Oral Manifestations of Multiple Endocrine Neoplasia 2B Syndrome: A Rare Case Report

Abstract

Multiple endocrine neoplasia (MEN) 2B syndrome is a rare autosomal dominant hereditary condition of neuroendocrine origin characterized by pheochromocytoma, marfanoid habitus, and mucocutaneous neuromas. Multiple mucosal neuromas on the tongue, lips, cheeks, and inner eyelids are often appeared as the earliest signs in most of the undiagnosed cases. Early diagnoses, recognition of phenotype, adequate surgery, and appropriate genetic counseling are very much essential as patients often develop medullary thyroid carcinoma (MTC) and pheochromocytoma. This case report would highlight the oral manifestations of MEN 2B in a 22-year-old female patient with multiple mucosal neuromas and a previous history of thyroidectomy due to MTC.

Keywords: *Medullary thyroid carcinoma, mucosal neuromas, multiple endocrine neoplasia 2B*

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Introduction

Multiple endocrine neoplasia (MEN) type 2B is a designation that has been proposed for the combination of medullary thyroid carcinoma (MTC), parathyroid adenoma, pheochromocytoma, mucosal neuromas, and somatic abnormalities.[1-3] The mucosal neural lesions are usually presented as a characteristic diffuse or nodular involvement of the tongue, lips, and buccal mucosa. Due to these multiple neuromas on the mucosal surfaces, this entity also became known as "multiple mucosal neuroma syndromes."[2-4] Early recognition of the oral lesions and peculiar facies present a pathognomonic pattern for this disease. The prognosis of MEN 2 is related to the aggressiveness of the MTC, which can develop early lymph node metastases as early as 3 years.[5,6] The oral manifestations include multiple neuromas on the anterior one-third of the tongue, lips, and the buccal mucosa adjacent to the oral commissures are the patterns that should alert the dental clinician to a potentially lethal set of sequela.

Case Report

A 22-year-old female patient reported to the department with chief complaints of bleeding gums for the past 2 to 3 months and the presence of multiple small enlargements on the tongue. On extraoral examination, coarse-appearing peculiar facies with anteverted eyelids and anteverted nostrils were observed [Figure 1a]. The lips were diffusely enlarged and appeared everted and patulous [Figure 1b]. The palpable masses were present on the upper and lower lips, the most prominent and unsighted mass was on the midline of the upper lip [Figure 1c]. The tongue appeared enlarged with multiple nodules on the tip and anterior one-third of the tongue [Figure 1d]. Nodular masses were also seen on the buccal and labial mucosa, which was asymptomatic, oval to round in shape with sessile base and smooth surface. The gingival tissue was not enlarged in size and shape but tended to bleed easily [Figure 1e]. Maxillary anterior teeth were protruded with spacing and rotated premolars, and high-arched palate [Figure 1f]. The radiograph revealed a full set of permanent teeth with impacted third molars [Figure 2]. On detailed enquiring about medical history, the patient revealed that she had a history of MTC and had undergone total thyroidectomy 2 years back. The patient was suffering from chronic constipation since childhood. The multiple mucosal neuromas on lips, tongue, oral cavity, and perioral areas now causing significant physical and

How to cite this article: Banerjee S, Kar D. Oral manifestations of multiple endocrine neoplasia 2B syndrome: A rare case report. Contemp Clin Dent 2024;15:54-7.

Submitted : 01-May-2023
Revised : 20-Jul-2023
Accepted : 29-Nov-2023
Published : 23-Mar-2024

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Access this article online

Website: https://journals.lww.com/cocd

DOI: 10.4103/ccd.ccd_215_23

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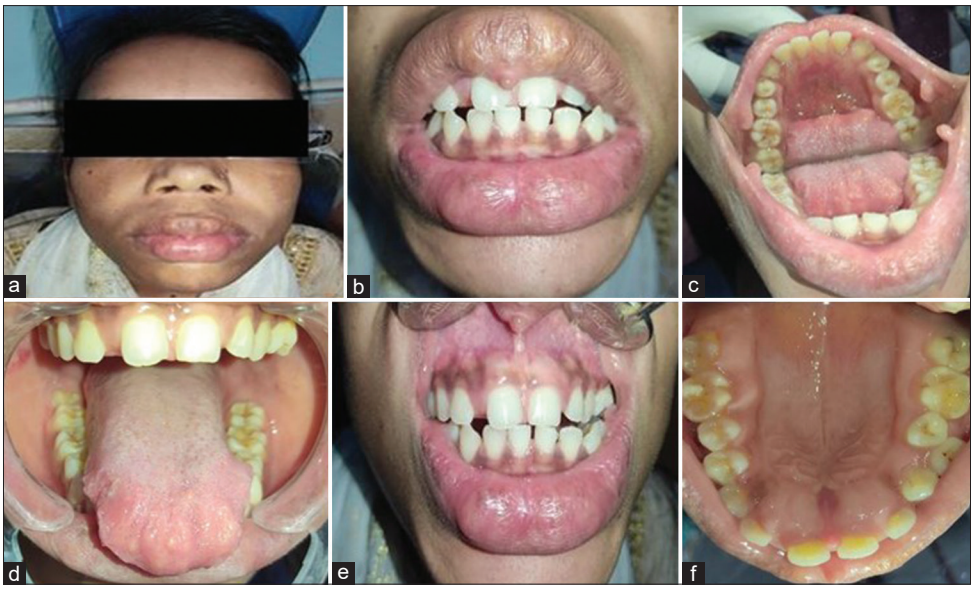

Figure 1: Clinical photographs of the patient. (a) Extraoral appearance of the patient. (b) Enlarged lips. (c) Multiple neuromas near commissural region. (d) Enlarged tongue with multiple nodules near the anterior third of the tongue. (e) Spacing of maxillary anterior teeth. (f) High-arched palate

mental distress to the patient, which basically forced her to visit to the dental hospital. General examination failed to reveal abnormalities such as cervical lymphadenopathy and café-au-lait spots. Biochemical analysis of the patient was within normal limits. A proper medical record of previous investigation and treatment could not be obtained as they were not properly maintained. Based on the clinical features and history of thyroidectomy, a clinical diagnosis of MEN2B was made. There was no history of cancer and thyroid abnormality in her family. This case mainly occurred due to *de novo* mutation since no family members were affected. Incisional biopsy was performed from the nodule of the commissural region under local anesthesia. Histopathological evaluation revealed well-circumscribed solitary mass lined by stratified squamous surface epithelium. The underlying connective tissue revealed nodule of proliferating, spindle-shaped disorganized, and tortuous nerve fibers surrounded by thickened perineurium, which was suggestive of mucosal neuromas [Figure 3]. Numerous bundles of elongated cells with wavy dark nuclei were identified. Some areas were also exhibit mild degree of hemorrhage, fibrosis, and very minute inflammatory changes.

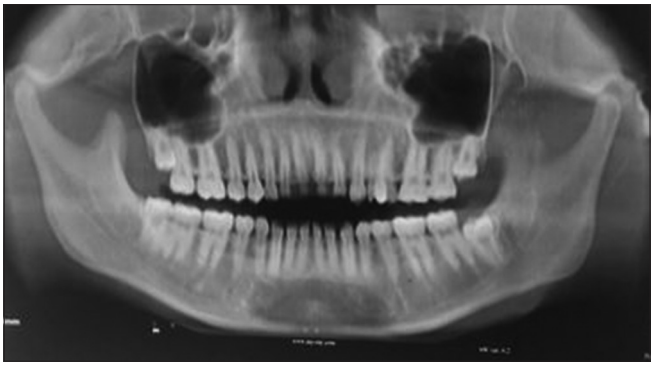

Figure 2: Radiographic examination of the jaws revealed a full set of permanent teeth

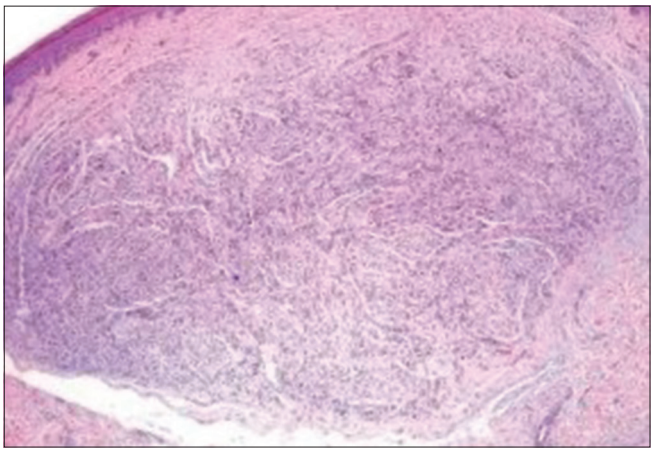

Figure 3: Scanning photomicrograph revealed tortuous and disorganized nerve fibers surrounded by perineurium (H and E, ×20)

Discussion

MEN 2B is relatively uncommon accounting for only 5% of all cases of MEN with prominent extraendocrine features (mucosal neuromas), a more aggressive presentation of MTC, and lack of parathyroid hyperplasia [Table 1].[1-6] It was initially described by Wagenmann in 1922.[1] It is mainly 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 MEN 2B syndrome.[5-7] 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.

Table 1: Multiple endocrine neoplasia 2 syndromes varieties and clinical features

Clinical features	MEN 2 syndromes		
	MEN 2A	MEN 2B	FMTC
Medullary thyroid carcinoma	Present	Present	Present
Pheochromocytoma	Present	Present	Not detected
Parathyroid hyperplasia	Present	Not detected	Not detected
Intestinal ganglioneuromas	Not detected	Present (earliest sign)	Not detected
Mucosal neuromas	Not detected	Present (earliest sign)	Not detected

FMTC: Familial medullary thyroid cancer; MEN: Multiple endocrine neoplasia

Table 2: Clinical characteristics of multiple endocrine neoplasia 2B syndromes

Clinical characteristics
Mucosal neuromas of the lips, eyelids, and buccal mucosa especially near commissural areas, tongue, palate, and intestinal mucous membrane
Intestinal ganglioneuromatosis (chronic constipation since childhood)
Medullary carcinoma of the thyroid (severe aggressiveness leading to life threat; early detection)
Skeletal abnormalities of the spine (kyphosis, scoliosis, lordosis) and pes cavus
Peculiar facies, anteverted, and flared nostrils with enlarged, bumpy lips
Thickened medullated corneal nerves (slit-lamp examination)
Marfanoid habitus
Pheochromocytoma

Table 3: Differential diagnosis of multiple endocrine neoplasia 2B syndromes

Differential diagnosis
Shprintzen–Goldberg syndrome
Ehlers–Danlos syndrome
Homocystinuria
Struge–Weber syndrome
Tuberous sclerosis
Von Hippel–Lindau syndrome
Von Recklinghausen disease
Familial hypocalciuric hypercalcemia

Table 4: Evaluation and management of multiple endocrine neoplasia 2B syndromes

Evaluation and Management of MEN 2B syndrome
Careful screening of oral mucosal neuromas
Careful screening of enlarged lips and other intraoral features and skeletal abnormalities
Consideration of history of gastro-intestinal obstruction, chronic constipation since childhood
Evaluation of any cold, solitary, thyroid nodule, and cervical lymphadenopathy for the possibility of medullary thyroid carcinoma (total thyroidectomy is mainstay of treatment)
Referral to endocrinologist
Biochemical analysis of blood and urine (high-serum calcitonin level)
Genetic screening and genetic counseling

MEN: Multiple endocrine neoplasia

Incidence is said to be 80%, 15%, and 5% for MEN 2A, familial MTC, and MEN 2B, respectively.[1-7] The clinical characteristics of MEN 2B syndromes are summarized in Table 2. The majority of the MEN 2B cases show diffuse ganglioneuromatosis present early in childhood even before the manifestation of medullary thyroid cancer. The patients often presented with chronic constipation and mucosal neuromas on the early stages. The serum calcitonin value, carcinoembryonic antigen, epinephrine, norepinephrine, dopamine and urinary concentrations of epinephrine and norepinephrine are also useful in early detection. Thyroid and adrenal scans are also important for diagnostic workups. Differential diagnosis [Table 3] includes Shprintzen–Goldberg syndrome, Ehlers–Danlos syndrome, and homocystinuria.[4-6]

Histopathological examination of mucosal neuromas usually reveals numerous bundles of disorganized and tortuous nerve fibers. The differential diagnosis for mucosal neuroma includes traumatic neuroma, palisaded encapsulated neuroma, Morton's neuroma, or neurofibroma. Mucosal neuroma has a distinctive clinical history that is not associated with a traumatic neuroma.[7-10]

As the majority of these cases arise due to de novo mutation, it is challenging for the clinicians to diagnose at early stages. Therefore, identification of hallmark diagnostic findings such as mucosal neuromas of the tongue, lips, buccal mucosa and inner eyelids along with musculoskeletal findings and gastrointestinal symptoms are the mainstay in identification and recognition [Table 4]. Early diagnoses, recognition of phenotype, adequate surgery, and appropriate genetic counseling with genetic screening are remains the essential mainstay management of the cases to improve the outcome. Educating health-care professionals about the presentation of this condition is the need of the hour for early diagnosis, thereby preventing lethal complications.

In this case, the diagnosis was made by the presence of multiple submucosal neuromas, a history of MTC, and histopathologic confirmation of mucosal neuromas.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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