

Solitary Oral Mucosal Neuromas: A Rare Case Report

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Abstract: Mucosal neuromas are a form of neurogenic tumour that arises in the oral cavity as a component of multiple endocrine neoplasia type 2b (MEN 2b). The syndrome is characterized with other features like tumors of the endocrine glands and skeletal abnormalities. Mutation at codon 918 of the RET protooncogene is a consistent feature among people affected with MEN 2. There are few reports describing pure mucosal neuromas without characteristics of MEN 2B. Analysis of the RET protooncogene among these cases have demonstrated no point mutation in the MEN 2B region (M918T). Hence, it is a subject of debate whether such anomalies should be considered as a different entity or a milder form of the MEN 2B syndrome. We report a case of 25 year old male patient who presented with multiple neuromas over the labial mucosa, tongue and floor of the mouth with no other features of MEN 2B.

Keywords: Mucosal Neuromas, Neurogenic tumor, Multiple Endocrine Neoplasia type 2B, RET protooncogene, Point mutations

INTRODUCTION

Multiple endocrine neoplasia type 2B (MEN 2B or MEN 3) also known as multiple neuroma syndrome is a rare autosomal dominant disorder characterized by medullary thyroid carcinoma, pheochromocytoma, and mucosal neuromas [1]. A point mutation at codon 918 of the RET protooncogene is considered as the cause of this syndrome in patients and families with MEN 2B [2]. Mucosal neuromas are considered pathognomonic feature of this condition and known to occur in 100% of patients with MEN 2B. Mucosal neuromas are benign tumors of peripheral nerves histologically characterized by irregular tortuous bundles of nerve cells with prominent perineurium that lie scattered throughout the submucosa. Mucosal neuroma of MEN type 3 are most commonly observed on the lips, tongue and eyelids, giving the patients characteristic features. Rarely such neuromas occur as a single entity without the other components of MEN 2b. Reports of solitary mucosal neuromas without other features MEN 2b are uncommon and described to occur in the rectosigmoid colon [3], bronchi [4], conjunctiva [5], larynx [6], tongue [7] and hard palate [8]. We describe a 25-year-old man with mucosal neuromas at multiple sites in oral cavity with no evidence of MEN 2B.

CASE REPORT

A 25 year old male patient reported to the department of Oral Medicine and Radiology, Government Dental College and Research Institute, Bangalore with a chief complaint of multiple growths in the mouth noticed since early childhood. Patient had no significant medical history. Patient's parents and family members presented with no similar complaints. Review of systems revealed no abnormality. Examination of oral cavity revealed multiple, non tender, soft, pebbly surfaced growths over the upper labial mucosa, floor of mouth and tongue (Fig. 1, 2 & 3).



Fig. 1: Multiple mucosal neuromas over upper labial mucosa



Fig. 2: Multiple mucosal neuromas over the tongue.



Fig. 3: Multiple mucosal neuromas in the floor of mouth

Histopathological examination showed irregular tortuous nerve bundles with prominent perineurium dispersed within the submucosa and mucosa with no nuclear palisade or encapsulation. A diagnosis of mucosal neuroma was made. Because of the possibility of MEN 2b, a thorough endocrine examination was carried out. There was no history of hypertension, which is usually present in pheochromocytoma. There were no other mucosal neuromas of the eyelids or lips. The thyroid gland was not palpable and thyroid scan and adrenal scan were normal. Thyroid gland function was also normal. Values for serum calcitonin, serum calcium, and 24-h urinary excretion of vanillyl mandelic acid were all within normal limits. There were no characteristics of MEN 2b and hence a diagnosis of isolated mucosal neuromas of oral cavity was made.

DISCUSSION

The syndrome of multiple mucosal neuromas is a rare but distinct entity; the most outstanding clinical feature of this syndrome is the presence of mucosal neuromas involving on the anterior third of the tongue, commissure of the lips, eyelids, pharynx and digestive system (intestinal ganglioneuromatosis). In addition, patients present with Marfanoid body habitus and a peculiar facies with thick and bumpy lips. Most

important and influential feature of this syndrome is medullary thyroid carcinoma and pheochromocytoma. 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 the diagnostic workup. Other features of the syndrome include skeletal abnormalities of the spine (lordosis, kyphosis, scoliosis), talipes equinovarus, kyphoscoliosis, joint laxity, pes cavus and thickened medullated corneal nerves. The case described here revealed no endocrinal abnormalities or tumors, skeletal deformities or involvement of eyelids, pharynx, and digestive system. The patient presented only with oral mucosal neuromas and hence the case is considered as a case of pure mucosal neuroma syndrome without features of MEN 2B.

The syndrome is hereditary with mode of inheritance being autosomal dominant, but many sporadic cases have been reported. The mucosal neuromas are generally noticed in early childhood. Germline mutations of the *RET* protooncogene causes MEN 2 [2]. This gene encodes a transmembrane glycoprotein receptor tyrosine kinase. The precise role of the RET protein in normal embryogenesis is unknown; it probably plays a role in the development of neural crest, peripheral neurons, and kidneys. The MEN 2B phenotype appears to result from a specific germline missense mutation in the tyrosine kinase domain of the *RET* protooncogene. A point mutation, results in a uniform single base pair transition within exon 16 (ATG to ACG at codon 918 of the *RET* gene) that replaces methionine with threonine, M918T [9]. The great majority (95%) of classic MEN 2B patients carry the codon 918 mutation. However, the etiology of solitary mucosal neuromas as in the case presented here remains unclear. Miura H *et al.* [4] believed that these neuromas originate from abnormal growth from the end portion of the vagus nerve. Pujol MR *et al.* [10] debated these neuromas to be a milder form of MEN 2B or a new entity. In the case described by them, Analysis of the *RET* protooncogene exons 10, 11, and 16 did not demonstrate point mutation in the MEN 2B region (M918T) [10]. A study by Gordon CM *et al.* [11] on four subjects of pure Mucosal Neuroma Syndrome revealed that all four subjects did not have the germline *RET* codon 918 mutation that is associated in patients with MEN 2B. It was hypothesized that the phenotype in these patients was a consequence of either a somatic *RET* M918T mutation restricted to mucosal nerves or germline mosaicism. Continued research and documentation of such pure forms of mucosal neuromas will further enhance our knowledge with regard to characteristics and etiology of these disorders.

REFERENCES

1. Khairi MRA, Dexter RN, Burzynsky NJ, Johnston CC; Mucosal neuroma pheochromocytoma and medullary thyroid carcinoma: multiple endocrine neoplasia type 3. *Medicine*, 1975; 54(2): 89-112.
2. Eng C; The RET proto-oncogene in multiple endocrine neoplasia type 2 and Hirschsprung disease. *N Engl J Med.*, 1996; 335: 943-951.
3. Attar B, Khurana D, Hlaing-Ray V, Levendoglu H; Mucosal neuroma of the rectosigmoid colon. *Gastrointest Endosc.*, 1986; 32(3): 219-220.
4. Miura H, Kato H, Hayata Y, Ebihara Y, Conullu U; Solitary bronchial mucosal neuroma. *Chest*, 1989; 95(1): 245-247.
5. Higashide Y, Nemoto Y, Imamura T; A case of conjunctival mucosal neuroma without multiple endocrine neoplasia [article in Japanese]. *J Jpn Ophthalmol Soc.*, 1997;101(7): 621-25.
6. Gomez JM, Biarnes J, Volpini V, Marti T; Neuromas and prominent corneal nerves without MEN 2B. *Ann Endocrinol.*, 1998; 59(6): 492-494.
7. Shimazaki T, Yoshida, Izumaru S, Nakashima T; Laryngeal solitary multiple mucosal neuromas without multiple endocrine neoplasia (MEN) type 2B. *Auris Nasus Larynx*, 2003; 30(2): 191-195.
8. Nishihara K, Yoshida, Onizawa K, Yusa H, Fujiwara M; Solitary mucosal neuroma of the hard palate: a case report. *Brit J Oral and Maxillofac Surg.*, 2004; 42(5): 457-459.
9. Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF *et al.*; The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2: International RET Mutation Consortium Analysis. *JAMA*, 1996; 276(19): 1575-1579.
10. Pujol RM, Matias-Guiu X, Miralles J, Colomer A, de Moragas JM; Multiple idiopathic mucosal neuromas: A minor form of multiple endocrine neoplasia type 2B or a new entity? *J Am Acad Dermatol.*, 1997; 37(2): 349-352.
11. Gordon CM, Majzoub JA, Marsh DJ, Mulliken JB, Ponder BA, Robinson BG *et al.*; Four Cases of Mucosal Neuroma Syndrome: Multiple Endocrine Neoplasia 2B or Not 2B? *J Clin Endocrinol Metab.*, 1998; 83(1): 17-20.