REVISTA MEXICANA DE ENDOCRINOLOGÍA, METABOLISMO & NUTRICIÓN CLINICAL CASE

Indolent metastatic medullary thyroid carcinoma: to treat or not to treat. Clinical case.

*Latife Salame, Dalia Cuenca, Carolina Blanco, Raquel Gerson and Moisés Mercado**

Cancer Center, American British Cowdray Medical Center, Mexico City, Mexico

ABSTRACT

Medullary thyroid carcinoma occurring either sporadically or in the context of Type 2A multiple endocrine neoplasia can follow a relatively indolent and asymptomatic course over many years, including some cases with metastatic disease. Although treatment with the recently approved tyrosine-kinase inhibitors is an option, the decision to indicate them should weight the potential benefits against the potential adverse events of these costly targeted therapies with consideration of the patient's wishes. (REV MEX ENDOCRINOL METAB NUTR. 2017;4:150-4)

Corresponding author: Moisés Mercado, moises.mercado@endocrinologia.org.mx

Key words: Medullary thyroid carcinoma. Type 2A multiple endocrine neoplasia. Pheochromocytoma. *RET* proto-oncogene. Tyrosine-kinase inhibitors.

RESUMEN

El cáncer medular de tiroides, ya sea esporádico o en el contexto de la neoplasia endocrina múltiple de tipo 2A, puede evolucionar de manera indolente y asintomática durante varios años, aun en casos con metástasis a distancia documentadas. Si bien el tratamiento con los recientemente aprobados inhibidores de la tirosina cinasa es una opción, la decisión terapéutica debe considerar los beneficios potenciales, pero también la posibilidad de reacciones adversas de estos costosos medicamentos, y, sin duda, tomar en cuenta los deseos de los pacientes.

Palabras clave: Carcinoma medular de tioroides. Neoplasia endocrina múltiple de tipo 2A. Protooncogén *RET*. Feocromocitoma. Inibidores de la tirosina cinasa.

INTRODUCTION

Medullary thyroid carcinoma (MTC) is the most consistent feature of the Type 2 multiple endocrine neoplasia (MEN 2) spectrum with 100% penetrance. It usually evolves from C-cell hyperplasia and carries a relatively benign prognosis when detected before the development of distant metastasis[1,2]. The mainstay of therapy for MTC is surgical resection of the lesion, as these tumors do not take up radioactive iodine and are relatively resistant to external beam radiotherapy[3,4]. Patients with persistent hypercalcitoninemia after surgical resection of MTC but without imaging evidence of metastatic disease usually have an indolent course and a 5-year survival rate of 80-86%, whereas those with documented liver or bone metastasis have a poor prognosis and

*Moisés Mercado
Sur 132, Número 142, Consultorio 210
Col. Las Américas
C.P. 01120, Ciudad de México, México
E-mail: moises.mercado@endocrinologia.org.mx

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a 45% mortality rate and a 10-year survival rate of only 40%[4-6]. Virtually, all cases of hereditary MTC are caused by activating mutations of the *RET* proto-oncogene (rearranged during transfection) with rather consistent genotype–phenotype correlations regarding the aggressiveness and age of onset of the tumor[4,7,8]. In the past decade, targeted therapies directed against RET and other tyrosine-kinase receptors have been developed, and some of them have been approved for the treatment of advanced metastatic MTC[4,6,9-11].

We herein present the case of a young woman with a widely metastatic MTC who has been living completely asymptomatic for over 12 years without any specific oncological treatment.

CASE REPORT

A 24-year-old, previously healthy woman was found to have a right thyroid nodule on neck ultrasound performed as a screening procedure because of a strong family history of MTC. Fine-needle aspiration biopsy of the lesion was reported as highly suspicious for MTC. Serum calcitonin (CT) levels were 1110 pg/mL and serum Ca, P, thyroid-stimulating hormone, and free T4, as well as plasma catecholamines, were reportedly normal. She underwent a total thyroidectomy and bilateral neck dissection and the histopathological diagnosis was a glandular pattern, MTC with extensive lymph node metastasis. MTC-affected family members include her mother and sister, as well as a maternal aunt and uncle who had both, MTC and pheochromocytoma (Fig. 1). Genetic evaluation revealed that all affected family members harbor the exon 11, Cys634Phe germ line mutation of the *RET* proto-oncogene.

On follow-up two years after thyroidectomy, she was found to be completely asymptomatic with a normal blood pressure. At this point, her laboratory work up showed a serum CT of 7377 pg/mL, a carcinoembryonic antigen (CEA) of 1218 ng/mL, serum Ca of 9 mg/dL with an intact parathyroid hormone (PTH) of 34 pg/mL, as well as urine catecholamines and metanephrines within the normal range.

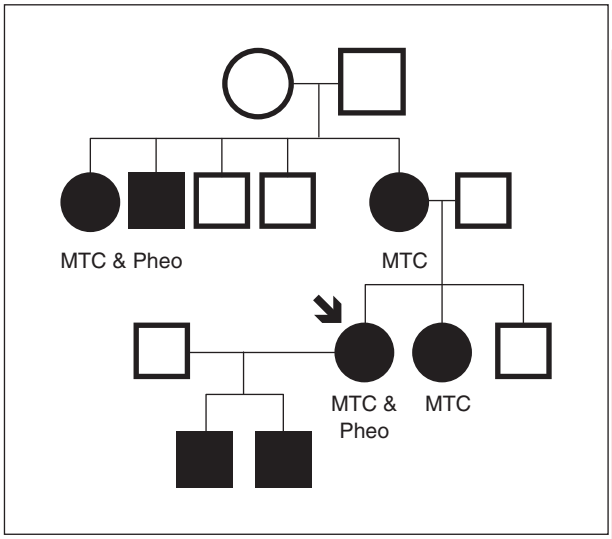

Figure 1. Family tree depicting four generations. Black squares and circles are members shown to harbor the germ line exon 11, Cys634Phe *RET* proto-oncogene mutation. The propositus or index case is indicated by the black arrow. MTC denotes medullary thyroid carcinoma, Pheo denotes pheochromocytoma.

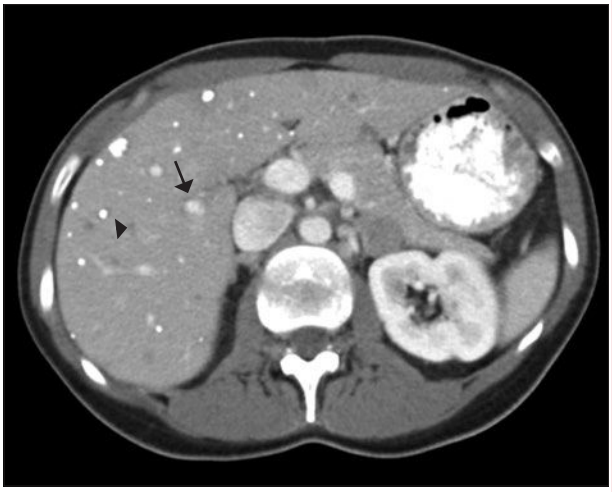

Figure 2. Computed tomography scan with contrast showing liver metastasis [arrow] with calcifications (arrowhead).

Imaging studies (magnetic resonance imaging [MRI] and computed axial tomography (CAT) revealed the presence of multiple metastatic lesions in her liver, left iliac bone, and eighth rib (Fig. 2). A neck ultrasound showed bilateral cervical lymph node enlargement. She underwent surgical exploration of her neck with the removal of 14 lymph nodes, of which only one had evidence of metastatic MTC. Post-operatively, her serum CT dropped slightly to

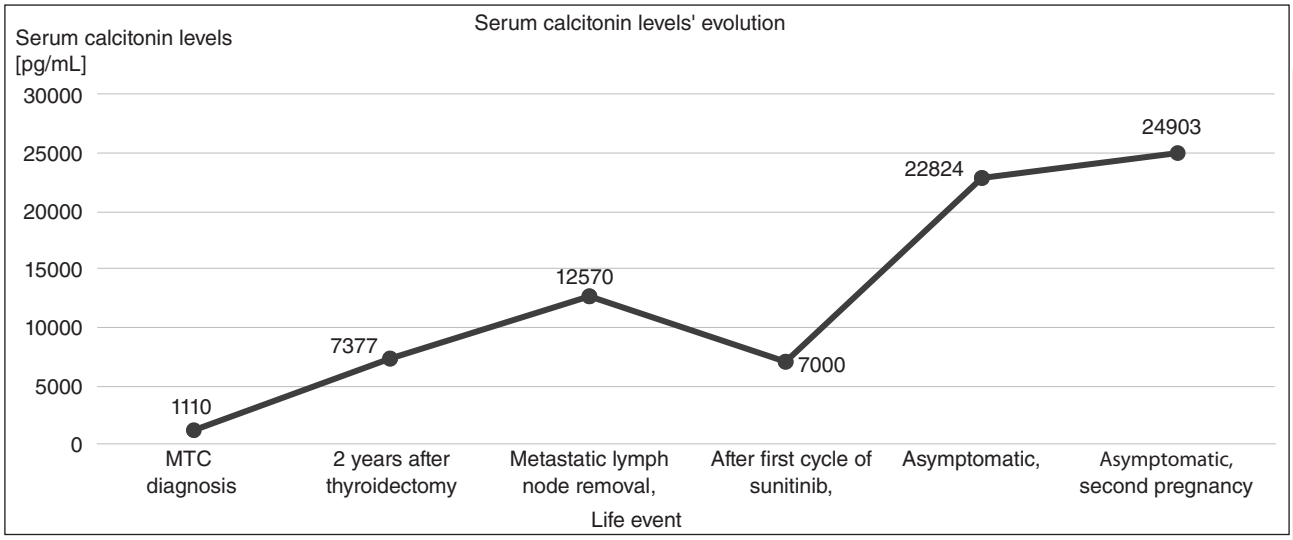

Figure 3. Patient course and evolution of serum calcitonin levels.

6633 pg/mL only to rise a few months later to 12570 pg/mL. She was started on the multitargeted tyrosine-kinase receptor inhibitor (TKI) sunitinib (37.5 mg daily), which had to be discontinued two months later because of severe hand-foot syndrome, mucositis, and pancytopenia; her serum CT decreased slightly but rose again a few months later (Fig. 3).

She returned for a follow-up visit 4 years later, again, reporting no symptoms and was found to be normotensive with no significant findings on physical examination. Her CT had increased to 22,824 pg/mL and her CEA to 1506 ng/mL; serum Ca, P, and PTH remained normal. Although urine catecholamines remained normal, her plasma metanephrines and normetanephrine levels were elevated (1.11 nmol/L [normal < 0.49] and 1.15 nmol/L [normal < 0.89], respectively). MRI showed the previously found liver and bone metastasis and a 2.7 cm left adrenal mass that was hyperintense on T2. The diagnosis of normotensive pheochromocytoma was entertained, but she became pregnant against medical advice. The pregnancy was rather uneventful, and she remained normotensive all through it. At the beginning of the third trimester, she underwent laparoscopic removal of the adrenal mass without complications; the histopathology report was that of a benign pheochromocytoma. Two months later she delivered a healthy boy after 6 hours of uncomplicated labor. The boy was genetically tested and proved to be homozygous for the same *RET* proto-oncogene mutation that her mother and other family members have. 18 months later, she became pregnant again and delivered a healthy boy without any complications. Her second child is also positive for the same *RET* proto-oncogene mutation.

After nursing for 4 months, she returned she returned o clinic for a follow up visit after having breast fed for 4 months. She was found completely asymptomatic, clinically and biocheically euthyroid on levothyroxine replacement. Laboratory studies showed a CT of 24903 pg/mL, a CEA of over 2000 ng/mL, normal serum Ca, P, and PTH, and serum and urine catecholamines and metanephrines within the normal range. She has declined to have a fluorodeoxyglucose positron emission tomography–computed tomography scan to evaluate tumor activity and has refused to consider prophylactic thyroidectomy for her two sons.

DISCUSSION

MTC originates from the neural crest-derived C-cells and represents 1-2% of all thyroid malignancies[1,2]. In 25-30% of cases, it is inherited as an autosomal dominant condition that occurs in the context of either the so-called familial MTC or, the MEN2 syndromes, and is caused by activating germ line mutations of

the *RET* proto-oncogene[1,2,8]. In the remaining 70-75% of the cases, MTC occurs sporadically and approximately 50% of these cases harbor somatic mutations of the *RET* proto-oncogene[1,2,8]. Hereditary MTC evolves from a premalignant stage of C-cell hyperplasia and in contrast to the sporadic form, it is usually bilateral and multifocal[2,3]. The clinical spectrum of MEN2 encompasses MEN2A, MEN2B, and familial MTC[12]. MEN2A is characterized by MTC, pheochromocytoma, and primary hyperparathyroidism, with a penetrance of 100%, 50%, and 30%, respectively[1,12]; cutaneous lichen amyloidosis and Hirschsprung's disease are considerably less frequent. Patients with MEN2B have a peculiar Marfanoid habitus as well as multiple mucosal neuromas, musculoskeletal abnormalities, and gastrointestinal ganglioneuromatosis; the penetrance of MTC and pheochromocytoma in MEN2B patients is also 100% and 50%, respectively, however, primary hyperparathyroidism does not occur in this syndrome[1,12].

The *RET* proto-oncogene is located in the centromeric region of chromosome 10 and consists of 21 exons encoding a 125-Kda tyrosine-kinase transmembrane receptor involved in the regulation of the survival, differentiation, and migration of cells of the enteric nervous system, the neural crest, and the kidney[13,14]. The extracellular portion of RET includes a cadherin-like domain, encoded by exons 8 and 9 that is responsible for ligand binding (its main endogenous ligand is the glial-derived neurotrophic factor), and a cysteine-rich domain, encoded by exons 10 and 11 that is crucial for receptor dimerization[15]. The intracellular domain is encoded by exons 13-16 and includes tyrosine phosphorylation sites that are linked to several transduction pathways such as PI3K/AKT/mTOR and Ras/Raf/MAPK which are involved in gene expression as well as cellular proliferation and survival[14,15].

More than 70 different *RET* proto-oncogene mutations have been described that result in varying phenotypes in terms of age of onset and aggressiveness of MTC and the presence of other endocrine neoplasms[7,8]. Although 85% of cases of hereditary MTC are caused by exon 11 mutations, phenotype–genotype correlations have established as the highest risk for aggressive MTC the exon 16 Met918Thr mutation, followed by the exon 11, Cys634Phe and exon 15 Ala883Phe mutations[4]. It is based on these categorizations that recommendations are made for the timing of thyroidectomy of individuals testing positive for *RET* proto-oncogene mutations.

Our patient belongs to a typical family with MEN2A, with some members having only familial MTC, whereas others the coexistence of MTC with pheochromocytoma. All members of this family harbor the exon 11, Cys634Phe mutation which is considered a high-risk mutation according to the revised guideline of the American Thyroid Association[4]. During the course of her illness, the increasing CT level (a doubling time less than 6 months) and the presence of distant metastasis (Stage IV by any staging system) prompted us to try therapy with sunitinib, despite her being completely asymptomatic. The results were almost catastrophic because she developed severe hand-foot syndrome, mucositis as well as pancytopenia and sepsis. After this unfortunate experience, the patient herself decided not to try any other type of targeted therapy, despite further increments of CT and a rapidly rising CEA level and the progressive appearance of metastatic lesions in her liver and axial and pelvic bones.

The main factors associated with poor prognosis in MTC include old age, large tumor size, the presence of local and distant metastasis, the presence of the Met918Thr *RET* mutation, and low CT and CEA doubling times[4]. The 10-year survival rate among unselected patients is 75%, but this figure drops to < 40% among patients with metastatic disease[4]. In patients whose CT doubling time is less than 6 months, as with our patient, the 5- and 10-year survival rates are 25% and 8%, respectively[4]. Cause-specific mortality in patients with MTC with TNM Stage IV disease is 44.5%[4,5]. Thus, the only favorable prognostic factors in our patient were her young age and her type of *RET* mutation. Surprisingly, our patient has lived and continues living a normal and functional life, without any symptoms attributable to her MTC. The fundamental question is whether or not she would benefit from treatment with either of the newer tyrosine TKIs vandetanib or cabozantinib. These costly drugs have been approved for the treatment of advanced, symptomatic metastatic MTC[9,16-20]. Although complete responses to either

vandetanib or cabozantinib have not been reported, both drugs have been somewhat effective in terms of significantly reducing CT and CEA levels and in improving short-term progression free survival (PFS)[19,20]. Unfortunately, neither of them has been proven to significantly increase overall long-term PFS[19,20]. On the other hand, these TKIs have some serious side effects, including diarrhea, hand-foot syndrome, and even prolongation of the QTc[4,19,20], therefore, they should not be used in the setting of asymptomatic or indolent MTC[4,6]. Thus, our patient's decision to decline further therapy with TKI, after her devastating experience with sunitinib, does not seem so unreasonable after all.

Normotensive pheochromocytomas are not uncommon among patients with incidentally discovered adrenal masses[21]. Since members of MEN2 families, routinely undergo biochemical screening for phechromocytoma they are also likely to be diagnosed at a subclinical and normotensive stage[1]. As in our case, patients with normotensive pheochromocytoma tend to have tumors secreting relatively lower amounts of catecholamines than in those patients with hypertensive pheochromocytomas[1,21]. She became pregnant against medical advice and her blood pressure remained normal until the adrenal lesion was removed laparoscopically[22], again without her developing any hemodynamic instability.

Finally, although she agreed to have both her children genetically tested for germ line *RET* proto-oncogene mutations and both turned out to be positive for the Cys634Phe mutation, she has consistently refused to have them undergo neck ultrasound, claiming that even if lesions are discovered, she would not authorize a prophylactic thyroidectomy.

In conclusion, MTC may follow a truly indolent course even in the presence of distant metastasis. Although therapy with the new TKI is certainly an option, it is not free of significant side effects that may compromise the quality of life of the patient and even his/her life expectancy. Cases as the one being presented should remind us as clinicians that medicine is still the art of listening to patients.

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REFERENCES

1. Wells SA Jr, Pacini F, Robinson BG, Santoro M. Multiple endocrine neoplasia Type 2 and familial medullary thyroid carcinoma: an update. J Clin Endocrinol Metab. 2013;98:3149-64.
2. DeLellis RA. The pathology of medullary thyroid carcinoma and its precursors. Monogr Pathol. 1993;3:72-102.
3. Cabanillas M, McFadden D, Durante C. Thyroid cancer. Lancet. 2016;S0140-6736:30172-6.
4. Wells SA Jr, Asa SL, Dralle H, et al. Revised American thyroid association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25:567-610.
5. Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer. 2000;88:1139-48.
6. Maia A, Magagnin S, Vaz C. Advances and controversies in the management of medullary thyroid carcinoma. Curr Opin Oncol. 2017;29:25-32.
7. Donis-Keller H, Dou S, Chi D, et al. Mutations in the RET protooncogene are associated with MEN 2A and FMTC. Hum Mol Genet. 1993;2:851-6.
8. Ceolin L, Romitti M, Siqueira DR, et al. Effect of 3'UTR RET variants on RET mRNA secondary structure and disease presentation in medullary thyroid carcinoma. PLoS One. 2016;11:e0147840.
9. Maxwell JE, Sherman SK, O'Dorisio TM, Howe JR. Medical management of metastatic medullary thyroid cancer. Cancer. 2014;120:3287-301.
10. Jarzab B, Krajewska J. Multikinase inhibitors for the treatment of progressive, metastatic medullary thyroid cancer-an evolving paradigm. Eur Endocrinol. 2014;10:145-50.
11. Kim BH, Kim IJ. Recent updates on the management of medullary thyroid carcinoma. Endocrinol Metab (Seoul). 2016;31:392-9.
12. Callender G, Rich T, Perrier N. Multiple endocrine neoplasia syndromes. Surg Clin N Am. 2008;88:863-95.
13. Ishizaka Y, Itoh F, Tahira T, et al. Human ret proto-oncogene mapped to chromosome 10q11.2. Oncogene. 1989;4:1519-21.
14. Ibáñez CF. Structure and physiology of the RET receptor tyrosine kinase. Cold Spring Harb Perspect Biol. 2013;5. pii: a009134.
15. Ceccherini I, Bocciardi R, Luo Y, et al. Exon structure and flanking intronic sequences of the human RET proto-oncogene. Biochem Biophys Res Commun. 1993;196:1288-95.
16. Kelleher FC, McDermott R. Response to sunitinib in medullary thyroid cancer. Ann Intern Med. 2008;148:567.
17. Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30:134-41.
18. Sherman S, Cohen E, Schoffski P, et al. Efficacy of cabozantinib [Cabo] in medullary thyroid cancer [MTC] patients with RAS or RET mutations: Results from a phase III study. J Clin Oncol. 2013;31:???.
19. Elisei R, Schlumberger MJ, Muller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31:3639-46.
20. Robinson B, Paz-Ares L, Krebs A, Vasselli J, Haddad R. Vandetanib [100 mg] in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab. 2010;95:2664-71.
21. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet. 2005;366:665-75.
22. Prete A, Paragliola RM, Salvatori R, Corsello SM. Management of catecholamine-secreting tumors in pregnancy: A review. Endocr Pract. 2016;22:357-70.