ISSN 0001-6012 eISSN 2215-5856
Rev. Acta Médica Costarricense
Edited by: Colegio de Médicos y Cirujanos de Costa Rica
2025 / January-March; 67 (1): 1-4

Clinical Case

Multiple Endocrine Neoplasia Síndrome

David Ricardo Guillén-Saborío[1], Alejandro Cob-Guillén[2]

Traducción original: Síndrome de neoplasia endocrina múltiple. Acta méd. costarric. 2025; 67(1):1-5. DOI: 10.51481/amc.v67i1.1448

Abstract

Multiple endocrine neoplasias are rare inherited syndromes, some with malignant potential. Multiple endocrine neoplasia type MEN2B is characterized by tumor formation such as medullary thyroid carcinoma, pheochromocytoma, and associated symptoms. Medullary thyroid carcinoma is usually the first tumor to appear and is the most common cause of death in these patients. This malignancy is particularly aggressive in MEN2B and can occur in childhood. Current American Thyroid Association guidelines recommend thyroidectomy in the first year of life.

We present the case of a 19-year-old female patient with symptoms since she was 9 months old, presented with bipodalic edema, constipation, and abdominal distension. At 6 years of age, she underwent a bilateral total thyroidectomy followed by radioiodine treatment. A thyroid biopsy revealed a poorly differentiated oncocytic papillary thyroid carcinoma. At 16 years of age, a neck ultrasound reported multiple nodules in the thyroid bed. An ultrasound-guided fine-needle aspiration biopsy was performed, the cytological findings of which were consistent with carcinoma, probably medullary. A left lateral dissection was performed with a biopsy of multiple nodules, confirming the diagnosis of medullary thyroid carcinoma. Phenotypic signs characteristic of MEN2B were identified, including ganglioneuromas in the oral mucosa and a marfanoid habitus. Genetic testing confirmed the presence of the M918T mutation in the RET proto-oncogene. As part of a comprehensive approach, screening for pheochromocytoma was performed. To date, the patient has not presented any signs of pheochromocytoma or hyperparathyroidism.

Keywords: medullary carcinoma, MEN2B, multiple endocrine neoplasia type 2B, proto-oncogene proteins c-ret, pheochromocytoma.

Received date: *11, febrero, 2025* ***Accepted date:*** *15, junio, 2025*

Authors' affiliation:
[1]Investigador independiente, San José, Costa Rica. guillendavid21@gmail.com
0009-0004-9128-384X
[2]Hospital San Juan de Dios, Endocrinología, San José, Costa Rica. alejandro.cobg@gmail.com
0000-0003-2826-5265

Abbreviations:
CMT; carcinoma medular de tiroides
HNN; Hospital Nacional de Niños, San José, Costa Rica.
MEN2; neoplasia endocrina múltiple
PAAF; biopsia por aspiración con aguja fina.

Conflict of interest: The authors declare that there is no conflict of interest that may be perceived as detrimental to the impartiality of this review.

✉ guillendavid21@gmail.com

Introduction

Multiple endocrine neoplasia type 2 (MEN2) is an inherited syndrome of autosomal dominant transmitted cancer, caused by a mutation in the RET proto-oncogene located on chromosome 10.[1-2] There are two distinct clinical entities: MEN2A and MEN2B. MEN2A is associated with medullary thyroid carcinoma (MTC), pheochromocytoma and hyperpa-

rathyroidism, mainly primary; while MEN2B is characterized by medullary thyroid carcinoma, pheochromocytoma, ganglioneuromatosis of the digestive tract, and musculoskeletal and ophthalmological abnormalities.[1-3] In both syndromes, multicentric tumors form in all organs in which the RET proto-oncogene is expressed. The thyroid, parathyroid, and are at risk of developing tumors of developing tumors that can reduce expectancy and quality of life. The excellent prognosis of sporadic and hereditary MTC diagnosed at its earliest stage stresses the importance of its timely diagnosis.[2]

MTC occurs in almost all patients with MEN2B. The tumor develops at a younger age and presents a more aggressive behavior than in MEN2A. Surgery is often not curative. For this reason, early diagnosis and prevention are crucial. In patients with MEN2B identified by genetic screening[2], thyroidectomy may be indicated in the neonatal period. Pheochromocytoma occurs in approximately 50% of patients with MEN2B. MEN2B syndrome also includes mucosal neuromas that usually affect the lips and tongue, as well as intestinal ganglioneuromas.[2] Its prevalence is estimated at 0.9 to 1.65 cases per million inhabitants, with an incidence of 1.4 to 2.6 cases per million live births per year.[4]

The vast majority of patients with MEN2B develop de novo mutations and have no significant hereditary family history. A detailed description of the phenotype, related to age, can contribute to the recognition of these patients before they develop an advanced MTC with a poor prognosis. Therefore, early diagnosis is essential, as this can have a positive impact on overall survival. The objective of this presentation is to offer information to primary care general practitioners and pediatricians about the clinical characteristics of multiple endocrine neoplasia (MEN), in order to strengthen their knowledge and promote the early identification of this pathology. In addition, it seeks to summarize the main updates of the diagnostic and therapeutic approach to multiple endocrine neoplasia and highlight the importance of its early diagnosis for the positive impact on overall survival.

Case report

We present the case of a female patient, 19 years old, with a confirmed diagnosis of multiple endocrine neoplasia type 2B (MEN2B), carrier of the RET M918T mutation, who is currently being followed up at the Endocrinology Service of the San Juan de Dios Hospital, Costa Rica.

According to the patient's mother, the first attributable symptoms attributable to MEN appeared at 9 months of age, when she developed edema in the lower limbs. At that time, the girl was evaluated at the National Children's Hospital (HNN) and was diagnosed with protein-calorie malnutrition, kwashiorkor type, which was attributed to a decrease in food intake. Subsequently, during a control at the first level of care, in which she was evaluated for constipation and abdominal distension, she was again referred to the HNN and hospitalized. Despite carrying out various studies, it was not possible to establish the underlying diagnosis.

At the age of 6 (in 2011), a nurse at the health center palpated thyroid nodules during a routine check-up, which motivated her referral to the HNN for evaluation. A neck ultrasound confirmed the presence of thyroid nodules, and on August 3, 2011, she underwent a bilateral total thyroidectomy, followed by radioiodine treatment. Biopsy of the thyroid gland revealed poorly differentiated papillary carcinoma of the thyroid oncocyte, with no associated genetic mutation yet identified. From age 13 on, she continued her follow-up at the San Juan de Dios Hospital.

During a follow-up appointment in 2021, a neck ultrasound reported multiple nodules in the thyroid bed. An ultrasound-guided fine-needle aspiration biopsy (FNA) was performed, whose cytological findings were compatible with carcinoma, probably of the medullary type, highlighting cells with enlarged nuclei, granular chromatin and atypical morphology. Given these findings, a left lateral dissection was performed with biopsy of multiple nodules and a nodule larger than 2 cm x 1.5 cm and tumor involvement were identified in 16 of 30 lymph nodes, confirming the diagnosis of MTC.

During clinical evaluation after the second surgery, phenotypic signs characteristic of MEN2B were identified, including oral mucosal ganglioneuromas and marfanoid habitus (Figure 1). In addition, the patient reported a history of chronic constipation and hip dysplasia. No relevant family history was documented.

Given the clinical suspicion, a genetic study was requested that confirmed the presence of the M918T mutation in the RET proto-oncogene. As part of the comprehensive approach, screening for pheochromocytoma was performed, which has been negative to date.

Currently, the patient is under regular follow-up in the Endocrinology Service. Follow-up ultrasound in 2023 reported a granuloma in the surgical site with no evidence of recurrence, and in 2024, a CT scan showed no lesions compatible with active disease, in addition, catecholamines were negative and calcitonin levels have continued to decrease.

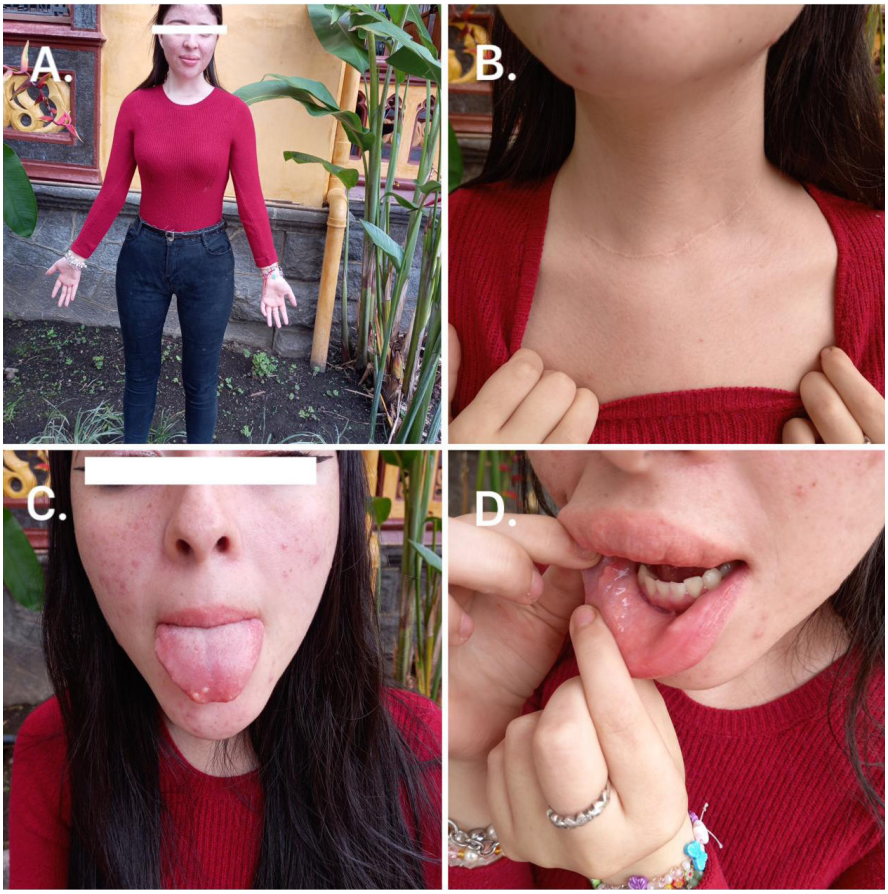

Figure 1. Images of the patient with MEN2B syndrome. A. Image showing a marphanoid habitus. B. Scar after total thyroidectomy. C. Mucous neuromas of the tongue. D. Mucosal neuromas of the lower lip. (Patient consent: both the patient and her mother obtained informed, voluntary, written consent for the publication of the images).

Discussion

Multiple endocrine neoplasia type 2 (MEN2) should be suspected in any patient with MTC or pheochromocytoma, particularly when tumors occur at a young age (<35 years), when they are multicentric, or when more than one family member is affected.[2] Patients with MEN2B have universal extraendocrine characteristics, mainly intestinal deficiency due to diffuse intestinal ganglioneuromatosis, in addition to mucosal neuromas and marfanoid body habitus, characterized by narrow and long facies, cavus foot, pectus excavatum, arched palate, scoliosis, sliding of the femoral head, epiphysis and arachnodactyly with some muscular atrophy.[5]

The pathogenesis of MEN2B involves proto-oncogene (RET). This gene encodes a transmembrane receptor tyrosine kinase that activates multiple pathways, which promotes cell growth and proliferation.

Initial genetic testing for the patient with the MEN2B phenotype should be for the RET codon M918T mutation in exon 16 and, if negative, for the A883F mutation in exon 15. If no mutations are identified, the entire coding region of RET should be sequenced.[2]

In patients with MEN2B, MTC often develops during childhood and is very aggressive, metastasizing to regional lymph nodes and beyond[5]. Approximately 95% of patients with MEN2B have germline mutations of the RET protooncogene of exon 16 (codon pM918T) and less than 5% have germline mutations of exon 15 of RET (codon pA883F).[5]

The diagnosis of MTC is usually made after FNA in a patient who has a solitary thyroid nodule.[6] MTC can spread by local invasion or metastasis within the neck or at a distance. When diagnosed by FNA, ultrasound of the neck is indicated to look for cervical lymph node involvement.[6]

Most patients require a biochemical evaluation to detect coexisting tumors (particularly pheochromocytoma and hyperparathyroidism) prior to thyroidectomy. For patients with unknown RET mutational status and for patients who have a end-line RET mutation, serum calcium (to rule out hyperparathyroidism requiring concomitant surgical intervention) and plasma fractionated metanephrines (as an initial examination of pheochromocytoma) are measured.[6]

In the clinical presentation, there are several associations of clinical signs in a patient, the presence of which should prompt the physician to measure a calcitonin level and perform genetic testing for MEN2B. Early recognition of these signs should allow thyroidectomy at a younger age and. In theory, lead to better results.[4]

The skeletal phenotype usually includes a variable expression of a marfanoid body habitus, characterized by tall stature, long limbs, thin and elongated face, and arachnodactyly of the fingers and toes. Skeletal abnormalities, such as lordosis, kyphosis, scoliosis, joint hypermobility, and slipped capital femoral epiphysis may also be observed.[4]

Mucous neuromas may be evident at birth in many patients with MEN2B. They are described as multiple small soft papules in or around the oral cavity, including the tip of the tongue and lips, in the nasal and laryngeal mucosa and in the conjunctivae. They appear as multiple painless, sessile, 2 to 7 mm and white nodules.[4]

Gastrointestinal signs, especially constipation, usually represent the first nonspecific clinical manifestation of MEN2B. Food intolerance can be observed in childhood. Gastrointestinal problems are due to diffuse intestinal ganglioneuromatosis and the final development of megacolon. Rectal biopsy can lead to the diagnosis of intestinal lymph node neuromatosis.[4]

Surgery is the only cure for MTC. In patients with MEN2, the surgical intervention indicated is prophylactic thyroidectomy, which should be performed at an early stage and be total, since MTC usually presents multifocal and bilateral growth of MTC.[1]

The American Thyroid Association recommends thyroidectomy before one year of age in patients with MEN2B with the goal of removing the thyroid before MTC metastases occur.[5] The extent of surgery should be based on available clinical data, including the presence of abnormal thyroid or lymphatic nodules on ultrasound examination and baseline calcitonin level.[4]

Mortality from MEN2B is mainly due to the stage of the MTC. Ten-year disease-specific survival rates for patients with MTC are 98% for stage I, 93% for stage II, 87% for stage III, and 53% for patients with stage IV MTC 1. A 10-year overall survival of 64% has been estimated[1]. Patients with MEN2A have a better prognosis due to earlier onset and delayed diagnosis of MTC in patients with MEN2B.[1]

Timely diagnosis of MEN2B offers opportunities to make appropriate preventive and therapeutic decisions that can change the natural course of the disease and its complications. It also allows for adequate investigation of associated diseases and appropriate counseling and evaluation of family members carrying the RET proto-oncogene mutation. Even patients with MEN2B who present typical physical characteristics may not be adequately recognized and may be followed up as sporadic cases.

Most patients will be asymptomatic at the time of diagnosis, which makes periodic follow-up necessary in asymptomatic carriers. All suspected cases of multiple endocrine neoplasia, based on phenotypic features, should undergo molecular genetic testing.[7]

References

1. Mathiesen JS, Effraimidis G, Rossing M, Rasmussen ÅK, Hoejberg L, Bastholt L, et al. Neoplasia endocrina múltiple tipo 2: Una revisión. Semin Cancer Biol., 2022; 79:163–79. DOI: 10.1016/j.semcancer.2021.03.035

2. Ball DW. Manifestaciones clínicas y diagnóstico de neoplasia endocrina múltiple tipo 2. En: Hu MI, editor. UpToDate [Internet]. Waltham, MA: UpToDate Inc.; 2023.

3. Redlich A, Lessel L, Petrou A, Mier P, Vorwerk P. Multiple endocrine neoplasia type 2B: Frequency of physical stigmata—Results of the GPOH-MET registry. Pediatr Blood Cancer. 2019;67, e28056. DOI: 10.1002/pbc.28056

4. Castinetti F, Moley J, Mulligan L, Waguespack SG. A comprehensive review on MEN2B. Endocr Relat Cancer. 2018;25: T29-T39. DOI: 10.1530/ERC-17-0209

5. Salazar-Vega J, Solís-Pazmiño P, Reyes C, Gálvez G, Granizo J, Pacheco R, et al. Multiple Endocrine Neoplasia Type 2B (MEN2B) delayed diagnosis: importance of opportune recognition of MEN2 Syndromes in pediatric thyroid cancer. Rev Argent Endocrinol Metab.2019; 56:60–69.

6. Tuttle RM. Medullary thyroid cancer: Clinical manifestations, diagnosis, and staging. En: Hu MI, editor. UpToDate [Internet]. Waltham, MA: UpToDate Inc.; 2022

7. Amodru V, Taieb D, Guerin C, Romanet P, Paladino N, Brue T, Cuny T, Barlier A, Sebag F, Castinetti F. MEN2-related pheochromocytoma: current state of knowledge, specific characteristics in MEN2B, and perspectives. Endocrine. 2020; 69,496-503. DOI: 10.1007/s12020-020-02408-z