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Exploring Multiple Endocrine Neoplasia Type 2B: Key Findings from a Case Report

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Abstract

Multiple endocrine neoplasia type 2B (MEN 2B) is an autosomal dominant syndrome primarily caused by the germline M918T RET mutation. It is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma (PC), and non-endocrine features. Symptoms depend on the glandular elements present. The initial diagnosis of MEN 2B is relatively late, and the diagnosis by non-endocrine components is extremely weak. The initial management consists of a total thyroidectomy with dissection of the lymph nodes. If PC is present, its treatment is surgical removal, which should be performed before thyroidectomy for MTC. The prognosis of MTC in MEN 2B depends on the stage at diagnosis, and only early diagnosis and intervention offer a chance of cure. It is necessary to underline the need to treat the extra-endocrine signs in these patients. We present below a case of MEN 2B who consulted late for a cervical tumor and morphological abnormalities of the lips and tongue.

Keywords: MEN 2B, medullary thyroid carcinoma, pheochromocytoma, RET mutation.

Introduction

Multiple endocrine neoplasia type 2 (MEN 2) is an autosomal dominant hereditary disease caused by an abnormality of the RET proto-oncogene (RET). MEN 2 is divided into two distinct clinical entities: MEN 2A and MEN 2B. The prevalence of MEN 2A and MEN 2B is 13–24 and 1–2 per million, respectively, while the incidence for MEN 2A and MEN 2B ranges between 8–28 and 1–3 per million live births per year, respectively [1,2].

In MEN 2B, the predominant symptomatology is endocrinological, although there are usually non-endocrine manifestations [3]. MEN 2B is associated with medullary thyroid cancer (MTC), pheochromocytoma, aerodigestive tract ganglioneuromatosis, and musculoskeletal and ophthalmological abnormalities [4].

The initial management consists of a total thyroidectomy with bilateral dissection of the central lymph node compartment. Serum calcitonin and carcinoembryonic antigen should be measured preoperatively. These can be tracked over time and used as markers of disease recurrence as their doubling times have been shown to correlate with disease progression and survival [5]. The prognosis of MEN 2 is related to the aggressiveness of MTC, which can develop early lymph node metastases. We present below a case of MEN 2B who consulted for a cervical tumor and morphological abnormalities of the lips and tongue.

Case report

A 26-year-old man was admitted to our unit for a tumor in the anterior cervical region, evolving for more than a year, without local compressive symptoms. The patient had no personal history of thyroid

disease, except for a goiter operated on in his paternal cousin (no pathological documents). There were no symptoms suggestive of thyroid dysfunction, except for recurrent diarrhea. He presented with headaches, palpitations, and excessive sweating reminiscent of a Ménard triad. On clinical examination, he had a marfanoid phenotype (long and slender limbs, joint hypermobility, pes cavus), bilateral ocular redness, and hypertrophied lips, with verrucous lesions on the tongue, upper eyelid, inner cheeks, and palate (Figures 1 and 2). Examination also revealed stage II goiter (World Health Organization classification).

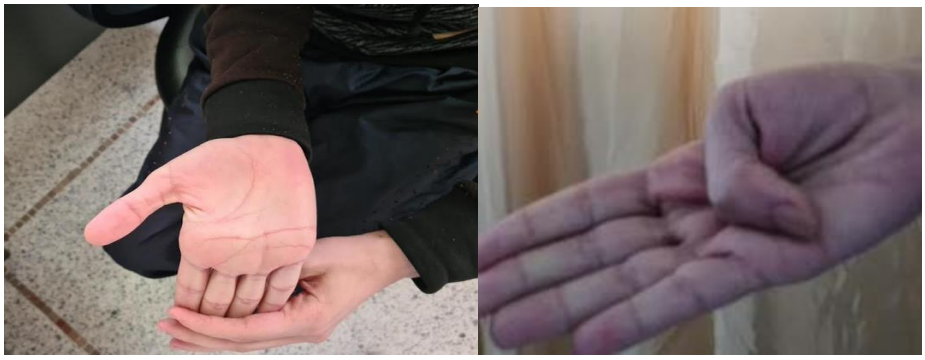

Figure 1 : joint hypermobility

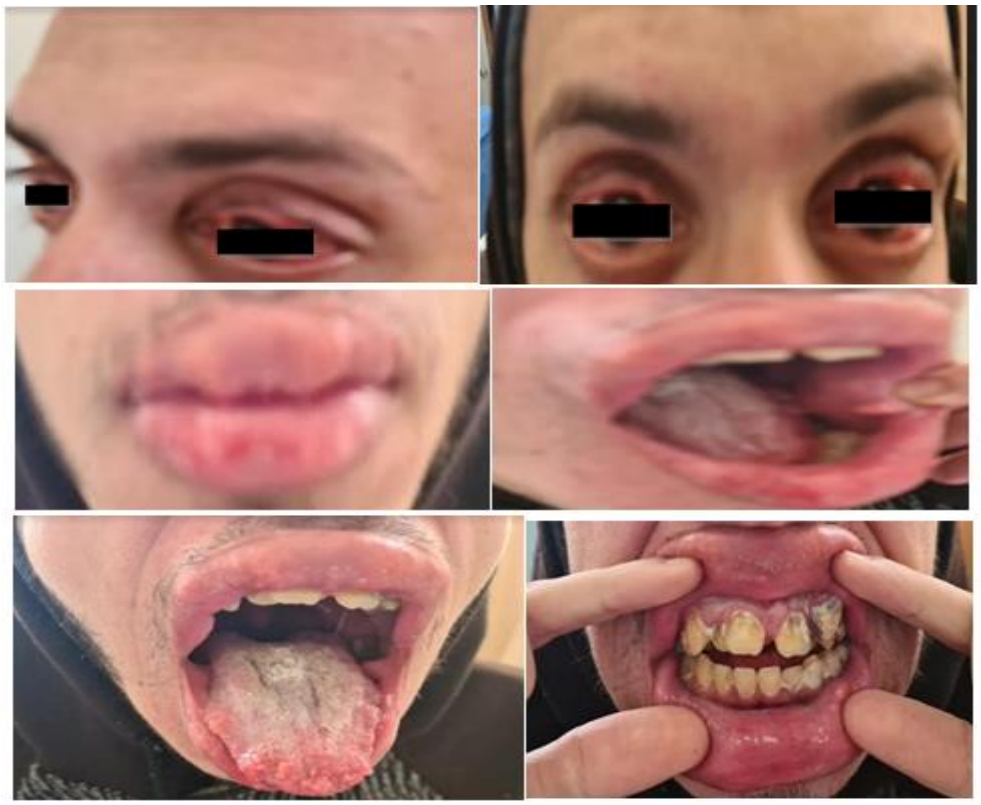

Figure 2: bilateral ocular redness and hypertrophied lips, with verrucous lesions on the tongue, upper eyelid, inner cheeks and palate

Calcitonin was >2000 ng/l (normal values [NV] < 11.5 pg/ml) and carcinoembryonic antigen (CEA) was 533 ng/ml (NV 2-4). The dosage of urinary methoxylated derivatives revealed a rate of normetanephrines at >5850 nmol/24h (NV < 281), metanephrines at >5590 nmol/24h (NV < 159), and 3-ortho methyl dopa at 1305 nmol/24h (NV < 3).

Cervical ultrasound showed a goiter with two nodular lesions in the right lobe classified EU-TIRADS IV and the upper left lobe classified EU-TIRADS V with suspicious cervical lymphadenopathy in lymph node areas II, III right, and VI. The cervico-thoraco-abdomino-pelvic CT scan detected two voluminous tissue masses at the expense of the adrenal glands, poorly limited, with irregular contours, presenting significant and heterogeneous enhancement, delimiting areas of central necrosis, measuring on the right 91 x 68 x 97 mm in diameter (AP x T x H) and 41 x 42 x 70 mm on the left.

MIBG scintigraphy revealed two foci of intense MIBG uptake suggestive of pheochromocytomas. The bone scintigraphy was negative. The results of the genetic study are in progress. Lip and tongue biopsy showed mucous neuroma. The patient initially underwent a bilateral adrenalectomy, followed by a total thyroidectomy and central and lateral lymph node dissection. Histological examination of the adrenal specimen showed an aspect of aggressive pheochromocytoma (PASS score = 10 on the right side and PASS score = 8 on the left side).

The pathological specimen of the thyroid showed a histological appearance compatible with MTC, classified pT3a on the right and pT2 on the left, with lymph node involvement and vascular emboli. The patient received hormone replacement therapy with hydrocortisone and L-thyroxine.

The clinical course was marked by clinical improvement, normalization of urinary methoxylated derivatives, and a significant decrease in calcitonin levels (25 pg/l) and carcinoembryonic antigen. Lifelong follow-up has been established for our patient.

Discussion

MEN 2B (Gorlin syndrome) was originally described by Wagenmann in 1922 [6]. It is a rare hereditary multiglandular disease (5% of MEN 2). Its prevalence is 1-2 per million, and its incidence ranges between 1–3 per million live births per year [1,2]. The phenotype of this syndrome is characterized by the presence of marfanoid features and mucocutaneous neuromas (lips, tongue, eyelids, connective tissue) and ophthalmologic abnormalities [5]. Our patient had a marfanoid phenotype with enlarged lips and verrucous lesions on the tongue, upper eyelid, and inner cheeks. MEN 2B is characterized by prominent extra-endocrine features, a more aggressive presentation of MTC, and the absence of PHPT. Pheochromocytoma occurs in 50% of patients with MEN 2B [7].

The value of serum calcitonin, carcinoembryonic antigen, and urinary methoxylates are useful in early detection [5]. In our case, there was hypercalcitoninemia, elevated carcinoembryonic antigen, and positive urinary methoxylated derivatives. The phosphocalcic balance was normal. Cervical ultrasound and imaging of the adrenal glands are also important for diagnosis [12], as was the case for our patient.

The histopathological signs of mucosal neuromas present a challenge for differential diagnosis with neuromas of other origins. Therefore, it is important to look for other indicative signs, such as mucosal neuromas of the tongue, lips, buccal mucosa, and inner eyelids, as well as musculoskeletal and gastrointestinal signs and symptoms [8].

There is a phenotype-genotype correlation, with 98% of MEN2B cases caused by a specific germline mutation of the RET proto-oncogene on chromosome 10q, and approximately 95% of patients having an M918T mutation [5]. The presence of this mutation is associated with a high risk of early MTC metastasis, aggressive growth, and poor prognosis. In our case, the genetic study was in progress.

About half of all MEN2B patients present with de novo RET germline mutations [9] (as seen in this patient). Given the aggressive nature of the tumor, it is advisable to conduct a genetic study of their

family (children) for early diagnosis and to perform early prophylactic thyroidectomy if the mutation is detected. The timing of prophylactic thyroidectomy is genotype-specific [4, 10].

Treatment for MTC is surgical, with total thyroidectomy and lymph node dissection of the central and lateral cervical compartments. Recently, tyrosine kinase inhibitors have been successfully used in MTC. Vandetanib, an oral RET inhibitor, has been shown to prolong survival in patients with advanced hereditary MTC [11]. Cabozantinib, an oral inhibitor of MET (hepatocyte growth factor receptor), VEGFR2, and RET, has demonstrated prolongation of survival in patients with metastatic MTC [12].

The treatment of PC is surgical, which should be performed before thyroidectomy for MTC [10]. Our patient initially benefited from an adrenalectomy followed by a total thyroidectomy with central and bilateral lymph node dissection. Post-surgical monitoring is based on the measurement of calcitonin, carcinoembryonic antigen (CEA), cervical ultrasound (if calcitonin is positive), and more in-depth imaging as dictated by the level and evolution of calcitonin and CEA.

The prognosis is determined by the characteristics at the time of diagnosis (size, extracapsular extension, presence of lymphadenopathy, and distant metastases), the type of MTC (familial or sporadic), as well as the sex and age of the patient.

Conclusion

Multiple endocrine neoplasia type 2B (MEN2B) is an extremely rare syndrome primarily caused by germline RET918 mutations. MEN2B typically leads to medullary thyroid carcinoma (MTC), pheochromocytoma, and extra-endocrine physical characteristics (cutaneous, digestive, etc.). MTC is the most significant determinant of mortality in patients with MEN2B. Establishing the diagnosis of MEN2B at a curative stage of MTC is crucial. The characteristic phenotype associated with MEN2B is almost always observed before the detection of MTC or pheochromocytoma, as in our patient. Knowledge about the non-endocrine manifestations of MEN2B should be shared among pediatricians, dermatologists, and gastroenterologists.

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