Case Report

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

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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).[1] 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.[2] MTC develops at an early age in MEN2B and more aggressive than MEN2A.[2] 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.[3]

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

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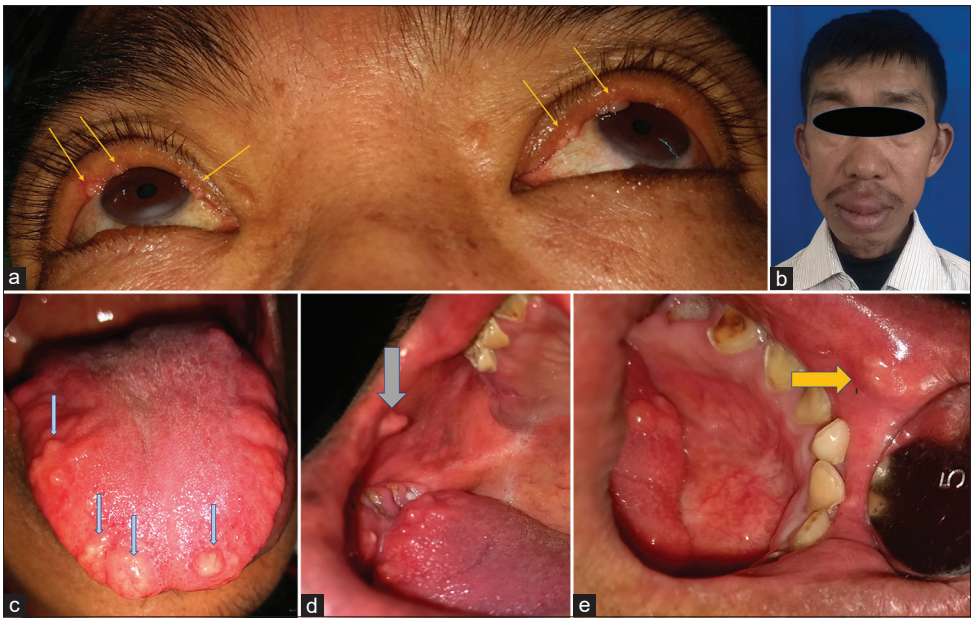

Figure 1: Clinical photographs of the patient. (a) Neuromas in the eyelids. (b) Enlarged lip. (c) Multiple neuromas present on the tip and lateral border of the tongue and enlarged tongue. (d) Neuromas in the buccal mucosa. (e) Neuromas in the labial mucosa

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

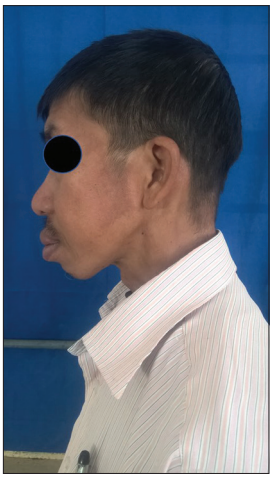

Figure 2: Side profile of the patient

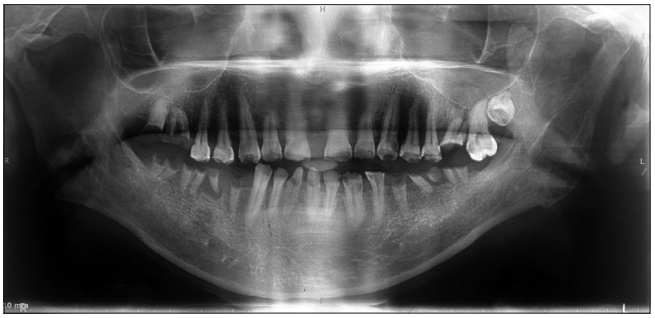

Figure 3: Orthopantomograph showing multiple root stumps and midline diastema

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.[4,5] Clinical features associated with MEN2 syndrome are shown in Table 1.[6] The complete syndrome with mucosal neuromas, pheochromocytoma and MTC may be evident in 50% of the cases.[1] About 95% of the MEN2B cases are caused due to a specific germline mutation in *RET* proto-oncogene on chromosome 10q. The mean age of 18 years is said to be diagnostic for MEN2B syndrome.[7] Around 10% of the cases have neuromas and pheochromocytomas alone, whereas the remaining cases have neuromas and MTC without pheochromocytoma.[8] *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.[9] 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.

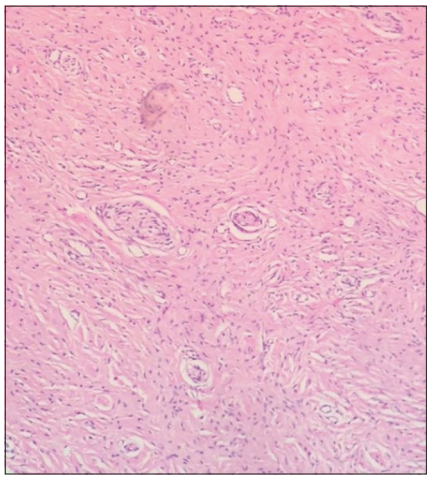

Figure 4: Photomicrograph showing disorganized and tortuous nerve fibers surrounded by a thickened perineurium and elongated cells with wavy dark nuclei (H&E, ×20)

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.[10] Most of the patients have gastrointestinal symptoms characterized by pain, diarrhea, constipation, bloating and even megacolon.[11] These symptoms are reported in children and young adults as well.[12] The clinical characteristics of MEN2B are summarized in Table 2.[12]

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.[13] 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.[5] 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.[14] The serum calcitonin value, carcinoembryonic antigen, epinephrine, norepinephrine, dopamine and urinary concentrations of epinephrine, norepinephrine and vanillylmandelic acid are useful in early detection.[5] Thyroid and adrenal scans are also important for diagnostic workup.[12] Some of the features such as neuromas, facial characteristics and gastrointestinal disorders are present

Table 1: Clinical Findings Associated with MEN2 Syndromes[6]

Syndrome	MTC	Pheochromocytoma	Parathyroid hyperplasia	Intestinal ganglioneuromas	Mucosal neuromas
MEN2A	Yes	Yes	Yes	No	No
MEN2B	Yes	Yes	No	Yes	Yes
FMTC	Yes	No	No	No	No

MEN2: Multiple endocrine neoplasia, MTC: Medullary thyroid cancer, FMTC: Familial medullary thyroid cancer

Table 2: Signs and Symptoms of MEN2B[12]

Clinical characteristics	Frequency (%)
Mucosal neuromas of the lips, eyelids, buccal mucosa, tongue, palate and intestinal mucous membrane (earliest sign)	100
Enteric ganglioneuromatosis	100
Medullary carcinoma of the thyroid (very young child)	90
Skeletal abnormalities of the spine (lordosis, kyphosis and scoliosis), talipes equinovarus, kyphoscoliosis, joint laxity and) and pes cavus	Common
Thickened medullated corneal nerves (slit-lamp examination)	
Facies with thickened lips	
Marfanoid habitus	65–75
Pheochromocytoma	45–50

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 neuromas 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 neuroma includes traumatic neuroma, palisaded encapsulated neuroma, Morton's neuroma or neurofibroma. Mucosal neuroma 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 neuromas 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 neuromas, a history of MTC and histopathologic confirmation of mucosal neuroma.

CONCLUSION

Early diagnosis is essential since many patients develop thyroid malignancy. MEN2B is of particular interest to the dental professionals since oral neuromas 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.

REFERENCES

1. Gundgurthi A, Dutta MK, Pakhetra R, Garg MK. Missed diagnosis of multiple endocrine neoplasia type 2B. Med J Armed Forces India 2010;66:295-7.
2. Sanso GE, Domene HM, Garcia R, Pusio E, Mondino AK, Roque M, *et al*. Very early detection of RET protooncogene mutation is crucial for preventive thyroidectomy in multiple endocrine neoplasia type 2 children: Presence of C-cell malignant disease in asymptomatic carriers. Cancer 2002;94:323-30.
3. Kaufman FR, Roe TF, Isaacs H Jr., Weitzman JJ. Metastatic medullary thyroid carcinoma in young children with mucosal neuroma syndrome. Pediatrics 1982;70:263-7.
4. Wagenmann A. "Multiple neurome des Auges und der Zunge". Ber Dtsch Ophthalmol Ges. 1922; 43:282-5.
5. Dharmshaktu P, Garg A, Manglani D, Dinesh Dhanwal D. MEN2B syndrome presenting as an acute respiratory emergency. BMJ Case Rep 2013:1-4. doi:10.1136/bcr-2013-201080
6. Qualia CM, Brown MR, Ryan CK, Rossi TM. Oral mucosal neuromas leading to the diagnosis of Multiple Endocrine Neoplasia Type 2B in a child with intestinal pseudo-obstruction. Gastroenterol Hepatol, 2007;3:208-11
7. Vasen HFA, Van der Feltz M, Krusemen AN. The natural course of multiple endocrine neoplasia type IIb: A study of 18 cases. Arch Intern Med 1992; 152:1250-2.
8. MSD Manual. Multiple Endocrine Neoplasia, Type 2B (MEN 2B). 2020. Available from https://www.msdmanuals.com/professional/endocrine-and-metabolic disorders/multiple-endocrine-neoplasia-men-syndromes/multiple-endocrine-neoplasia,-type-2b-men-2b. [Last accessed on 2020 March 24].
9. Yasir M, Mulji NJ, Kasi A. Multiple Endocrine Neoplasias, Type 2 (MEN II, Pheochromocytoma and Amyloid Producing Medullary Thyroid Carcinoma, Sipple Syndrome) [Updated 2020 May 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519054/ [Last accessed on 2020 May 25].

10. Norton JA, Krampitz G, Jensen RT. Multiple Endocrine Neoplasia: Genetics & Clinical Management. Surg Oncol Clin N Am. 2015;24:795-832.
11. Fernando AR, Samarasekera DN, and Bulathsinghela RP. Constipation with megacolon in a 36 years old man: A rare presentation of MEN2B from Sri Lanka. BMJ Case Rep. 2019;12:1-4.
12. Camacho CP, Hoff AO, Lindsey SC, Signorini PS, Valente F, Oliveira M et al. Early diagnosis of Multiple Endocrine Neoplasia Type 2B: A challenge for Physicians. Arq Bras Endocrinol Metab 2008;52:1393-8.
13. Camacho CP, Hoff AO, Lindsey SC, Signorini PS, Valente F, Oliveira M et al. Early diagnosis of Multiple Endocrine Neoplasia Type 2B: A challenge for Physicians. Arq Bras Endocrinol Metab 2008;52:1393-8
14. Majidi M, Haghpanah V, Hedayati M, Khashyar P, Mohajeri T, Larijani BA. A family presenting with multiple endocrine neoplasia type 2B: A case report. J Med Case Reports 2011;587:1-3. https://doi.org/10.1186/1752-1947-5-587. [Last accessed on 2019 November 24].