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# Multiple endocrine neoplasia, Type 2B, with medullary thyroid carcinoma: a diagnostic potential for dentistry*

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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] The neural lesions produced a characteristic diffuse or nodular involvement of the tongue, lips, and buccal mucosa. Because of these multiple neuromas on the mucosal surfaces, this entity also became known as "multiple mucosal neuroma syndrome."[2] Early recognition of the oral lesions and peculiar facies present a pathognomonic pattern for this disease. It is a pattern which should alert the dental clinician to a potentially lethal set of sequelae.

Three forms of MEN have been defined. They are Type 1, Type 2A, and Type 2B which is also called Type 3 by some authorities.[3] Type 1 involves the pituitary and adrenal glands.[3] Type 2A includes MTC, pheochromocytoma, and parathyroid adenoma.[5] In addition to the same involvement as Type 2A, Type 2B (or Type 3) also includes the entities of mucosal-neuromas, peculiar facies, and other somatic abnormalities.[6]

The mucosal neuromas, which are microscopically composed of enlarged tortuous nerves, constitute a valuable clinical marker of the syndrome since they are present in childhood and generally antedate clinical presentation of the thyroid and adrenal neoplasms. They produce characteristic enlargement of the lips and nodularity of the tongue, and, although they are asymptomatic and benign, they cause psychologic upset because of unsightliness and may require surgical correction of the deformity.[1] Other areas of mucous membrane which lend themselves to clinical examination by the dentist would include the conjunctiva. Such mucosal neuromas are likewise found in this area.[7] (Fig. 1).

Clinical characteristics include marfanoid habitus with long limbs, scoliosis, chest deformities, pes cavus, and hyperextensible joints. These patients present also with thickened, anteverted eyelids; nasal mucosal neuromas; and a peculiar facies, which has been described as "coarse-appearing" (Fig. 2).

The manifestations in the oral cavity include multiple neuromas on the anterior one-third of the tongue, upper and lower lips, the buccal mucosa adjacent to the oral commissures, and occasionally the palate and mandible. A complete review of 51 cases with characteristic oral findings has been reported in literature.[1]

The absence of a palpable thyroid mass in persons with the other clinical signs and symptoms is not reason enough to discount the almost certain presence of a MTC. Thus, in an effort to aid in early detection and minimal metastases, these patients should be evaluated immediately.

## Report of a Case

D.H., a 15-year-old male, was referred to the Department of Pediatrics and Adolscent Medicine at the University of South Dakota in late 1976 by this pediatric dentist who recognized peculiar facies and oral lesions (Figs. 2 and 3).

Constipation, the first manifestation of chronic disease, had begun at age four months. The patient was hospitalized on five separate occasions between 1963 and 1969 for chronic constipation. A barium enema in 1965 was interpreted as normal; however, in 1969 a barium enema revealed dilatation of the colon. At the laparotomy in 1969, the colon was found to be diffusely thickened with nodular growths. A total colectomy and ileoprocto-anastomosis was performed.

The Armed Forces Institute of Pathology diagnosed ganglioneuromatosis from histologic section.

Following the colectomy, the patient experienced episodes of abdominal distention and discomfort

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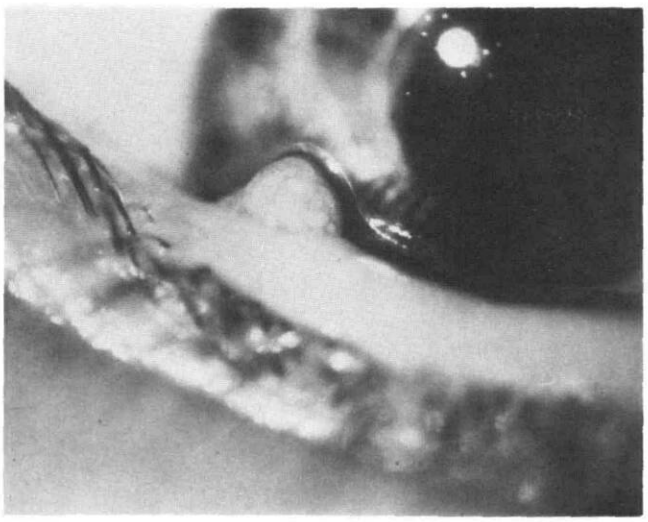

Fig. 1.

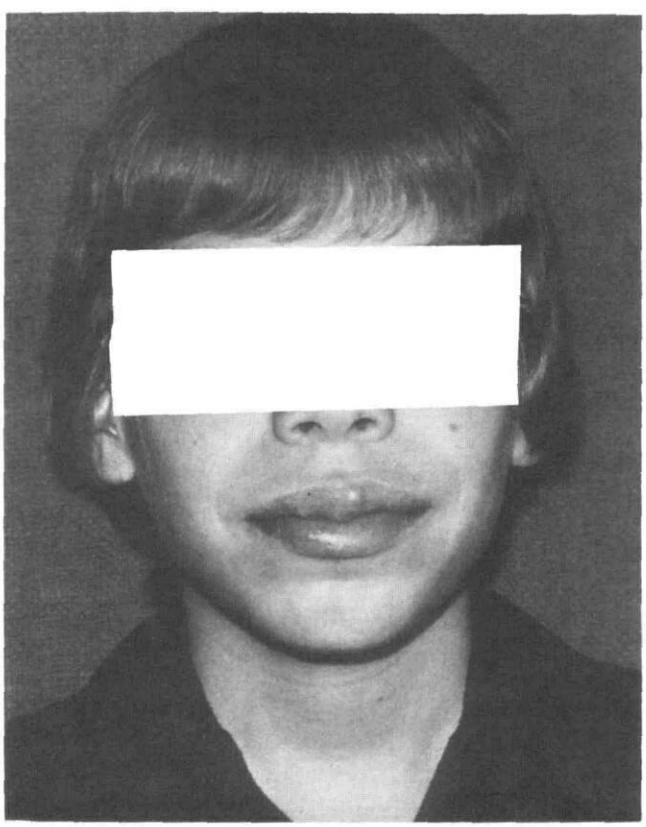

Fig. 2.

which simulated small bowel obstruction. He was hospitalized five times from 1969 to 1971 for this problem, twice undergoing laparotomy for lysis of adhesions. The patient gave no history of flushing, excessive sweating, or "spells." He had experienced nocturnal enuresis since the time of the colectomy.

His weight and height were above the fiftieth percentile in 1969. Both parameters were at the third percentile in 1977. The conjunctival surfaces of the upper and lower eyelids exhibited neuromas (Fig. 1). Corneal nerves were thickened on slit lamp examination.

Family history was negative for coarse-appearing facies, thyroid cancer, or sudden deaths.

## Oral findings

The lips were diffusely enlarged and appeared everted and patulous (Fig. 2). There were palpable masses in both the upper and lower lips. The most prominent and unsightly mass was in the midline of the upper lip. There were flattened, plate-like projections just adjacent to the labial commissure, bilaterally. The anterior one-third of the tongue presented with regularly shaped, round, raised lesions which resembled the size of typical circumvallate papillae, *i.e.*, 0.3 × 0.5 mm in diameter with sessile base attached. The tongue appeared to be long and narrow, having normal functional movements. On the other hand, the lips were flaccid and exhibited little muscular tonus. Multiple diastemata between the permanent teeth and anterior protrusion of maxillary and mandibular dental arches were present (Fig. 4).

This middle and lower face protrusion is reflected in the cephalometric tracing of a lateral radiograph of the head. The sella-nasion-A point of the maxilla (SNA) is 86 degrees, with 81 degrees being the normal range. The sella-nasion-B point of the mandible (SNB) is 80 degrees, with 78 degrees being normal. The incisal labial inclination of the anterior teeth is reflected in the inter-incisive angle. This measures 107 degrees compared to a more obtuse angle of 128 degrees being normal. Cephalometric measurements have not been documented in previous cases.

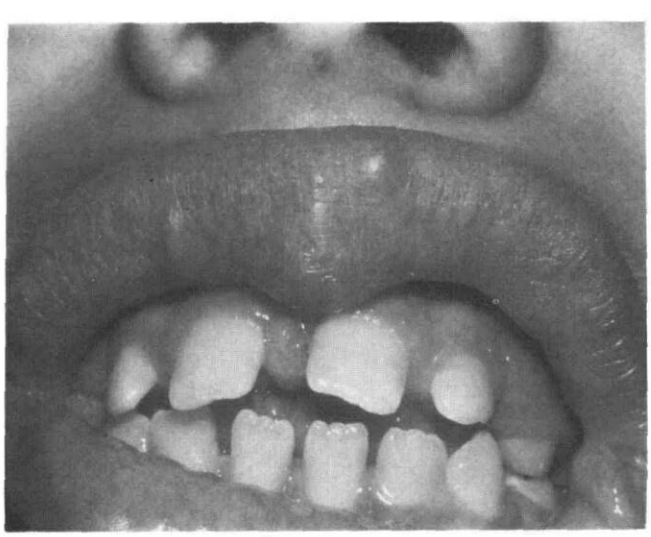

Fig. 3.

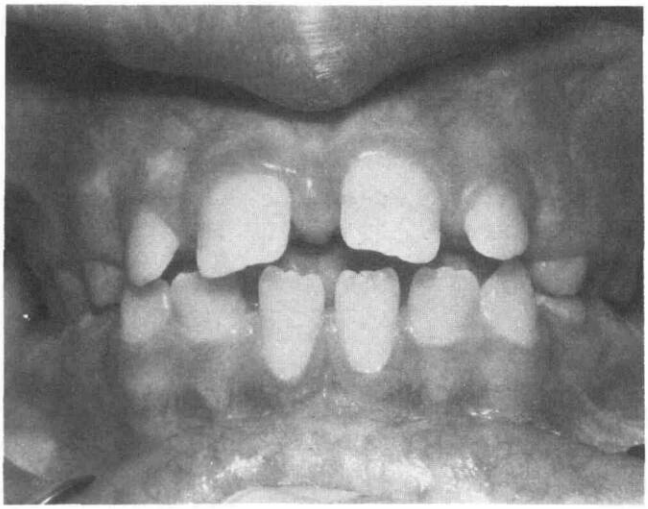

**Fig. 4.**

Permanent teeth exhibited a marked delay in the exfoliation schedule. At age 15, only 12 permanent teeth were erupted, and 12 primary teeth remained to exfoliate.

The gingival tissue was not hypertrophied; however, it was inflamed and tended to bleed easily. Oral hygiene was excellent. The patient complained of discomfort throughout the course of physiologic tooth exfoliation.

No thyroid nodules or cervical adenopathy were noted. No cafe-au-lait spots, diffuse pigmentation, or neurofibromas were found on the trunk or extremities.

Thyrocalcitonin levels were markedly elevated. This hormone is made by the c-cells of the thyroid medulla. An increase in thyrocalcitonin levels is seen in c-cell hyperplasia and MTC.

With the data obtained, the patient was referred to the Mayo Clinic in August, 1977, for confirmation of diagnosis. There the patient underwent total thyroidectomy with a modified radical neck dissection. A 12-g gland with multiple, palpable nodules was removed. Medullary carcinoma with amyloid stroma was seen on microscopic sections. Metastatic involvement was present in multiple jugular and tracheoesophageal nodes and in one mediastinal node. A parathyroid adenoma was identified and removed.

## Discussion

The characteristics of patients with MEN, Type 2B, can be easily overlooked in the routine clinical examination. Patulous, nodular lips, nodular lesions on the tongue, anteverted eyelids, and peculiar facies led the clinician to the possibility of MEN Type 2B. Early recognition of this syndrome will contribute to early diagnosis of MTC and pheochromocytoma. Many institutions are stressing the need for a prophylactic thyroidectomy.

In the study of Carney *et al.*,[8] 15 of 17 patients with gastrointestinal problems of MEN syndrome, such as constipation, diarrhea, and cramping, had obvious oral lesions at birth or in early childhood. In two of these patients, the oral lesions were present for 26 years or more before other symptoms of the disease appeared. It is important to reemphasize that GI problems such as constipation, cramping, diarrhea, etc., combined with distinctive oral lesions are signs of the MEN syndrome.

Little has been written about the cephalometric assessment of these patients. An anterior position of both mandibular and maxillary segments relative to the cranial base was noted here. The anterior mandibular and maxillary permanent teeth were flared and exhibited multiple diastemata. This could be attributed to a muscular imbalance between the muscular tongue and flaccid lips.

This syndrome follows a strong autosomal dominant inheritance pattern. With this in mind, the clinician should thoroughly examine siblings and other immediate family members for potential occult involvement.

The patient discussed experienced slowing of growth and short stature rather than the usually tall, marfanoid appearance. Many factors may have influenced his growth failure; among them are intestinal malabsorption and excess thyrocalcitonin.

The preoperative clinical evaluation of this patient demonstrated no objective anatomic evidence for MTC or metastases. The decision to remove this patient's thyroid was made because of the very high incidence of MTC in patients with distinctive phenotypic features of the syndrome of MEN Type 2B due to the increased thyrocalcitonin levels. MTC is the single most important cause of mortality in the MEN Type 2B syndrome.

No chemotherapy or suppressive protocols have been used on this individual since the cells involved in this type of carcinoma do not respond well to chemotherapy.

## Summary

(1) Because of the craniofacial anomalies in this syndrome, the dentist should be able to diagnose MEN Type 2B. It is important that the dentist be aware of this syndrome, since these patients have potentially lethal endocrine neoplasia.

(2) Oral lesions of ganglioneuromatosis or unexplained GI problems such as constipation, diarrhea, etc., should prompt consideration of MEN Type 2B in the diagnosis.

(3) Total thyroidectomy should be considered for all

patients with the syndrome since MTC is potentially preventable if removed in the early stage of c-cell disease.

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