Multiple endocrine neoplasia type 2B: A report of a rare case

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Abstract

Multiple endocrine neoplasia type 2 (MEN2) is caused by RET proto-oncogene mutations and characterized by the presence of medullary carcinoma of the thyroid, pheochromocytoma, marfanoid features and mucosal neuromas of the tongue, lips, inner cheeks and inner eyelids. MEN type 2B is also known as mucosal neuroma syndrome. Oral presentations are sometimes the earliest signs of this condition. Early identification of this syndrome is important because affected patients often develop medullary thyroid carcinoma and pheochromocytoma. This article reports a 43-year-old male patient with mucosal neuromas and previous history of thyroidectomy due to medullary carcinoma.

Keywords: Marfanoid habitus, medullary thyroid carcinoma, mucosal neuroma, multiple endocrine neoplasia type 2B

INTRODUCTION

Multiple endocrine neoplasia (MEN) syndromes are autosomal dominant hereditary conditions of neuroendocrine origin. These produce specific syndromes due to the hormone secretion. MEN can be classified as MEN1 (primary hyperparathyroidism [PHPT], pituitary adenomas and pancreatic islet cell tumors), MEN type 2A (MEN2A) (medullary thyroid carcinoma [MTC], pheochromocytoma and PHPT) and MEN2B (MTC, pheochromocytoma, marfanoid habitus and mucocutaneous neuromas). Rare variants of MEN2 have been associated with Hirschsprung disease and cutaneous lichen amyloidosis. MTC is found in patients as young as 17 months as a manifestation of MEN2A. MTC develops at an early age in MEN2B and more aggressive than MEN2A. The prognosis of MEN2 is related to the aggressiveness of the MTC, which can develop early lymph node metastases. Metastases have been reported in patients as young as 3 years.

CASE REPORT

A 43-year-old male reported to the Department of Oral Medicine and Radiology with the chief complaint of tooth pain on the right lower back tooth region. Extraoral examination revealed multiple nodules on the conjunctival surfaces of the upper and lower eyelids [Figure 1a]. The lips were diffusely enlarged and appeared everted and...
bumpy on palpation [Figure 1b]. On intraoral examination, multiple nodules were seen on the tip and lateral borders of the tongue [Figure 1c]. Tongue appeared enlarged, and no functional abnormality was detected. Nodular masses were also seen on the buccal mucosa [Figure 1d] and labial mucosa [Figure 1e]. The nodules were asymptomatic, oval-to-round shape, measuring 0.8 cm × 0.5 cm in dimension with sessile base and smooth surface. The patient gave a history of carcinoma of the thyroid, and a total thyroidectomy was done in a cancer institute 20 years back. There was no history of cancer and thyroid abnormality in his family. The patient gave a history of chronic constipation since childhood. Anterior maxillary and mandibular teeth appeared to be protruded from side profile view [Figure 2]. On hard tissue examination, multiple root stumps were present in all the four quadrants. Extraction and prosthetic rehabilitation was advised. Midline diastema was clearly evident in the maxillary anterior region [Figure 3].

General examination failed to reveal abnormalities such as cervical lymphadenopathy, café-au-lait spots and diffuse pigmentation of neurofibroma on the trunk or extremities. Blood pressure and pulse rate were within the normal limits ruling out pheochromocytoma. A proper medical record of previous investigation and treatment could not be obtained from the patient since they were not maintained properly. At present, he was not under any treatment. Based on the clinical features and history, a clinical diagnosis of MEN2B was made. There was no history of cancer and thyroid abnormality or similar syndromes in his family. Since none of the family members were affected, this case was considered to be due to de novo mutation. Biochemical analysis of the patient was within the normal limits. Incisional biopsy was
done from nodule on labial mucosa. Histopathological examination revealed bundles of disorganized and tortuous nerve fibers surrounded by a thickened perineurium which was suggestive of mucosal neuromas [Figure 4]. Numerous bundles of elongated cells with wavy dark nuclei were identified. The patient was further referred to the Department of Endocrinology for further management.

**DISCUSSION**

MEN2B or multiple mucosal neuroma syndrome was initially described by Wagenmann in 1922. Clinical features associated with MEN2 syndrome are shown in Table 1. The complete syndrome with mucosal neuromas, pheochromocytoma and MTC may be evident in 50% of the cases. About 95% of the MEN2B cases are caused due to a specific germline mutation in the *RET* proto-oncogene on chromosome 10q. The mean age of 18 years is said to be diagnostic for MEN2B syndrome. Around 10% of the cases have neuromas and pheochromocytomas alone, whereas the remaining cases have neuromas and MTC without pheochromocytoma. *RET* protein is expressed from the neural crest, including C-cells of the thyroid, adrenal medulla and enteric ganglia, and encodes a member of the receptor tyrosine kinase family of transmembrane receptors. Incidence is said to be 80%, 15% and 5% for MEN2A, familial MTC and MEN2B, respectively. The actual epidemiology of MEN2B is unknown. The MEN2B prevalence is estimated to be between 1 in 600,000 and 1 in 4 million. Among subtypes, type 2A is the most common, followed by familial MTC. MEN2B is relatively uncommon, accounting for only 5% of all the cases of MEN with prominent extra-endocrine features, a more aggressive presentation of MTC and the lack of PHPT unlike MEN2A. MTC develops within the 1st year of life, and patients die before the age of 30 years.

Patients with MEN2B do not have parathyroid disease but do have a characteristic appearance including marfanoid habitus, pectus abnormalities, mesodermal abnormalities, corneal nerve hypertrophy, labial and mucosal neuromas and intestinal ganglioneuromatosis. Marfanoid body habitus is also seen in Shprintzen–Goldberg syndrome, Ehlers–Danlos syndrome and homocystinuria. The majority of the MEN2B cases show diffuse ganglioneuromatosis present early in childhood with pseudo-Hirschsprung’s features, even before the manifestation of medullary thyroid cancer. Most of the patients have gastrointestinal symptoms characterized by pain, diarrhea, constipation, bloating and even megacolon. These symptoms are reported in children and young adults as well. The clinical characteristics of MEN2B are summarized in Table 2.

Mucocutaneous neuromas on the tongue and subconjunctiva in early childhood may be one of the earliest presentations and may be considered as clinical markers for the diagnosis of this condition. The clinical features of MEN2B are enlargement of the lips, multiple mucosal neuromas over the eyelids, lips, tongue and buccal mucosa associated with a MTC and a bilateral pheochromocytoma. Other intraoral features are high arched palate, gingival hyperplasia, prognathic mandible and spacing of anterior teeth which were present in our case. Pheochromocytoma occurs in 50% of the patients with MEN2B. However, it was not found in the present case. The majority of the patients show the presence of intestinal ganglioneuromatosis. The next common component is MTC which can have an early onset. The serum calcitonin value, carcinoembryonic antigen, epinephrine, norepinephrine, dopamine and urinary concentrations of epinephrine, norepinephrine and vanillylmandelic acid are useful in early detection. Thyroid and adrenal scans are also important for diagnostic workup. Some of the features such as neuromas, facial characteristics and gastrointestinal disorders are present...
at an early age, the syndrome may not be diagnosed until MTC or pheochromocytoma manifests in later life and some of the musculoskeletal features which manifest in young adults are pectus excavatum, loose joints, abnormal curvature of the spine and marfanoid habitus.[12]

Histopathological examination of mucosal neumomas usually reveals numerous bundles of disorganized and tortuous nerve fibers with elongated cells showing wavy dark nuclei surrounded by a prominent perineurium scattered throughout the submucosa. The differential diagnosis for mucosal neuma includes traumatic neuroma, palisaded encapsulated neuroma, Morton’s neuroma or neurofibroma. Mucosal neuma has a distinctive clinical history which is not associated with traumatic neuroma.

As the majority of the cases of MEN2B arise due to de novo mutation, it is challenging for a general practitioner to diagnose this condition and so they should look for the hallmark diagnostic findings such as mucosal neumomas of the tongue, lips, buccal mucosa and inner eyelids, musculoskeletal findings and gastrointestinal symptoms.[12] Early diagnoses, recognition of phenotype, adequate surgery and appropriate genetic counseling with genetic screening (RET gene mutation analysis) are essential to improve the outcome of persons with MTC. Educating health-care professionals about the presentation of this condition is the need of the hour for early diagnosis, thereby preventing the late complications.

The diagnosis in the present case was made by the presence of marfanoid habitus, multiple submucosal neumomas, a history of MTC and histopathologic confirmation of mucosal neuma.

CONCLUSION

Early diagnosis is essential since many patients develop thyroid malignancy. MEN2B is of particular interest to the dental professionals since oral neumomas are one of the earliest manifestations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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