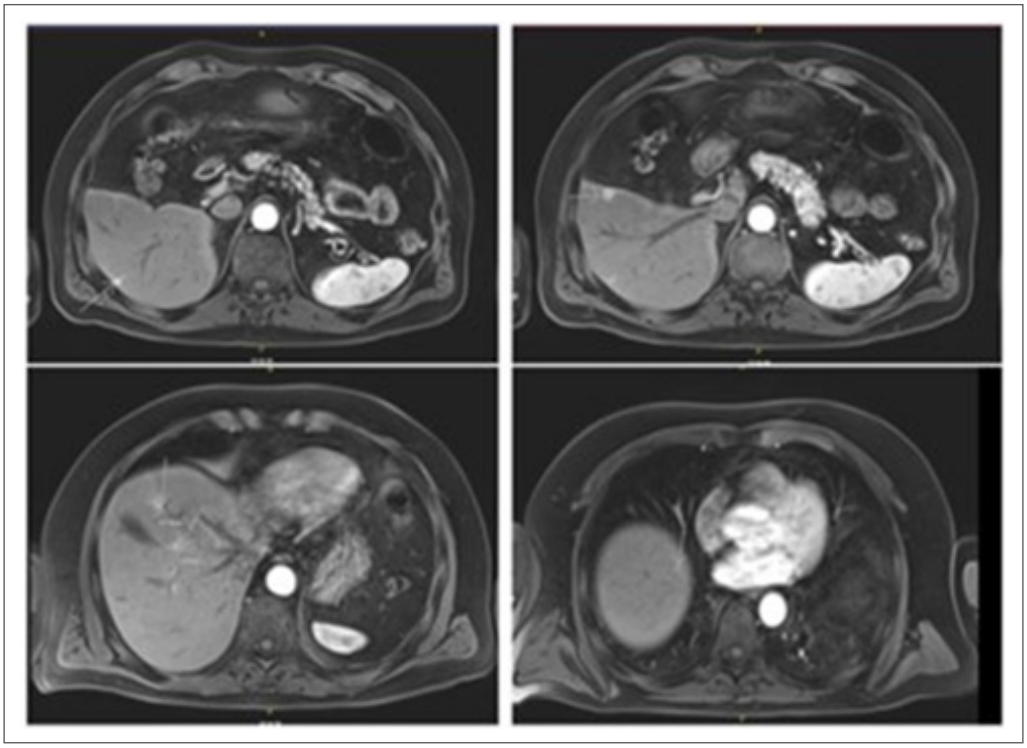

Figure 1. Liver magnetic resonance.

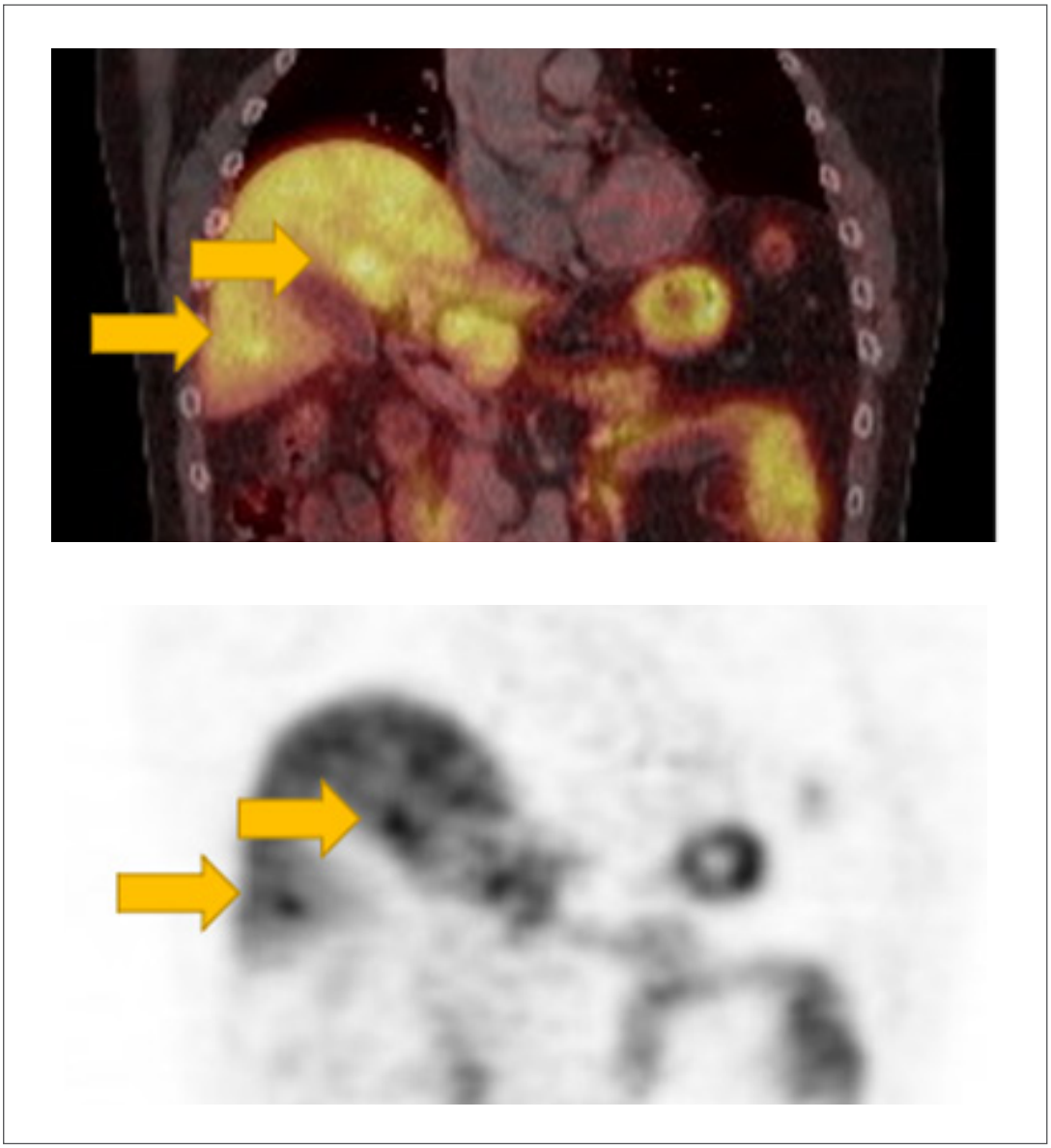

Figure 2. A and B: Galium DOTATATE PET.

ve 500 pg/mL in the superior mediastinum and at a distance[8]. A biochemical cure is highly unlikely in patients with preoperative serum calcitonin levels greater than 1,000 pg/mL[4,8]. Recent studies also relate high levels of preoperative CTN with structural recurrence[9].

During postoperative follow-up, control of serum CTN and its doubling time is essential as a prognostic factor and a biochemical remission of the disease. The doubling corresponds to the time it takes for the MTC to double the CTN levels. Therefore, at least 4 to 5 measurements should be made during the first 2 to 3 years of follow-up (there are online tools to calculate it https://www.kuma-h.or.jp/english/about/doubling-time-progression-calculator), and it is essential to start measuring it at the first six weeks to increase sensitivity[10].

The sensitivity and specificity of CTN as a predictor of structural recurrence with levels greater than 10 pg/mL are 80.5% and 84.3%, respectively, and are related to lymph node metastases at these levels; distant metastases were found with values greater than 150 pg/mL[11].

Its interpretation to guide follow-up is described in various clinical guidelines. Its use in isolation and without a global interpretation, which also considers the preoperative CTN, can lead to conclusions that are not entirely correct for making therapeutic decisions. Thus, it is also essential to rule out other pathologies that could raise these values[12]. Both the ATA (American Thyroid Association), NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) guidelines recommend postoperative management based on CTN levels. Since serum CTN declines slowly, the timing of CTN level measurement after surgery is crucial. The ATA recommends that serum levels of CTN and CEA be measured three months after the operation, while the ESMO and the NCCN recommend that it should be measured between 30 and 60 days and 2 to 3 months after surgery, respectively. In general, a cut-off point is proposed to search for distance disease, beyond the cervical area, with values greater than 150 pg/mL[11,13]. Those patients with low or initially undetectable levels of calcitonin, which rise during follow-up, should be considered indicators of residual disease and put the physician on alert, regardless of whether these do not exceed the usual limits. Up to 94% of patients with a doubling time of fewer than 24 months have progressive disease. Studies show that the survival rate in those who had a CTN doubling time at six months is 23% at five years and 15% at ten years, versus a doubling time at two years of follow-up with a considerably more favorable prognosis, of 100% in both cases. Regarding the doubling of CEA, the survival rate at six months is 0% at 5 and 10 years, versus a doubling at two years of follow-up with a considerably more favorable prognosis of 100 and 96%, respectively[6].

There are rare cases of MTC with low or undetectable calcitonin reported in the literature, the cause of this discrepancy between tumor and CTN levels is not clear. It has been proposed assay interference, loss of synthesis or secretion functions by these malignant parafollicular cells[14].

Conclusion

Although clinical guidelines may help to standardize the management of various pathologies based on the evidence available at the time, they should always be placed in the context of the patient. In this case, if the recommendations of any of the published international guidelines had been strictly followed, it probably would not have been possible to detect liver metastases within a window of opportunity in which a surgical resection could be carried out to improve the patient's prognosis and survival.

Patient consent

The patient provided written informed consent for the publication of medical information and images.

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