

Multiple Neuroendocrine Neoplasia Type 2B: rare clinical presentation associated with mutagenic activity

Julia Pastorello ^{1,2}, Emanuela Lando ^{2,*}, Wagner Rosso ³, Nicolas Almeida Leal da Silva ⁴

¹ Department of Clinical Oncology, Hospital de Clínicas de Passo Fundo - HCPF, Passo Fundo, Rio Grande do Sul, RS, Brazil.

² Academic League of Oncology and Hematology – LANC-HCPF, Hospital de Clínicas de Passo Fundo - HCPF, Passo Fundo, Rio Grande do Sul, RS, Brazil.

³ Department of Head and Neck, Hospital de Clínicas de Passo Fundo - HCPF, Passo Fundo, Rio Grande do Sul, RS, Brazil.

⁴ Department of Urology, Hospital de Clínicas de Passo Fundo - HCPF, Passo Fundo, Rio Grande do Sul, RS, Brazil.

* Correspondence: manu.lando@hotmail.com.

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Abstract: Multiple Neuroendocrine Neoplasia (MEN) gained notoriety after its initial descriptions, but cases of MEN are extremely rare, especially MEN type 2B, characterized by a clinical presentation involving Medullary Thyroid Carcinoma (MTC), pheochromocytoma, and mutagenic alterations with a focus on the RET proto-oncogene. Surgical intervention stands out as the primary curative treatment, but in cases of metastatic conditions, antityrosine kinase agents (TKI) and radiotherapy may be considered. Due to the scarcity of reported cases associated with MEN Type 2B, we present a detailed case study highlighting the associated mutagenic activity.

Keywords: Multiple Neuroendocrine Neoplasia; Medullary Thyroid Carcinoma; Pheochromocytoma Mutagenic Activity.



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1. Introduction

In 1968, Multiple Neuroendocrine Neoplasia (MEN) Type 2 was described for the first time, providing differentiation guidance in relation to other presentations of MEN [1-4]. MEN Type 2 is further classified into subtypes A and B. Typically, MEN Type 2A is diagnosed between the third and fourth decades of life and is more prevalent in the Brazilian population. On the other hand, MEN Type 2B stands out due to its earlier clinical presentation, hereditary history linked to genetic abnormalities, and particularly the involvement of the RET proto-oncogene [8-13].

The clinical manifestations associated with MEN vary depending on the affected site and the associated mutagenic activity. Genetic-laboratory tests are performed for diagnosis and disease monitoring [14]. Surgical treatment is considered the primary approach for MEN, as chemotherapy has not shown any survival benefits. However, in selected cases, anti-tyrosine kinase therapy (TKI) shows promise as a treatment, given the pathophysiology associated with MEN, especially for metastatic cases [11-23].

Due to the rarity of current cases in the oncology literature, it is of utmost importance to present this case report, providing insights into the clinical manifestations, associated mutagenic activity, and approaches against MEN Type 2B, while correlating with data from other parts of the world.

2. Case Report

Patient, 58 years old, with a history of hypertension and non-insulin dependent diabetes, presented with a weight loss of 10 kilograms over 3 months, accompanied by episodes of diarrhea. Laboratory tests on 08/10/2022 revealed elevated CEA (172.60) and Calcitonin (1,108). Further investigation was conducted, starting with a colonoscopy on 08/16/2022, which revealed a Tubular Adenoma with low-grade dysplasia. Due to a positive family history of Medullary Thyroid Carcinoma, a thyroid ultrasound was performed on the same day, showing a heterogeneous nodular formation measuring 2.0 cm in the right thyroid lobe. A computed tomography scan on 08/16/2022 confirmed the thyroid ultrasound findings and also identified a 1.6 cm nodular presence in the left adrenal region. Magnetic resonance imaging on 08/17/2022 revealed the presence of two nodules in the left adrenal region, with the larger one measuring 1.7 cm in the lateral rod region, and the smaller one measuring 1.5 x 0.8 cm in the medial rod. A fine-needle aspiration biopsy of the thyroid region on 08/22/2022 showed compatibility with an atypical follicular lesion. PET-CT on 08/30/2022 (Figure 1, 2A and 2B), confirmed the previously identified findings with greater specificity, thus strengthening the suspicion of associated malignancy.

Given the patient's clinical presentation and family history of rare malignancies, including 5 family members with MTC and 1 family member with MEN Type 2 and positive RET, the possibility of Multiple Neuroendocrine Neoplasia Type 2 was suggested. Consequently, a surgical procedure was performed, consisting of thyroidectomy followed by left adrenalectomy on 11/01/2022. The anatomopathological analysis confirmed the presence of Medullary Thyroid Carcinoma and Pheochromocytoma, leading to the diagnosis of Multiple Neuroendocrine Neoplasia Type 2B.

Following the surgical procedures, adjuvant treatment was not required due to staging pT2N0M0. Currently, the patient remains asymptomatic, and subsequent laboratory tests on 03/27/2023 indicate normal ranges for CEA (1.0) and Calcitonin (2.0). The patient is in regular follow-up and is currently in remission regarding the presentation of malignancy.

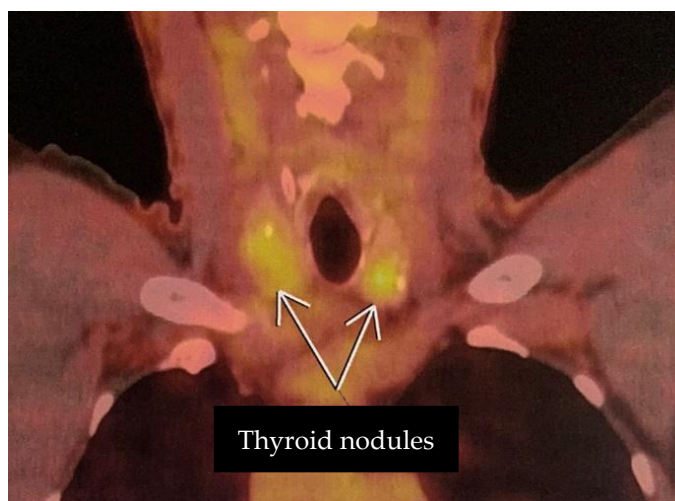


Figure 1: PET-CT (08/30/2022): Thyroid nodules, Right lobe 2.0x2.0 cm and left lobe: 1.5x1.2 cm.

3. Discussion and conclusion

In 1968, Steiner et al. aimed to differentiate between Multiple Neuroendocrine Neoplasia Types. They described MEN Type 1, which involves the pancreas, pituitary, and parathyroid sites to a greater extent, and Multiple Neuroendocrine Neoplasia Type 2 (MEN 2), characterized especially by sporadic or hereditary Medullary Thyroid Carcinoma (MTC), hyperparathyroidism, and pheochromocytoma [1-2]. MEN Type 2 is further subdivided into subtypes A and B, with type B being particularly distinctive due to its

clinical presentation, which usually occurs in childhood. In contrast, MEN Type 2A is typically diagnosed between the third and fourth decades of life. Additionally, MEN Type 2B is strongly associated with a hereditary history of genetic abnormalities, primarily the RET proto-oncogene [3-4, 5, 7].

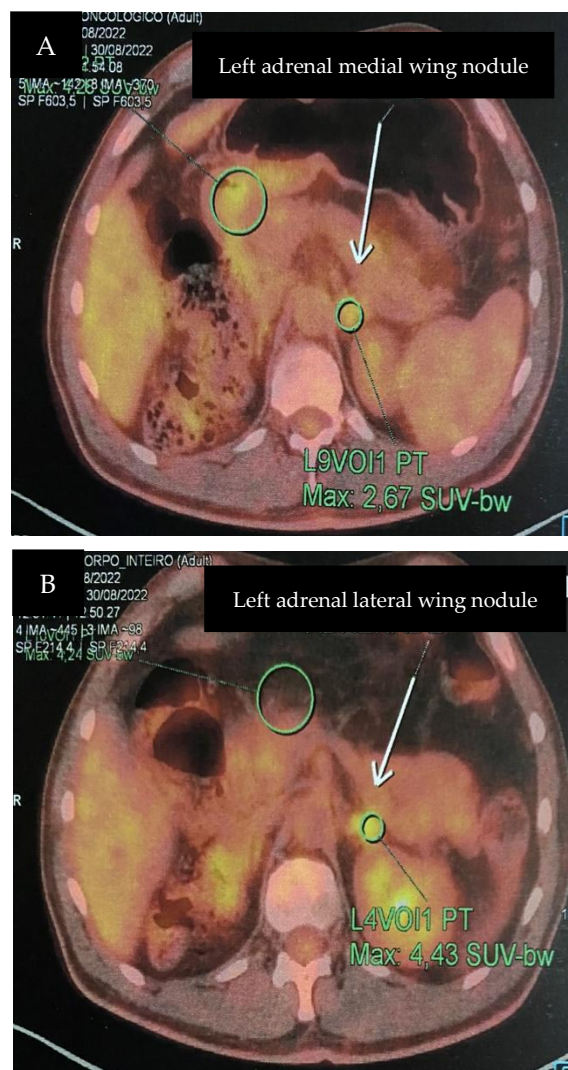


Figure 2: PET-CT (08/30/2022): Nodules in the Adrenal Region on the left, 1.5x 0.8cm in the medial wing region (A) and 1.7x 1.5cm in the lateral wing region (B), respectively.

Multicenter studies corroborate that in the Brazilian population, MEN Type 2A is the most prevalent [8-13]. This data supports the rarity of the current case being presented. The clinical picture presented by the patient in our study aligns with the literature, illustrating that MEN Type 2B is characterized by ganglioneuromatosis in all cases, with involvement in the ocular region, oral mucosa, and gastrointestinal tract. Furthermore, the patient exhibits MTC in 90% of cases, as well as marfanoid habits in 65%, epiphyseal and osteoarticular alterations, and pheochromocytoma in 45% of cases [4, 5].

The measurement of calcitonin (CT), calcitonin gene-related peptide (CGRP), carcinoembryonic antigen (CEA), amyloid, somatostatin, and adrenocorticotrophic hormones (ACTH) is of paramount importance for the biochemical-laboratory diagnosis. These substances are essential due to their involvement with MTC, which causes changes in their levels through C cells [14]. The laboratory data presented by the patient under study, especially regarding calcitonin and CEA, supports this approach. Despite the pathogenicity

of the *RET* proto-oncogene in MEN Type 2, it is crucial to consider its measurement since the TGF- β peptide (transforming growth factor), glial-derived neurotrophic factor (GDNF), plays a significant role in receptor dimerization and tyrosine kinase autophosphorylation, leading to neoplastic activity [15-20].

Genetic tests, particularly focusing on the *RET* gene and the presentations of Multiple Neuroendocrine Neoplasia, are reinforced based on rare studies mentioned above. A multicenter study involving 477 families diagnosed with MEN Type 2 and *RET* mutations emphasized that different phenotypes related to MEN Type 2 were attributed to different mutagenic sites in the codon. Codon 918 was exclusively related to MEN Type 2B, while mutations remaining in codon 634 were intrinsically related to cases of hyperparathyroidism and pheochromocytoma [4]. A French study involving 147 patients with MTC and related germinal processes associated with the *RET* proto-oncogene showed that MTC was associated with exon 10, while exons 13 to 15 were related to non-cysteine probability, with such changes present in 59.5% of study participants [27].

Regarding the risk criteria associated with mutagenic location, a study emphasized that codons 618 and 634 carry the highest risk of mutagenic transformation, while codons 611, 620, and 790 have intermediate associated risks [7]. A European study further reinforced previously presented data on severity criteria, indicating that patients with codon 634 were considered at high risk. Additionally, C634R patients had significantly more distant metastases than individuals with the cysteine-tyrosine genotype at codon 634Y [28].

In cases of MEN Type 2, the treatment should consider the tumor stage, and surgical procedures are generally the initial approach for associated presentations. For MTC, total thyroidectomy with lymphadenectomy is indicated, and family members with a positive history of MTC and a positive *RET* gene should undergo early thyroidectomy, before 6 months of life. The management of the presented case followed the recommended indications in the literature, aiming for a lower recurrence of malignancy and increased survival rates (29-33).

Regarding pheochromocytoma, bilateral adrenalectomy is the most indicated therapeutic approach, although association with other factors should be considered before making the final decision [34-35]. A rare case report supports the consideration of a unilateral approach, citing 20 patients who underwent unilateral adrenalectomies, and only 2 cases required a contralateral approach during 6 years of follow-up [36]. Chemotherapy treatments' results are limited, and usual agents have shown little potential to alter patient survival, even when combined. Radiotherapy solely for CMT has not been effective, but it may be indicated for patients with bone metastases, in addition to bisphosphonate agents [21-24, 37-38].

Radioimmunotherapy and gene therapy, including the introduction of tumor suppressor genes and anti-tyrosine kinase agents, show promise as therapeutic modalities for CMT, although some are still in the experimental phase [13, 39-43]. Vandetanib, Cabozantinib, and Sorafenib are the agents with the most significant impact on the treatment and survival of patients with Type 2 MEN, particularly those associated with CMT due to their mechanism of action [25-26].

Post-surgical follow-up should include evaluation every 2 months, focusing on CEA and calcitonin levels to assess the possibility of developing associated metastases [7, 46]. The laboratory results from the follow-up of the case presented in the study confirm the disease is in remission. Therefore, the present case report is of utmost importance, given the rarity of cases of Multiple Neuroendocrine Neoplasia Type 2B in the literature. It provides a detailed description of the associated mutagenic activity and follows the recommended pattern, as evidenced in rare cases of MEN Type 2B. This study significantly contributes to technical/scientific development, seeking to improve knowledge about these rare conditions in the field of clinical oncology.

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Conflicts of Interest: None.

Supplementary Materials: None.

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