Case Report

Multiple Endocrine Neoplasia-2B Presenting with Orthodontic Relapse

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ABSTRACT

The multiple endocrine neoplasia (MEN) syndromes are a relatively uncommon group of genetic disorders characterized by the development of tumors in various endocrine organs. MEN type 2B is of particular interest to the dental profession because of its oral manifestations, which are often some of the earliest clinically detectable signs of the disorder. Early identification of this syndrome is critical because affected patients often develop a characteristic malignancy, medullary carcinoma of the thyroid, at a very early age. We describe a 17-year-old male whose initial diagnosis of MEN-2B was triggered by his orthodontist's request for an oral and maxillofacial pathology consultation to evaluate the patient's oral abnormalities. (*Angle Orthod.* 2010;80:585–590.)

KEY WORDS: Multiple endocrine neoplasia; Orthodontic; Diastema; Oral plexiform neuroma; Medullary thyroid carcinoma

INTRODUCTION

The multiple endocrine neoplasia (MEN) syndromes are a group of genetic conditions that are characterized by the development of tumors affecting certain endocrine glands. While these syndromes are usually inherited in an autosomal dominant pattern, a significant percentage represent new mutations. These syndromes are classified as MEN-1, MEN-2A (also designated as MEN-2), and MEN-2B (or MEN-3). MEN-1, known eponymously as Wermer syndrome, is caused by a mutation in the tumor suppressor gene menin, which is located on chromosome 11.[1,2] MEN-1 is distinguished by tumors of the pancreatic islets, pituitary gland, and parathyroid glands.[1,2] Patients with MEN-1 are affected by hyperparathyroidism and pancreatic islet tumors leading to peptic ulcers, with pancreatic malignancies being the most worrisome aspect of this syndrome.[1,3,4] MEN-2A, also known as Sipple syndrome, is characterized by the development of pheochromocytoma of the adrenal medulla, parathyroid hyperplasia, and C-cell hyperplasia, with medullary carcinoma of the thyroid occurring in over 90% of affected individuals.[1,3,4] Familial medullary thyroid cancer (FMTC) is a variant of MEN-2A in which the only manifestation of the syndrome is medullary thyroid carcinoma.[2] The mutations responsible for FMTC or MEN-2A are frequently identical, and they are located in the extracellular domain of the RET proto-oncogene; it is unknown, however, why the expression of these syndromes is different.[5,6] MEN-2B shares the thyroid and adrenal manifestations with MEN-2A, but lacks the primary hyperparathyroidism of MEN-2A.[1,3,4] Of particular interest to dental professionals are the characteristic orofacial manifestations in patients with MEN-2B syndrome. The most commonly noted manifestations of the syndrome are listed in Table 1.[1–4,7,8]

MEN-2B is far less common than MEN-2A (1:9) but the medullary thyroid carcinoma that develops in this variant is far more aggressive, it tends to occur in younger patients, and it has a worse prognosis.[7] This syndrome is known to be caused by an autosomal dominant mutation with a high penetrance and variable expressivity.[7,8] Approximately 50% of the mutations occur de novo.[6–8] The mutation responsible for this disorder occurs in the RET protooncogene, and in 95% of affected patients, there is substitution of methionine for threonine at codon 918 (M918T).[6–8] This proto-oncogene is composed of 21 exons, located on chromosome 10 (10q11.2), and it encodes a tyrosine kinase receptor.[4,6,7] Within the intracelluar domain of the protein are two tyrosine kinase domains, TK1 and TK2; the M918T mutation found in 95% of MEN-2B

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Table 1. Common Manifestations of MEN-2B

Manifestation of MEN-2B	Notes
Medullary thyroid carcinoma	Average age at death: 21 years
Pheochromocytoma	Found in ~50% of affected individuals
Marfanoid habitus	Tall with elongated limbs
Mucosal neuromas	Lips, tongue, buccal mucosa, inner eyelid
Ophthalmologic	Thickened corneal nerves, decreased tear production
Diffuse intestinal ganglioneuromatosis	Present in 40% of individuals, frequently have gastrointestinal problems in childhood
Elongated facies	Thick, prominent lips and thickened, sometimes everted eyelids
High-arched palate, mandibular retrognathism or prognathism	Can be variable in presentation

cases affects the second kinase domain.[4,6,7] This mutation changes the recognition pocket in the tyrosine kinase catalytic core, thereby promoting cell growth and differentiation of tissues of neural crest origin (eg, C cells of the thyroid and adrenal medulla).[6,7] In MEN-2A and FMTC, several different mutations (codons 609, 611, 618, 620, 634) have been identified in the cysteine-rich extracellular domain of RET.[4,6,7]

Historically, diagnosis of the MEN-2 syndromes was done via measurements of plasma calcitonin levels, though this has now been replaced with direct genetic testing.[1,7] Patients with MEN-2B are at very high risk of eventually developing MTC (nearly 100%, according to some investigators) and the disease has been detected in patients less than 1 year of age.[7] Once the diagnosis has been confirmed, it is generally recommended that affected individuals have prophylactic thyroidectomy and neck dissection between ages 4 and 6, or before age 1 if they have the most common and high-risk M918T mutation.[5,7,9] MTC is not sensitive to currently available radiation or chemotherapy regimens; therefore, surgical resection is the only option for cure.[7,9,10]

Pheochromocytoma occurs in approximately 50% of patients with MEN-2B, and greater than half of these affected patients have bilateral tumors, compared with 10% in sporadic pheochromocytoma.[5] These patients frequently have signs and symptoms of pheochromocytoma, such as hypertension, headaches, and palpitations due to catecholamine release. If a pheochromocytoma is identified, then surgical management is appropriate[5,9]; however, the anesthesiologist must exercise extreme caution because the tumor may release endogenous catecholamines, leading to a fatal hypertensive crisis during surgery.[5,7] Patients and their families should undergo medical evaluation to detect other affected individuals, and those who are affected

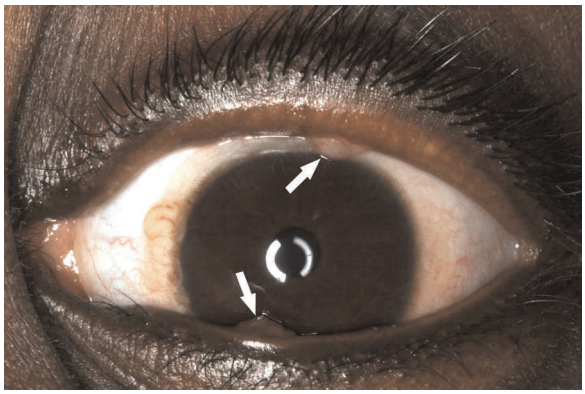

Figure 1. Mucosal neuromas are seen on the margins of the eyelids.

should be offered genetic counseling.[5] Long-term care includes thyroid hormone replacement therapy to achieve euthryroidism; regular serologic studies to monitor calcitonin, carcinoembryonic antigen (CEA), and catecholamine levels; and ultrasound imaging of the neck to monitor development of medullary thyroid carcinoma.[5,7,9]

Case Report

A 17-year-old African American boy presented with his mother to the Orthodontic Screening Clinic at The Ohio State University College of Dentistry with the chief complaint of spacing between his maxillary incisors. He had previously completed orthodontic treatment with a private orthodontist approximately 3–4 years prior, and he and his mother stated that his maxillary anterior teeth were not spaced on completion of his orthodontic therapy. His medical history was significant for asthma and allergies to fish and iodine. At age 8 he was hospitalized for evaluation of gastrointestinal problems (“large bowel movements,” constipation) and a possible intestinal mass. He was discharged on a high fiber diet that apparently had controlled his gastrointestinal distress. His family history was negative for any syndromes or cancer.

Examination showed a tall, thin male with a height of 6′ 2″ and weight of approximately 130 lb. This was consistent with a marfanoid habitus. His eyelids had small (1–2 mm) sessile papules associated with the margins of the lids bilaterally (Figure 1). Oral examination showed thick, prominent lips (Figure 2), papules affecting the lateral and dorsal tongue and anterior buccal mucosa bilaterally (Figures 3 and 4), and diastemata of the maxillary anterior dentition (Figure 5). Upon further questioning, the patient and his mother related that he did not produce tears. An ophthalmologic examination 10 months earlier was found to be within normal limits, with the physician apparently attributing his lack of tears to a blocked duct. Additionally, his mother noted that he was

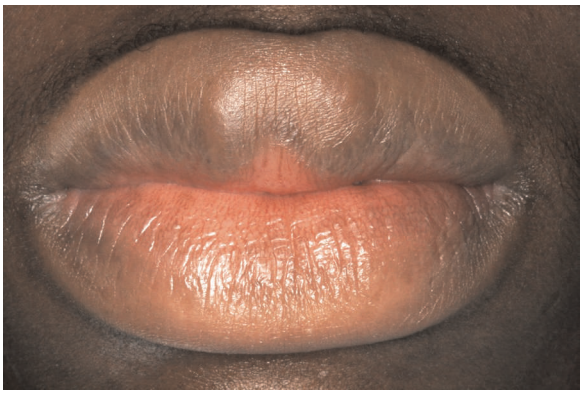

Figure 2. Prominent thickening and fullness of the patient's lips are evident.

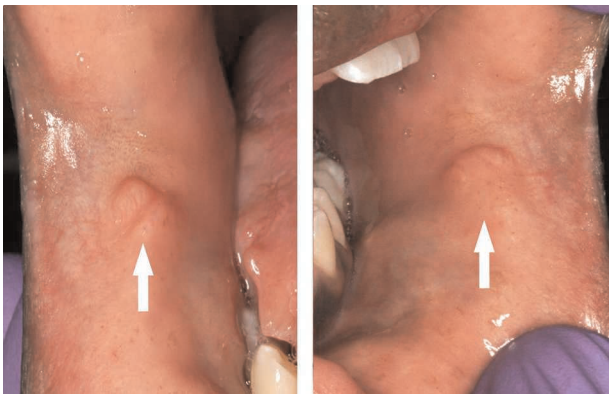

Figure 4. Sessile mucosal papules, representing plexiform neuromas, are also noted on the anterior buccal mucosa bilaterally.

approximately a foot taller than his older brother and that he did not resemble his full siblings.

Based on the clinical findings, a presumptive diagnosis of MEN-2B was made, and he was referred to the Oral and Maxillofacial Surgery Clinic for biopsies of the tongue and buccal commissure papules. Histopathologic examination of both samples showed proliferation of large, hyperplastic nerve bundles set in an otherwise normal connective tissue background (Figure 6). These features were consistent with a diagnosis of plexiform neuroma.

Since the patient's clinical and histopathologic findings were strongly suggestive of MEN-2B syndrome, he was referred to the Division of Human Genetics at The Ohio State University for additional clinical evaluation and genetic testing. Molecular genetic studies confirmed the presence of the M918T mutation of the RET proto-oncogene, thereby verifying the diagnosis of MEN-2B. An eye examination found thickened corneal nerves, another finding consistent with the syndrome. They decided that since his RET mutation was most likely a new mutation, no testing of his siblings was necessary.

The patient was subsequently referred to the Division of Endocrinology for management. Their examination showed a thyroid gland that was approximately three times normal size, with no palpable lymphadenopathy. A thyroid ultrasound showed large bilateral nodules measuring 1.5 × 1.2 × 1.9 cm on the left side of the gland, and two nodules on the right measuring 1.3 × 1.3 × 1.6 cm and 0.4 × 0.9 × 0.7 cm. Also detected on ultrasound were a 1.1 × 0.8 × 1.0 cm nodule in the middle of the neck, and some lymphadenopathy on the left side of the neck. A CT

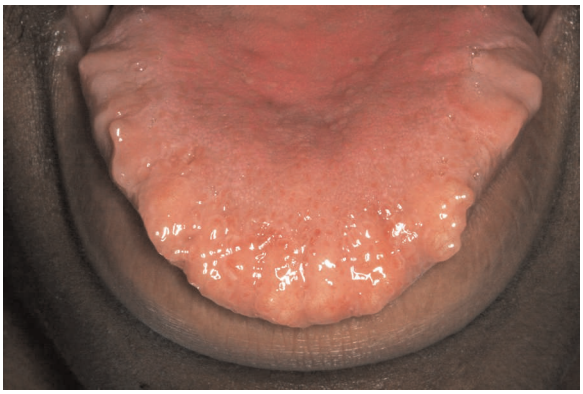

Figure 3. Multiple sessile papules that histopathologically proved to be plexiform neuromas are seen on the lateral borders of the tongue.

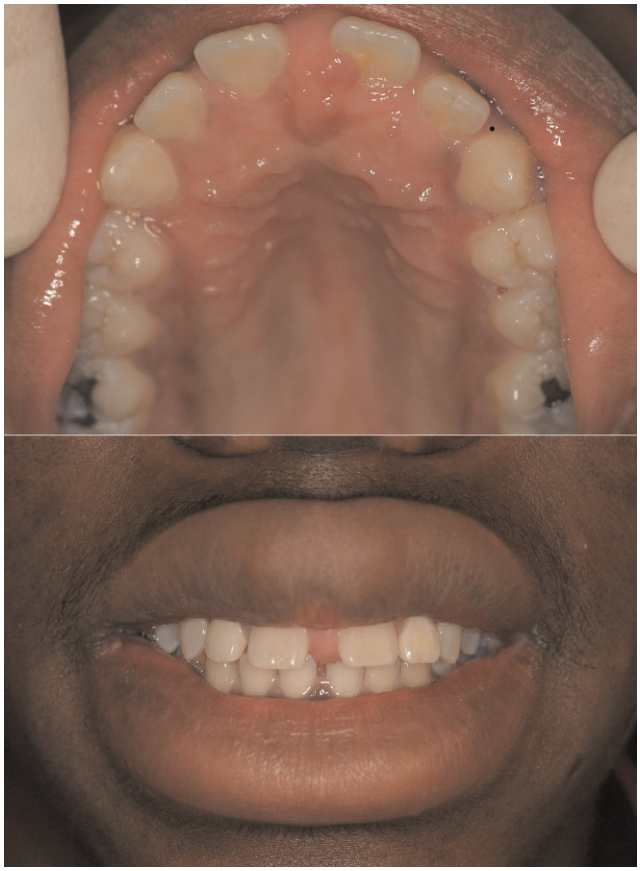

Figure 5. Occlusal view (top) and front view (bottom) demonstrating diastemata in maxillary anterior dentition.

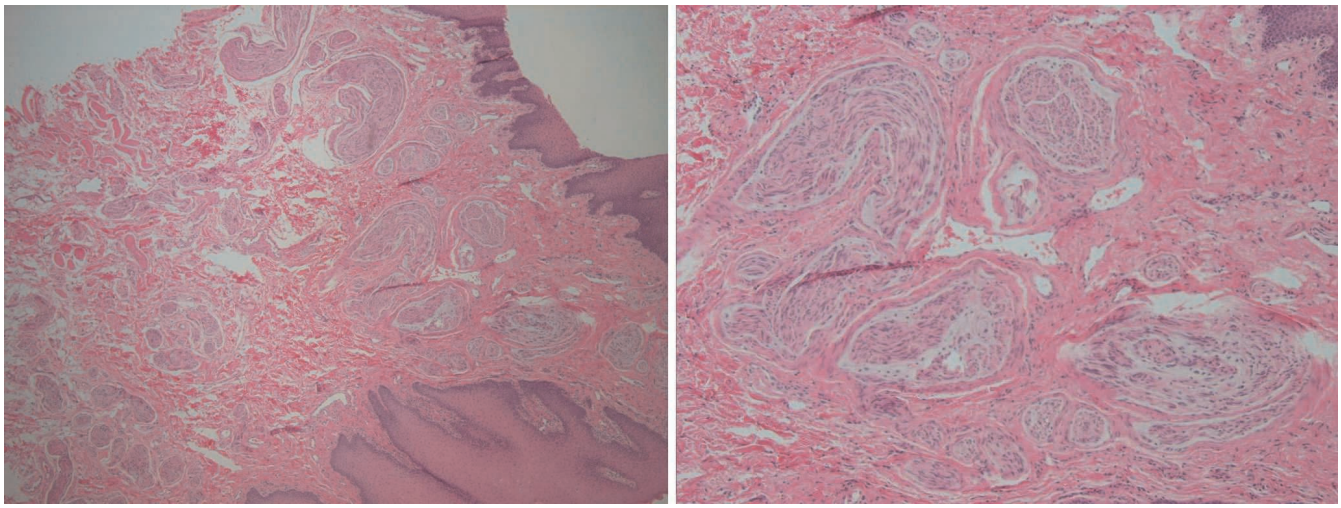

Figure 6. Low (left) and high (right) power photomicrograph of plexiform neuroma from the patient's labial commissure.

scan of the chest and abdomen was negative for any abnormal findings and, most notably, there were no masses noted in or around the adrenal glands. Serologic studies showed markedly elevated calcitonin and carcinoembryonic antigen (CEA), with all other values being within normal limits. Of particular note, biochemical tests for pheochromocytoma were negative. These results were consistent with a diagnosis of medullary thyroid carcinoma with metastases to regional lymph nodes.

The patient was then appointed with the Division of Surgical Oncology, and he was treated surgically with total thyroidectomy, left modified radical neck dissection, and bilateral central neck dissection. The final pathologic report confirmed bilateral medullary thyroid carcinoma with 16 of 45 lymph nodes positive for metastatic tumor. He is currently taking only levothyroxine (Synthroid, Abbott Laboratories, N. Chicago, IL), though he initially required calcium supplementation for hypocalcemia, which resolved 5 months postresection. An ultrasound 6 months postresection showed no residual thyroid tissue or metastatic disease in the neck. He appears to be free of obvious disease 9 months postsurgery, and his only notable side effects have been occasional constipation and orthostatic hypotension. Annual serologic studies will be conducted to evaluate thyroid hormone production and CEA levels, and to screen for pheochromocytoma. Ultrasound examinations of the neck will also be routinely done to detect recurrent medullary thyroid carcinoma. Finally, he will receive full genetic counseling in the near future, which was deferred until after his treatment was completed.

DISCUSSION

While reports of the oral mucosal manifestations of MEN-2B occasionally appear in the medical and dental literature, relatively few have mentioned dentoalveolar changes such as spacing of the dentition.[11–13] Older reports mention neuromas of the gingiva, but this was before the MEN syndromes were adequately described.[14,15] These cases were often poorly documented and the neuromas were sometimes misdiagnosed as neurofibromas.[15] More recent reports also mention mucosal neuromas on the gingivae,[11,12] but accurate, well-documented reports with corresponding histopathology verifying mucosal neuromas on the gingivae are scarce.[14,16]

This particular case was notable because the patient presented with a relapse of diastemata between his maxillary incisors after having successfully completed orthodontic treatment a few years earlier. Unfortunately, his records were not available from the previous orthodontic treatment for comparison, but both the patient and his mother insisted that the development of the diastemata were recent. These could have resulted from a number of causes, including fibro-osseous bone lesions, periodontal disease, tongue thrust, or other parafunctional habits. However, we found no evidence of these possible causes in our examination. A more common reason for relapse is inadequate retention of orthodontic space closure of previous diastemata, but since his previous records were not available we cannot comment further. While it is theoretically possible that growth of the gingival neuromas led to the diastemata in this particular case, we did not obtain a biopsy of the incisive papilla area to confirm this. Additionally, a diagnosis of plexiform neuroma in the area of the incisive papilla could be challenging, given the normal presence of numerous nerve bundles of varying sizes in this anatomic site.

In this particular case of MEN-2B, the following stigmata of the syndrome were present: medullary thyroid carcinoma; marfanoid habitus; plexiform neu-

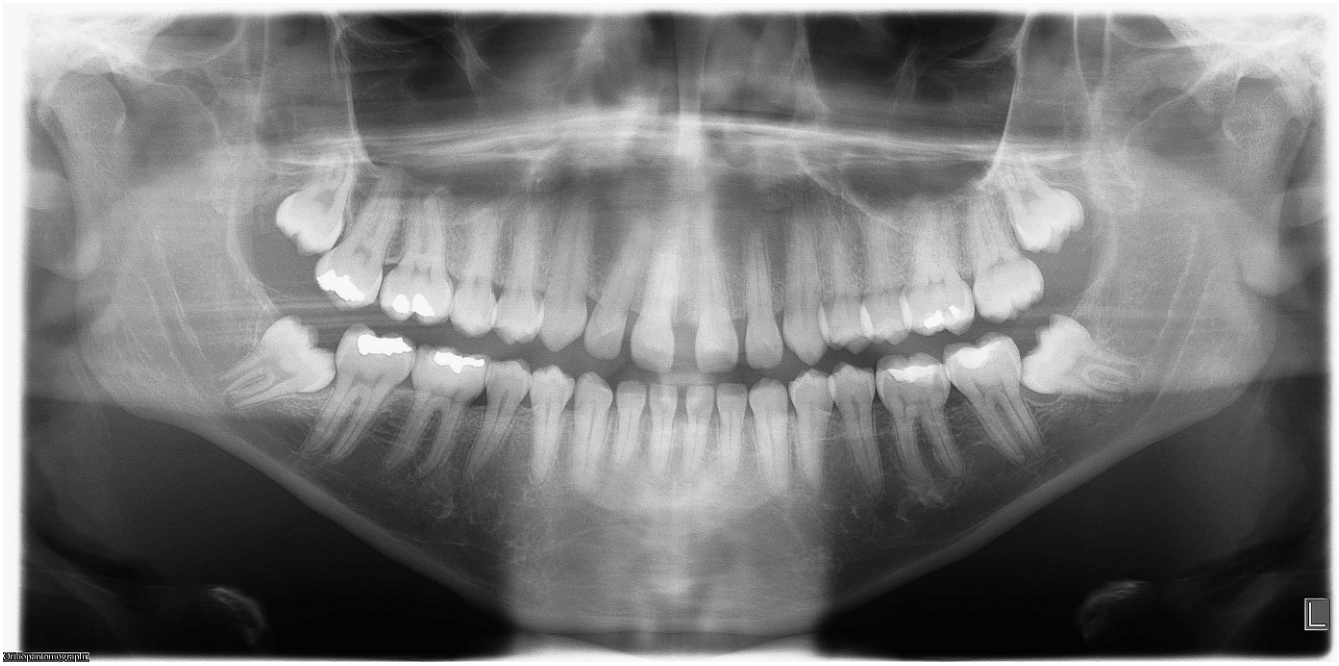

Figure 7. Patient's panoramic radiograph.

romas of the tongue and labial commissures; thick, prominent lips; thickened corneal nerves; spacing of the anterior dentition; neuromas of the palpebral conjunctiva; and insufficient tear production. Other manifestations associated with MEN-2B such as high-arched palate, steep mandibular plane, mandibular retrognathism or prognathism, shortened mandibular incisor roots, enlarged mandibular canal (Figure 7), pheochromocytomas, and definitive gastrointestinal problems were equivocal.

It is our desire with this case report to raise awareness in the orthodontic community regarding this family of syndromes. Dentists in particular are ideally positioned to initially identify patients with MEN-2B because of the oral manifestations of this syndrome. The relapse of diastemata is not uncommon and is a frequent complaint when presenting to an orthodontist. Attention however, must be paid during a thorough head and neck exam to other unusual orofacial features (such as the lips, tongue, and eyes in this case), and appropriate referral made when atypical findings are present. Early identification provides a great service to the patient and family so that they can undergo curative surgery for the medullary thyroid cancer, identify and treat other affected relatives, and pursue genetic counseling.

In this individual's case, his initial presentation was likely at age 8 with gastrointestinal symptoms, though this has not been proven. Furthermore, his insufficient tear production and thickened corneal nerves are likely other manifestations that were overlooked during an ophthalmologic examination. A recent review[17] found that the time between initial presentation with an obvious MEN-2B–related complaint and recognition of the syndrome was conservatively estimated to be 2 years. The study found the most common presenting symptom to be mucosal neuromas ("tongue bumps"), but only 27% were identified as neuromas and none were appreciated as being pathognomonic of MEN-2B. Additionally, it was found that 73% of affected individuals had had gastrointestinal symptoms in infancy or childhood. Another recent study[18] surveyed the parents of 25 patients diagnosed with the M918T mutation in MEN-2B regarding the initial appearance of symptoms of the syndrome. Investigators found that in the first year of life, dry eyes with an inability to cry tears (86% vs 0% of controls) and frequent constipation (61% vs 0% of controls) were the most common early symptoms. These findings are most interesting because the symptoms could conceivably be used to detect MEN-2B patients at a very early age so they could receive potentially curative thyroid surgery. The authors caution that these are limited results subject to recall bias, and they require verification in an independent series. An additional troublesome aspect of the mismanagement of these patients is that they often receive inadequate initial surgical therapy, thereby requiring reoperation with associated risks and morbidity such as recurrent laryngeal nerve injury and permanent hypoparathyroidism.[17] The authors conclude by emphasizing that long-term cure of medullary thyroid cancer is dependent on prompt diagnosis early in life and a

thorough initial surgery by an experienced surgeon, as patients delaying thyroidectomy until the teenage years or adulthood have a remote potential for cure.[17]

Given that this patient had a large number of lymph nodes positive for metastatic medullary carcinoma, it is unlikely that he will ever be completely cured of his disease. In all likelihood, this will be a slowly developing, long-term process requiring regular monitoring and treatment as needed.

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