Neural hyperplasia in maxillary bone of multiple endocrine neoplasia type 2B patient

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Multiple endocrine neoplasia (MEN) type 2B is the rarest and most aggressive form of MEN syndrome. MEN 2B patients manifest characteristic oral and facial features besides the neural crest cell–derived tumors, including medullary carcinoma, pheochromocytoma, mucosal neuroma, and ganglioneuromatosis of the gut. We report a case of MEN 2B diagnosed on the basis of the warning signs of mucosal neuroma and multiple neural hyperplasias in the maxillary bone resected during orthognathic surgery. A subsequent systemic examination under the pathologic diagnosis of neural lesions revealed medullary thyroid carcinoma, megacolon, thickened corneal nerves, and *RET* gene mutation, thus verifying the diagnosis of MEN 2B. An immunohistochemical study revealed an increased number of unmyelinated Schwann cells in the hyperplastic nerves. We suggest that intraosseous neural hyperplasia is a specific finding of the MEN 2B syndrome in addition to the known oral and facial manifestations. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:783-790)**

Multiple endocrine neoplasia (MEN) syndromes are inherited tumor syndromes characterized by the coexistence of various tumors affecting certain endocrine organs that originate from the neural crest cells.[1-3]

MEN syndromes are classified as types 1, 2A, and 2B and familial medullary thyroid carcinoma. In patients with MEN 2B, also known as mucosal neuroma syndrome, pheochromocytoma of the adrenal gland and medullary carcinoma of the thyroid gland are observed as seen in MEN 2A patients, but the primary hyperthyroidism present in MEN 2A is absent. The other characteristic features of MEN 2B include a long narrow face, prominent lips, and multiple mucosal neuromas involving the oral mucosa (the oral and facial manifestations are listed in Table I). MEN type 2 is an autosomal dominant inherited tumor syndrome caused by the germ line–activating mutations of the *RET* proto-oncogene on chromosome 10 (10q11.2), which encodes a receptor tyrosine kinase that appears to transduce the growth and the differentiation signals in several developing tissues, including those derived from the neural crest cells. Although the genetic abnormalities of *RET* have been observed in nearly 100% of the family members of MEN 2A patients, patients with MEN 2B often do not have a family history of the disease; >50% of the cases are due to de novo germ line mutations.[1-3]

Although MEN 2B is less common than MEN 2A, the mean survival time of patients with MEN 2B is considered to be less than that of MEN 2A, because of the early progression of medullary thyroid cancer in the context of C-cell hyperplasia.[3-5] This fact emphasizes the importance of early diagnosis, early detection of *RET* gene mutation, and subsequent prophylactic thyroidectomy, which could improve the quality of life and prolong the life expectancy.[5] However, because of its rareness and de novo occurrence, early diagnosis of MEN 2B is still difficult.

We report a unique case wherein the pathologic examination of a jaw bone resected by orthodontic surgery enabled an early detection of MEN 2B. To the best of our knowledge, we are the first to report the presence of intraosseous neural hyperplasia in a case of MEN 2B.

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Table I. Oral and facial manifestations of multiple endocrine neoplasia type 2B

Characteristic	*Notes*	*References*
Facies		
Elongated thin face	The lower face appears long	6, 8, 12, our case
Wide-eye expression		6, 8, 12, our case
Broad-based nose		6, 13, our case
Facial asymmetry		12
Marfanoid habitus		6, 8, 11, 13
Oral manifestations		
Prominent lips	Diffusely enlarged lips due to increased number and size of labial nerves	6-8, 10, 11, 13, our case
Multiple mucosal nodules	Multiple neuroma involving lips, tongue, buccal mucosa, gingiva, and palatal mucosa	6-13, our case
High palatal vault		6, 12, 13, our case
Malocclusion	Anterior open bite, diastema, posterior crossbite, prognathic and retrognathic mandible, edge-to-edge occlusion	6, 8, 10-13, our case
Spacing of teeth	Anterior teeth	11, 13
Early eruption	Primary teeth, starting at age 3 mo	12
Radiographic findings		
Shortened mandibular incisor roots		11-13, our case
Progressive shortening of molar roots		12
Widened mandibular canal		11-13

CASE REPORT

An 18-year-old Japanese man presented to the Oral and Maxillofacial Surgery Department at the Kobe City General Hospital with the chief concern of skeletal open bite, which was scheduled for orthodontic surgery. Since malocclusion had been observed during the dental examination at the age of 14 years, the patient had received presurgical orthodontic treatment by his private-practice orthodontist. He was otherwise healthy with no significant medical history. He did not have a family history of any syndrome or malignancies.

Oral examination showed thick prominent lips and multiple submucosal tumors affecting the tongue, bilateral buccal mucosa, and the lips (Fig. 1, *A-D*). Although the presurgical orthodontic therapy had been administered for 4 years, marked open bite and high-arched palate were still visible, which necessitated surgical intervention (Fig. 1, *E* and *F*). The orthopantomogram before surgery showed marked open bite and shortened roots of the mandibular incisors. The cephalometric radiograph confirmed massive skeletal open bite with steep mandibular plane and large gonial angle. Facial asymmetry, widened mandibular canal, and other osseous lesions were not visible (Fig. 2). Results of routine preoperative blood examinations were unremarkable. Under general anesthesia, Le Fort I–type osteotomy, vertical ramus osteotomy, and excisional biopsy of the buccal submucosal tumor were performed. Besides the excised submucosal tumor, the resected bilateral maxillary bones were pathologically examined, because the surgeon noted that the bone was soft and fibrous compared with normal maxillary bone.

Excised tissues were fixed in 10% neutral-buffered formalin and embedded in paraffin wax. Before embedding, bone tissues were decalcified in Plank-Rychlo solution overnight at room temperature. The 4-μm-thick hematoxylin-eosin (HE)–stained sections were studied. Histologic examination of the buccal lesions showed irregular tortuous nerve bundles in the submucosa. Each nerve bundle was large and hyperplastic, and a thickened perineurium was prominent. The lesion was not encapsulated; nuclear palisading and atypia were absent (Fig. 3, *A* and *B*). Therefore, the buccal lesion was diagnosed as mucosal neuroma. Histologic examination of both maxillary bones showed many aggregated tortuous nerve bundles in the cortical bone, bone marrow space, and submucosal tissue of the floor of the maxillary sinus (Fig. 3, *C* and *D*). As observed in the mucosal neuroma, a thickened perineurium was not prominent in these hyperplastic nerves (Fig. 3, *D inset*). Because we could not find any suitable diagnosis for the bony lesions, we diagnosed this condition as "intraosseous multiple neural hyperplastic lesions" (Fig. 4).

Because the presence of buccal neuroma and intraosseous neural hyperplasia indicated a potential MEN syndrome, the patient was referred to the departments of endocrinology, otolaryngology, internal medicine, and ophthalmology. The serum levels of thyrocalcitonin and carcinoembryonic antigen (CEA) were markedly increased (3,580 pg/mL [normal ≤100 pg/mL] and 94.8 ng/mL [normal ≤2.5 ng/mL], respectively). A subsequent systemic examination revealed that the patient had bilateral thyroid tumor, megacolon, and thickened corneal nerves. Pheochromocytoma and marfanoid habitus (characteristics of MEN 2B syndrome) were clinically undetectable. Molecular genetic studies confirmed the presence of the mutation of codon 918 (exon 16) in the *RET* proto-oncogene, which resulted in an ATG (methionine) to ACG (threonine) substitution (M918T), thereby confirming the diagnosis of MEN 2B. The patient underwent total thyroidectomy and bilateral neck dissection. Histopathologic examination revealed bilateral multinodal medullary thyroid carcinoma with lymph node metastasis (1/54). The postoperative serum thyrocalcitonin and CEA levels were within the normal limits (27 pg/mL and 2.1 ng/mL, respectively, 3 months after thy-