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 \textit{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.\textsuperscript{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 1). MEN type 2 is an autosomal dominant inherited tumor syndrome caused by the germ line–activating mutations of the \textit{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 \textit{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.\textsuperscript{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.\textsuperscript{3,5} This fact emphasizes the importance of early diagnosis, early detection of \textit{RET} gene mutation, and subsequent prophylactic thyroidectomy, which could improve the quality of life and prolong the life expectancy.\textsuperscript{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.
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-
roidectomy), and the patient did not show any obvious signs of the disease 1.5 years after the surgery.

To confirm the abnormality in the nerve bundles of the maxillary bone in this case, the maxillary bone was investigated in detail (Fig. 4) with informed consent according to the guidelines of the Ethical Committee of Kobe City Medical Center General Hospital. Control samples were collected from similar-aged patients who underwent Le Fort type–I osteotomy (Fig. 4, B and D). S-100 (Dako, Glostrup, Denmark; polyclonal, diluted) and glial fibrillary acidic protein (GFAP; Dako; polyclonal, diluted) were immunostained for detecting the total number of Schwann cells and unmyelinated Schwann cells, respectively. Immunohistochemistry (IHC) using anti-epithelial membrane antigen (EMA) antibody (Dako; clone E29, diluted) was performed for the identification of the perineurium. IHC were conducted ac-

Fig. 1. Oral and facial findings. A, Lateral view. B, Anterior view. Patient aged 18 years showing diffusely enlarged lips and a long narrow face. C, Submucosal nodule is visible on the lower left portion of the lip (arrows). D, Multiple hemispherical nodules on the surface of the tongue (arrow). E, Preoperative examination shows marked open bite. Submucosal nodule is visible in left buccal mucosa (yellow arrowhead). F, High-arched palate.
 According to the manufacturer’s instructions. Histologic analysis revealed that the control bone showed some nerve bundles in the same portion as the bones with the MEN 2B tissue. Despite the similar-sized arteries (in Fig. 4, C and D, arrows) and veins located along the peripheral nerves, each peripheral nerve bundle in the bone of the MEN 2B patient showed a conspicuous thickening (Fig. 4, C, asterisks) unlike the nerve bundle in the control nerves (Fig. 4, D, asterisks). Under high magnifications of HE-stained sections, the single nerve fascicle (cut in transverse section) of the normal peripheral nerve was not significantly different from that of the MEN 2B peripheral nerve (Fig. 4, E and F, left). Although the total number of Schwann cells (S-100–positive cells) of the normal and MEN 2B nerves did not show a significant difference, IHC using GFAP revealed an increased number of Schwann cells of unmyelinated nerve fibers in the peripheral nerve of the MEN 2B. IHC with anti-EMA antibody revealed a slightly thickened perineurium (Fig. 4, E and F).

**DISCUSSION**

Multiple endocrine neoplasia type 2B, the most rare and aggressive form of MEN type 2, represents an inherited autosomal dominant syndrome characterized by medullary carcinoma, pheochromocytoma, mucosal neuromas, and ganglioneuromatosis of the gut. Because the high morbidity and mortality of patients with MEN 2B syndrome is related to the early onset of medullary thyroid cancer and a more advanced tumor stage at presentation (size of tumor and lymph node involvement), early thyroidectomy based on diagnosis and identification of the RET gene mutation is necessary. In the present case, mucosal neuromas and multiple hyperplastic neural lesions found in the maxillary bone, which was excised in the time of orthognathic surgery, enabled us to diagnose MEN 2B in its
early stages. We suggest intraosseous neural hyperplasia as one of the specific findings of MEN 2B. Although reports of the manifestations of MEN 2B occasionally appear in the medical and dental literature, early diagnosis of MEN 2B is still difficult and challenging.7,17 The key reason for the late diagnosis of MEN 2B may be attributed to its rarity and variable clinical characteristics. Although nearly 100% of the MEN 2A patients have familial genetic abnormalities, patients with MEN 2B often do not have a family history of the disease.1-3 In newborns, the characteristic MEN 2B phenotype is often absent and only constipation is observed because of intestinal ganglioneuromatosis.6 Another reason for overlooking its manifestations is that the physical characteristics associated with MEN 2B are apparently unrelated to the endocrine features.6,7

The facial and oral characteristics of MEN 2B are one of the first features of the syndrome that are observed.6 Such features have been described in the literature as multiple mucosal neuromas, elongation of the skull with a long narrow face, mandibular prognathism, prominent lips, wide-eyed expression, broad-based nose, and a thickened tarsal plate.6 Orthodontic studies on MEN 2B have shown malocclusion, including diastemata between the maxillary incisors, anterior open bite, high-arched palate, and facial asymmetry (Table I).6-13 Of these facial and oral characteristics, multiple mucosal neuromas are the most distinct and the easiest detectable lesions, affecting nearly 100% of the MEN 2B patients.18 Vasen et al. analyzed the natural course of MEN 2B; the first presenting sign was a thyroid nodule, but their retrospective analysis revealed that oral mucosal neuromas were found to have been the first sign before detection of a thyroid nodule.19

Another important finding of the present report is the neural hyperplasia found in the maxillary bone. MEN 2B is a hereditary cancer syndrome caused by missense gain-of-function mutations, especially in codons 918 and 883 encoding the tyrosine kinase domain of the RET protein, which transduces the growth, differentiation, and survival of neurons. The RET protein is highly expressed in the facial, glossopharyngeal, trigeminal, and vagus cranial ganglia as well as in the central motor, dopamine, and noradrenaline neurons.20-26 A phenotypic study using transgenic mice led us to speculate that the neural hyperplasia in the present bone tissue may have arisen from the RET-expressing trigeminal nerves, resulting from the constitutive acti-
Fig. 4. Peripheral nerves of multiple endocrine neoplasia type 2B (MEN 2B) patient (A, C, and E) and histologically normal patient (22-year-old woman; B, D, and F). A, B, Peripheral nerves located in submucosal tissue of the base of maxillary sinus. Thickened and hyperplastic nerve bundles are prominent in MEN 2B patient (A) (arrowheads; hematoxylin-eosin [HE] stain). C, D, Peripheral nerves found in medullary cavity. Each nerve bundle in MEN 2B shows conspicuous thickening (C) compared with control nerves (D) (asterisks). Similar-sized arteries are indicated with arrows. E, F, Histopathologic and immunohistologic examination of single nerve fascicle of MEN 2B (E) and normal patient (F). No significant difference was observed with HE stain. Increased GFAP-expressing Schwann cells and slightly thickened EMA-positive perineurium was revealed (arrow). Original magnification: A and B, ×40 (bar = 100 μm); C and D, ×100 (bar = 100 μm); E and F, ×400 (bar = 10 μm).
viation of the signaling pathway due to the mutation, considering that the transgenic mice developed benign neuroglial tumors that were histologically identical to human ganglioneuromatosis.25,26

Although intraosseous neural hyperplasia in a case of MEN 2B has been reported here for the first time, thickened peripheral nerves of normal-appearing skin, cornea, and thickened tympanic membrane in MEN 2B patients have been reported earlier.27-30 Our immunohistochemical analysis revealed the presence of an increasing number of GFAP-expressing unmyelinated Schwann cells in this syndrome. Moreover, earlier histologic and electron microscopic studies have shown that the number of unmyelinated nerve fiber–associated Schwann cells was increased in the corneal nerves.29,30 These findings suggest that unmyelinated nerve fibers may contribute to the enlargement of the nerve bundles in cases of MEN 2B.

In the present report, we emphasize the importance of recognizing the oral and facial manifestations of MEN 2B for the early diagnosis of this condition. In addition, we have documented intraosseous neural hyperplasia as a new finding in MEN 2B patients. However, the contribution of the hyperplastic lesion to the clinical manifestations remains unknown.

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REFERENCES


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