

Failure to Recognize Multiple Endocrine Neoplasia 2B: More Common Than We Think?

Curtis J. Wray,¹ Thereasa A. Rich,¹ Steven G. Waguespack,² Jeffrey E. Lee,¹
Nancy D. Perrier,¹ and Douglas B. Evans¹

¹Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

²Endocrine Neoplasia and Hormonal Disorders, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

Background: Multiple endocrine neoplasia 2B (MEN2B) has a classic childhood phenotypic presentation characterized by mucosal neuromas and marfanoid habitus. However, the diagnosis of MEN2B is often delayed beyond childhood, at which time medullary thyroid carcinoma (MTC) may be regionally advanced or metastatic. We examined the extent of this delay and its impact on the treatment of MTC.

Methods: Patients in the MEN database were retrospectively analyzed to determine the age at first presentation for a MEN2B-related complaint and the subsequent time to correct diagnosis. Operative and pathology reports were reviewed to determine the extent of thyroidectomy and cervical lymphadenectomy during the initial and subsequent neck operations.

Results: We identified 22 patients with MEN2B, 20 were de novo cases and a M918T *RET* gene mutation was confirmed in 18 of the 22 patients. Median age at diagnosis of MTC was 13 years (range 6–25 years). The median delay in diagnosis was 26 months (range 0–18 years). Persistent local-regional MTC was present following the initial cervical operation in 12 of 22 patients (55%); including 4 of 13 with MEN2B diagnosed prior to initial surgery and 8 of 9 with MEN2B diagnosed after initial surgery.

Conclusions: Most patients displayed phenotypic characteristics of MEN2B long before the correct diagnosis was made. Half of the patients failed to undergo complete resection of MTC at their initial thyroid surgery. Early recognition of the MEN2B phenotype with a thoughtful approach to preoperative staging and surgery will maximize control of MTC and minimize the need for reoperation.

Key Words: Multiple Endocrine Neoplasia—RET—Medullary thyroid cancer—MEN 2B.

CASE REPORT

A 21 year-old college student noticed swelling in her neck and was evaluated by her primary care physician. She was found to have a thyroid mass and underwent a fine-needle aspiration (FNA) biopsy that

suggested medullary thyroid cancer (MTC). She underwent thyroidectomy that revealed bilateral, multifocal MTC. She was then referred to a radiation oncologist for adjuvant external-beam radiation therapy who recognized mucosal neuromas on her tongue and suspected the diagnosis of multiple endocrine neoplasia (MEN) 2B (Fig. 1). Genetic testing of the *RET* proto-oncogene revealed the classic M918T mutation, and she was referred to The University of Texas MD Anderson Cancer Center (MDACC) for further evaluation and treatment. She had a normal heart rate and blood pressure, palpable cervical lymphadenopathy, a serum calcitonin of 937 pg/mL, and elevated plasma metanephrines and nor-

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Address correspondence and reprint requests to: Douglas B. Evans; E-mail: devans@mdanderson.org

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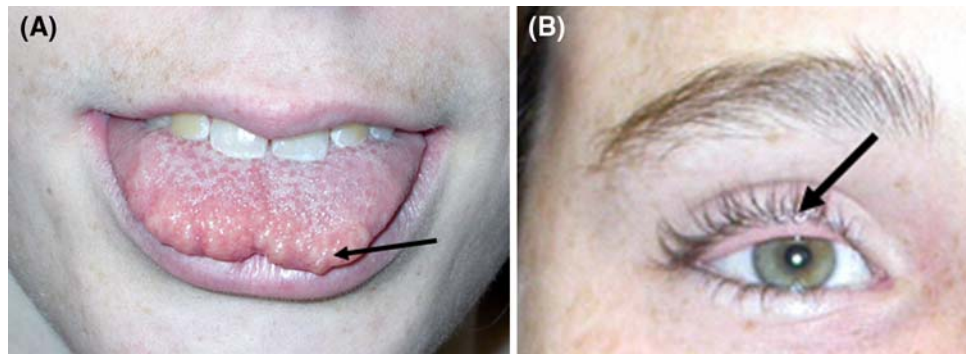


FIG. 1. Patient photographs displaying the common facial features of the MEN 2B phenotype, including mucosal neuromas of the tongue (A) and everted upper eyelids (B).

metanephrines. Abdominal imaging revealed a right adrenal mass consistent with pheochromocytoma. She subsequently underwent minimally invasive right adrenalectomy revealing a 2-cm pheochromocytoma followed by reoperative bilateral neck dissection.

INTRODUCTION

MEN 2B is associated with the early onset of medullary thyroid cancer (MTC), the development of pheochromocytoma in approximately 50% of patients, and a distinct physical appearance.¹ Mucosal neuromas of the tongue, lips, inner cheek, and inner eyelids are a hallmark feature of MEN 2B. These neuromas contribute to the characteristic facial features, which include thickened lips and eyelids. Also, individuals with MEN 2B often have a characteristic slender build, long limbs, and high arched palate (often referred to as a “Marfanoid” body habitus). This body shape may be associated with increased joint mobility, scoliosis, or other bony abnormalities.² Diffuse intestinal ganglioneuromatosis is present in approximately 40% of individuals with MEN 2B and can occur anywhere along the gastrointestinal tract and lead to loss of normal bowel tone, distention, segmental dilatation, and megacolon. Intestinal involvement usually presents early in childhood before other extrathyroidal manifestations are appreciated. Many patients describe a long history of constipation since early infancy. Histology of the colon demonstrates hypertrophy and disorganization of the myenteric plexus and proliferation of ganglions, which may cause defective peristalsis and poor contractility.^{3,4}

MEN 2B is caused by germline mutations of the *RET* (rearranged during transfection) proto-onco-

gene.⁵ A single amino acid substitution of a threonine for the normal methionine (M918T) is present in 98% of MEN 2B patients, although an alanine to phenylalanine mutation at codon 883 (A883F) is also associated with MEN 2B.⁶ The *RET* proto-oncogene encodes a receptor tyrosine kinase that is activated by the glial-derived neurotrophic factor (GDNF) family of ligands and is involved in signal transduction and activation of the mitogen-activated protein (MAP) kinase and other signaling pathways that promote cell growth and survival. *RET* mutations associated with MEN 2B lie within the substrate-binding pocket of the intracellular tyrosine kinase domain.⁷ The M918T mutation is thought to alter substrate specificity by inducing a conformational change in the kinase catalytic core, leading to ligand-independent activation of *RET* and constitutive activation of downstream target genes that cause MTC and may account for the MEN 2B phenotype.^{8,9} Recent studies have shown that aberrant expression of the gene Chondromodulin-1, a known mediator of cartilage and bone growth, is upregulated in MEN 2B patients and may lead to the observed skeletal abnormalities in MEN 2B patients.¹⁰

MTC is an uncommon form of thyroid cancer that arises from the parafollicular (C-cells) of the thyroid and accounts for approximately 2–3% of thyroid cancer in the United States. MTC is associated with germline *RET* mutations in approximately 25% of cases. In addition to MEN 2B, *RET* mutations more commonly cause MEN 2A, which is associated with the risk for MTC and pheochromocytoma as well as parathyroid hyperplasia/adenoma. Certain *RET* mutations are also associated with a familial non-syndromic form of MTC (familial MTC; FMTC).¹¹ MEN 2B represents only 5% of the patients with MEN 2.

For MEN 2–related MTC, the age of MTC development and its biologic aggressiveness is mutation dependent, allowing for the stratification of *RET* mutations into three risk levels: level 1: high risk, level 2: higher risk, and level 3: highest risk.¹² The risk levels are used to define the age at which prophylactic thyroidectomy is recommended for mutation-positive individuals. Patients with MEN 2B have the highest risk for the early development and aggressive growth of MTC, and recent treatment recommendations suggest that prophylactic thyroidectomy should be performed before 6 months of age.¹³ If thyroidectomy is not performed until the teenage years or in adulthood, the potential for cure is remote due to regional lymph node and distant metastases that may prove fatal even at a young age.

The majority of cases of MEN 2B are actually the result of de novo *RET* mutations, which are not inherited from either parent. Therefore, most patients with MEN 2B lack a family history of the disease that would otherwise alert physicians and other health-care providers to the need for early genetic testing and prophylactic thyroidectomy. Furthermore, MEN 2B is rare and is unfamiliar to most primary care physicians who often fail to recognize the neuromas on the lips and tongue as a characteristic of this disease.¹⁴ As such, MEN 2B patients often experience a delay in diagnosis until signs of palpable thyroid tumors are appreciated, at which time MTC has usually spread outside the thyroid gland. Importantly, unless the phenotypic presentation of MEN 2B is appreciated, an invasive MTC can develop and metastasize to regional lymph nodes and distant sites even before a thyroid mass is apparent.

For those patients who are diagnosed with MEN 2B-associated MTC later in childhood or during the teenage years, lymph node metastases are present in almost all patients. An appreciation of this rapid spread to regional lymph nodes has resulted in the surgical recommendation for central (level VI) and often lateral (levels IIA, III, IV, V) neck dissection.¹² However, few surgeons are experienced in the operative management of regionally advanced thyroid cancer in children, which may result in the operation being less extensive than would otherwise be performed in an adult with a similar extent of disease. If an adequate cervical lymphadenectomy is not performed, serum calcitonin and carcinoembryonic antigen (CEA) levels remain elevated, which usually prompts further radiographic imaging and consultation at a referral center such as ours. In this manuscript, we investigate the relationship between age of diagnosis, extent of cervical lymphadenectomy,

recurrence, and survival in our patients with MEN 2B, with particular focus on the presenting features of patients for whom the diagnosis was delayed beyond childhood.

METHODS

Patients with MEN 2B were identified from the MEN database in the department of surgical oncology at MDACC. This work was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board. Operative records were retrospectively reviewed to determine the extent of lymph node dissection performed at initial and subsequent cervical operations. Cervical lymphadenectomy was anatomically defined as: central neck (level VI) and lateral neck (levels IIA, III, IV, and V) based on review of operative dictations. Complete resection of neck disease was defined as resection of all palpable or radiographically imaged (ultrasound or computed tomography) disease. Persistent disease was defined as the presence of palpable or radiographically imaged residual lymph node metastases or incomplete thyroid resection following the first neck operation. Recurrent cervical disease was defined as the development of palpable or radiographically imaged neck recurrence following a previously negative postoperative examination (performed after initial operation or reoperation for persistent disease). Serum calcitonin and/or CEA levels were not used to define persistent or recurrent disease in this study. For those patients whose initial operation was performed prior to referral, prereferral medical records were obtained to determine the extent of cervical lymphadenectomy. After primary surgery, follow-up management was determined by the individual treating physicians and often included ultrasound of the neck and computed tomography imaging of the chest and abdomen. Clinical and pathologic factors and the *RET* codon mutation status were obtained from the MEN database and when necessary the medical record. Initial pathologic tumor and node staging were determined from pathology reports corresponding to all operations performed within 6 months of the patient's first operation.

For purposes of generating the scatter plots, patients' cumulative disease status at last follow-up was categorized as N0, N1a, N1b, or metastatic. Patients were classified as having N0 disease if their MTC did not involve regional lymph nodes, N1a if disease was restricted to the thyroid and central

TABLE 1. Frequency of extrathyroidal manifestations

Feature	Mucosal neuromas	Musculoskeletal abnormality	GI dysmotility	Enlarged corneal nerves	Pheochromocytoma
Present, <i>n</i> (%)	22 (100%)	10 (45%)	16 (73%)	9 (41%)	10 (45%)
Absent, <i>n</i> (%)	0 (0%)	5 (23%)	3 (14%)	4 (18%)	11 (50%)
Not reported or assessed, <i>n</i> (%)	0 (0%)	7 (32%)	3 (14%)	9 (41%)	1 (5%)

compartment (level VI) lymph nodes, N1b if metastatic disease was present in the lateral neck (levels IIA, III, IV, V) lymph nodes, and metastatic if MTC had spread beyond the neck. Delay in diagnosis of MEN 2B was defined as the time from presentation to a physician or other health-care provider for a documented MEN 2B-related complaint (e.g., mucosal neuromas, intestinal ganglioneuromatosis, Marfanoid habitus, enlarged corneal nerves) to the date of correct MEN 2B diagnosis. Patients' vital status at last follow-up was categorized as no evidence of disease (NED), alive with disease (AWD), and dead of disease (DOD). Patients considered AWD had clinical or radiographic evidence of recurrent MTC. Patients with detectable basal calcitonin levels but without clinical or radiographic evidence of recurrent MTC were considered NED for purposes of this report.

RESULTS

Patients

The endocrine surgery database contained information on 312 patients with MEN (MEN1, 126; MEN 2A/FMTC, 164; MEN 2B, 22) seen at our institution from 1973 to 2006. Of the 22 patients with MEN 2B, there were 13 females and 9 males. The classic methionine to threonine substitution at codon 918 of the *RET* proto-oncogene was confirmed in 18 of the 22 patients (82%). The remaining four patients did not undergo *RET* testing, but had the phenotypic appearance of MEN 2B and histologically proven MTC. De novo MEN 2B was observed in 20 of the 22 patients; 2 patients inherited MEN 2B from a parent.

The median age at diagnosis of MTC was 13 years (range 6–25 years). In all patients, the classic phenotypic features of the disease were present prior to MTC diagnosis, but in eight cases the phenotype was not recognized as MEN 2B by family members and/or prereferral physicians or health-care providers before the time of thyroidectomy. The median delay

in diagnosis from onset of a MEN 2B complaint to the correct diagnosis of MEN 2B was 26 months (range 0–18 years). The most common presenting feature specific to MEN 2B and present in all patients was neuromas, most often of the tongue, followed by the lips, eyelids, and other oral mucosa. In six (27%) of the 22 patients, the “tongue bumps” were recognized as neuromas by the patients' physician or even confirmed pathologically, but the neuromas were not appreciated as being pathognomonic of MEN 2B. Gastrointestinal symptoms were also a common finding, being reported in 16 of 22 patients (73%) and often started in infancy or early childhood. Such symptoms frequently included failure to thrive, poor feeding, constipation, and diarrhea; one patient was hospitalized and three required partial colectomy at ages 7, 18, and 23. Most patients had documented colonic distention, dilation, or megacolon. Skeletal abnormalities were also common, some being present at birth, and included congenital foot deformities in two patients, genu varus in two patients, and eight patients (36%) also had one or more other “Marfanoid” features that included a thin body habitus (but not necessarily being tall), long thin fingers, hyperextensible joints, scoliosis, high arched palate, and/or pes cavus. Corneal nerve enlargement was not consistently assessed in all patients, but was a presenting feature leading to a diagnosis of MEN 2B in two patients. In addition to foot deformities and gastrointestinal symptoms, other major birth histories included one patient who had bilateral inguinal hernias, one patient with pyloric stenosis, and several patients with failure to thrive and/or jaundice requiring extended hospitalization. Table 1 provides a summary of the frequency of extrathyroidal manifestations in our MEN 2B population.

Adrenalectomy was performed in 11 patients, 10 for pheochromocytoma and one patient had adrenal medullary hyperplasia. The average age of diagnosis of pheochromocytoma was 25 years (range 19–33 years), and only one patient was diagnosed with pheochromocytoma prior to the diagnosis of MTC. Two patients had synchronous diagnoses of pheochromocytoma and MTC.

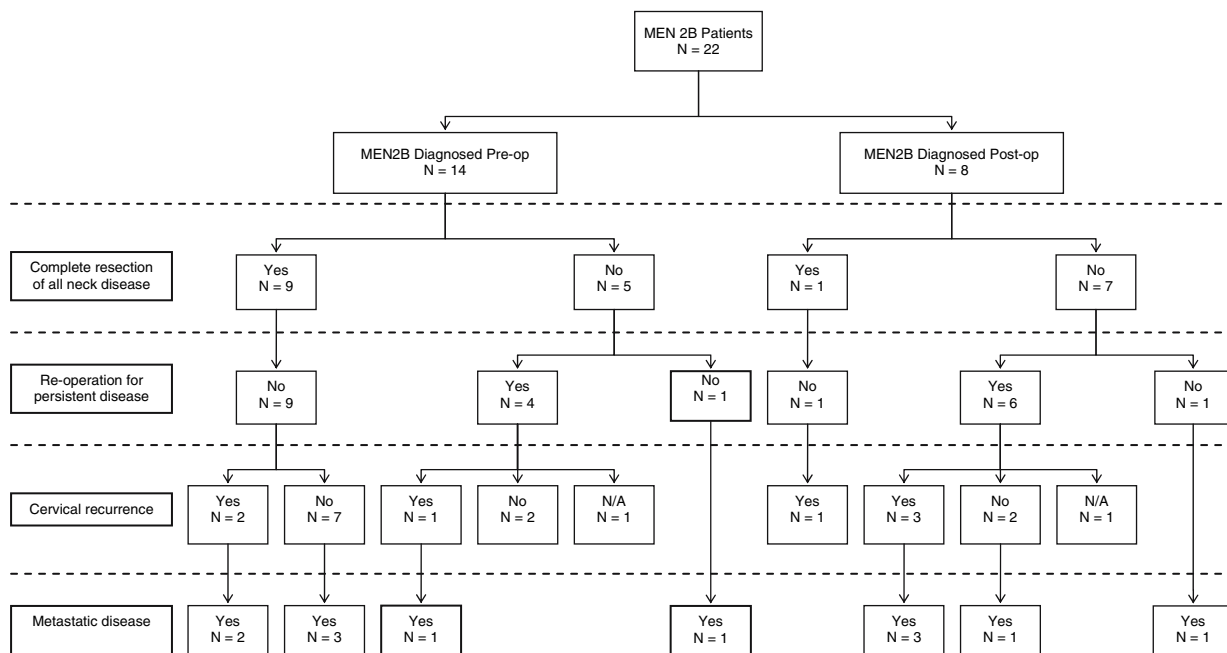


FIG. 2. Flow diagram depicting the diagnosis and surgical management of MEN 2B patients treated at MDACC. Cervical recurrence was listed as N/A for 2 patients with a less than 1 year follow-up.

Timing of Diagnosis and Initial Cervical Operation

The diagnosis of MEN 2B was made prior to the initial cervical operation in 14 of the 22 patients (64%) (Fig. 2). Of these 14 patients, 4 were referred to MDACC for initial surgery and underwent total thyroidectomy, central and bilateral neck dissection that successfully removed all gross disease. The initial cervical operation was performed prior to referral in 10 of the 14 patients; 5 of these 10 patients had complete resection of all gross disease in the neck. Their operations consisted of thyroidectomy and central neck dissection in three patients and thyroidectomy, central and bilateral neck dissection in two patients. The remaining five patients underwent surgery for established MEN 2B-related MTC but did not have all gross disease removed from the neck; grossly positive cervical lymph node metastases remained in situ following thyroidectomy and central neck dissection (N = 3), thyroidectomy and removal of selected lymph nodes (N = 1) or thyroidectomy alone (N = 1).

The diagnosis of MEN 2B was not appreciated until after the initial cervical operation in 8 of the 22 patients (36%). Only one of these patients had complete resection of all gross disease in the neck and underwent thyroidectomy, central and unilateral neck dissection. An incomplete resection of all gross disease was performed in seven patients who under-

went thyroidectomy alone (N = 4), thyroidectomy and central neck dissection (N = 2) or thyroidectomy and removal of selected lymph nodes with other than formal comprehensive compartment-oriented dissection (N = 1).

Persistent and Recurrent Disease

Persistent local-regional MTC was present following the initial cervical operation in 12 of the 22 patients (55%); in 5 with MEN 2B diagnosed prior to initial operation and in 7 with MEN 2B diagnosed after initial operation. Reoperation was performed in 10 of these 12 patients and all gross disease was successfully resected in all 10. Two patients had widespread distant organ metastases upon referral to our institution and therefore did not undergo reoperative neck dissection despite the presence of gross residual disease.

Overall, 20 patients had all gross neck disease in the neck surgically removed in either one or two operations, and cervical recurrence was diagnosed in seven (35%). The sites of cervical recurrence included a previously dissected central compartment in four patients, a previously dissected lateral neck compartment in two patients, and a nonoperated lateral neck compartment in one patient. All four patients who developed a central compartment recurrence had

their initial central compartment dissection performed prior to referral to our institution. Only one of the seven patients with cervical recurrence had undergone a thyroidectomy, central and bilateral neck dissection at their first operation; in this patient, the recurrence occurred in a lateral neck compartment. Overall, six of the seven patients (86%) who developed cervical recurrence went on to develop distant metastatic disease.

Metastatic disease developed in 12 of the 22 patients (55%) and proved to be the cause of death in 5 patients (23%). The median age of those who died was 26 years (range 11–37 years). The sites of metastases included lung ($N = 8$), mediastinum ($N = 6$), bone ($N = 6$), liver ($N = 4$), brain ($N = 1$), and skin ($N = 1$).

Of the 10 patients who had all gross disease removed from the neck at their initial operation, clinical recurrence has occurred in six, cervical recurrence in one, distant recurrence in three, and cervical and distant recurrence in two. Of the 10 patients who required two operations to remove all gross disease from the neck, clinical recurrence has occurred in five, distant recurrence in one, and cervical and distant recurrence in four. As noted previously, there were two patients who did not undergo a second operation to remove neck disease as they already had distant metastases upon presentation to MDACC.

At last follow-up, eight patients were without evidence of disease by physical examination or diagnostic imaging studies (age range 7–41 years), yet serum levels of calcitonin were measurable in seven of these eight patients (calcitonin levels were 12, 21, 23, 31, 113, 363, and 463 pg/mL). Nine patients were AWD (age range 17–43 years) and as stated, five patients are DOD.

Impact of Delay in Diagnosis

The median time from initial presentation to a prereferral physician or health care provider for a MEN 2B-related complaint to the date of correct MEN 2B diagnosis (delay in diagnosis) for the 12 patients who developed metastatic disease was 5 months (range 0–18 years). The median age at thyroidectomy for these patients was 13 years (range 6–25 years). For the 10 patients who have not developed metastatic disease, the median delay in diagnosis was 5 years (range 0–17 years) and the median age at thyroidectomy was 13 years (range 7–22 years). The cumulative disease extent did not appear to vary based on delay in diagnosis or age at thyroidectomy (Figs. 3 and 4).

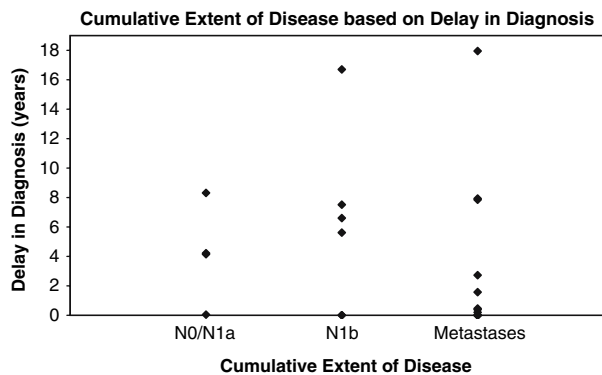


FIG. 3. Scatter plot demonstrating the delay in diagnosis of MEN 2B. Patients are grouped based on their cumulative cervical lymph node status or the development of extra-cervical metastases: N0/N1a—MTC did not involve regional lymph nodes or was restricted to the thyroid and/or central compartment (level VI) lymph nodes, N1b—MTC was restricted to the thyroid and central and lateral neck (levels IIA, III, IV, V) lymph nodes, metastatic—MTC had spread beyond the neck.

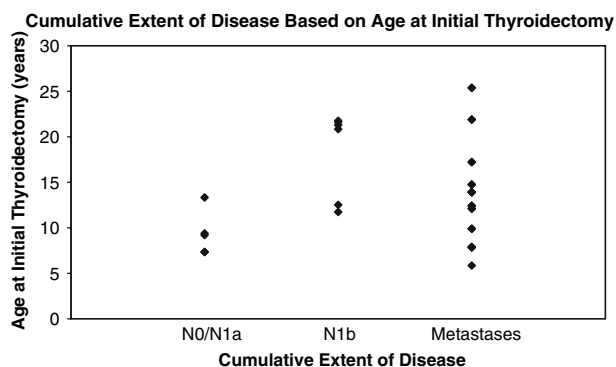


FIG. 4. Scatter plot demonstrating the age at initial thyroidectomy. Patients are grouped based on their cumulative cervical lymph node status or the development of extra-cervical metastases: N0/N1a—MTC did not involve regional lymph nodes or was restricted to the thyroid and/or central compartment (level VI) lymph nodes, N1b—MTC was restricted to the thyroid and central and lateral neck (levels IIA, III, IV, V) lymph nodes, metastatic—MTC had spread beyond the neck.

DISCUSSION

Despite a broad understanding of the genetic basis and clinical presentation of MEN 2B, there is widespread failure of clinical recognition of the disease, due in part to the rarity of the condition and because most patients have de novo mutations without a family history of MTC or pheochromocytoma. In this series, there was a median time of 2 years between presentation to a physician or other health-care provider for an obvious MEN 2B-related complaint and the successful recognition of MEN 2B. This 2-year delay is a conservative estimate as we recorded

only definitive, well-documented evidence of presentation to a physician or other health-care provider for a MEN 2B-specific complaint. Importantly, the delay in diagnosis occurred even though the clinical manifestations of MEN 2B were present at a young age in all patients and are sensitive and specific for the diagnosis of MEN 2B. For example, Brauckhoff et al. reported on the early clinical manifestations of 21 patients with MEN 2B.¹⁵ Before age 6, the most common overt physical manifestations included mucosal or tongue neuromas and foot abnormalities, each present in at least 60% of patients. The frequency of features increased with age, with essentially all patients developing one or more stigmata of MEN 2B by the age at which the diagnosis of MTC was made. The most common finding was “bumpy lips”, which were present in all patients older than age 7. In this report, the diagnosis of MTC was made in only 1 of 22 patients (5%) prior to the age of 7. This patient was the youngest to undergo thyroidectomy, which occurred at 6 years. Brauckhoff et al. also reported that 74% of the patients developed intestinal dysfunction in early childhood, typically manifested by constipation followed by diarrhea.¹⁵ Severe intestinal dysfunction requiring surgical intervention was associated with the earlier diagnosis of MTC (at or before the age of 12 years), likely due to the greater exposure of these patients to physicians and hospitals.

The difficulty in establishing a correct diagnosis of MEN 2B is illustrated by the mother of a 12-year-old boy, included in this report, who had long suspected that there was something wrong with her child since he experienced poor feeding, chronic diarrhea, and an abnormal appearing tongue. A physician told her that her son had pes cavus (high arched foot that does not flatten with weight bearing). She became frustrated with the lack of response from her physician team and performed an Internet search of his phenotypic characteristics and symptoms. The search yielded web pages describing MEN 2B and the associated phenotype, all of which perfectly described her son. She brought him to a genetics clinic where genetic testing revealed the M918T *RET* mutation. Although the correct diagnosis of MEN 2B was made prior to his first neck operation, all gross disease was not removed prompting his referral to our institution for reoperation.

The potential for a surgical cure of MEN 2B-related MTC is dependent on the extent of disease at diagnosis and the adequacy of the initial operation. When possible, surgery for MTC should be performed before the abnormal C-cells transform from

hyperplasia to invasive MTC. The recommended age for thyroidectomy in children with MEN 2B is before 6 months of age, with some suggesting that surgery be performed even earlier.¹⁶ Yet surgery is rarely performed this early in life as the disease is usually not recognized.¹⁷ In this series, the median age at thyroidectomy was 13 years. If MEN 2B is not recognized and thyroidectomy is not performed until the teenage years or in adulthood, the potential for cure is remote. In the experience reported herein, no patient underwent initial thyroidectomy prior to the age of 6 years, and only 6 of the 22 patients (27%) underwent initial thyroidectomy prior to age 10. This delay in thyroidectomy occurred despite the obvious phenotypic appearance of MEN 2B that was present in all of our patients.

Due to the rapid development and aggressive biology of MEN 2B-related MTC, a central and bilateral lateral neck dissection is usually recommended unless the diagnosis is made in the first few years of life. A complete operation, that removes all gross disease, is much more likely to be performed if the diagnosis of MEN 2B is made prior to surgery. A correct preoperative diagnosis of MEN 2B was made in only 13 of the 22 patients. Of these 13 patients, 9 had all gross disease removed from the neck. In contrast, of the nine patients in whom the diagnosis of MEN 2B was not appreciated until after initial thyroid surgery, only one had complete surgical resection of all gross disease in the neck.

A finding that is perhaps surprising is that the delay in diagnosis and the age at thyroidectomy did not appear to vary based on disease extent at last follow-up as shown in Figs. 3 and 4. To some extent, this reflects the finding that all patients were diagnosed late, at a time when MTC was either regionally advanced or metastatic. However, it also suggests a varied natural history even within the spectrum of the codon 918 mutation. The heterogeneous nature of the biology of MEN 2B-related MTC is further illustrated by the pathology findings from a recent patient operated on at our institution. A 7.5-year-old girl was evaluated by her pediatrician after her father noticed a neck mass. A cervical ultrasound demonstrated bilateral thyroid nodules, and biopsy revealed MTC prompting *RET* proto-oncogene testing, which was positive for the M918T mutation. Both serum levels of calcitonin and CEA were elevated at 1881 pg/mL and 161 ng/mL, respectively. A repeat cervical ultrasound at MDACC demonstrated bilateral thyroid nodules as well as borderline enlarged level 3 and 4 cervical lymph nodes. Duplex scanning of these nodes demonstrated normal vascular flow, suggesting

that they may be normal and enlarged simply due to her young age. Serum metanephrines and normetanephrines ruled out pheochromocytoma. Based on the diagnosis of MEN 2B-related MTC, a positive genetic test for a mutation in codon 918 of the *RET* proto-oncogene, and her elevated levels of calcitonin and CEA, her cervical operation included a thyroidectomy, central and bilateral lateral neck dissection. Pathology demonstrated multifocal, bilateral MTC in the background of C-cell hyperplasia, yet all 109 resected lymph nodes were negative for MTC. Post-operatively her serum calcitonin is undetectable and her CEA is normal. While this case was unique in our series, it does illustrate the heterogeneous biology and natural history of inherited MTC even within a group of patients who have the same *RET* codon mutation.

When the diagnosis of invasive MTC is confirmed by fine-needle aspiration biopsy of a thyroid nodule in the presence of an elevated serum level of calcitonin, the extent of surgery should be based on pre-operative imaging (ultrasound and/or computed tomography) and knowledge of contemporary published guidelines.¹⁸ If the surgeon performing the initial consultation is not comfortable performing neck dissection for cancer, the initial thyroidectomy should not be performed and the patient referred to a center more experienced with this disease. Reoperation on the central neck, in contrast to the initial operation, carries a higher risk for recurrent laryngeal nerve injury and a significantly higher risk for permanent hypoparathyroidism.¹⁹ Such risks are markedly reduced if the necessary operation can be performed in one stage rather than two. Importantly, any devascularized parathyroid glands can be autografted into the neck (sternocleidomastoid muscles) in patients with MEN 2B due to the lack of hyperparathyroidism in these patients.

For children beyond the age of 2 or 3 years with disease that appears limited to the thyroid gland, our practice has typically also included central and bilateral neck dissection due to the known aggressiveness of MTC in MEN 2B patients.²⁰⁻²² In addition, cervical ultrasound is not as specific in children, compared with adults, due to the common finding of benign cervical lymphadenopathy, which may represent a normal age-associated variation.²³ The single case illustrated previously reminds us of the heterogeneous nature of this disease and the difficulty in developing management guidelines, especially in young children. The overwhelming majority of patients diagnosed at or after the age of 10 will have obvious metastatic cervical adenopathy. In such patients, we usually perform computed tomography

imaging to more carefully examine the region of the thoracic inlet as ultrasound evaluation of the low neck, at the thoracic inlet, is often suboptimal. In such patients, a complete neck dissection is performed involving the central and both lateral neck compartments.^{24,25}

If the serum calcitonin levels are elevated after primary thyroid surgery, it is important to define the extent of local and distant metastatic disease. In general, we consider reoperative neck surgery only when disease is apparent on imaging studies. Due to the obvious association of elevated serum levels of calcitonin with persistent MTC and the emotional nature of a cancer diagnosis in children, we have considered reoperative elective neck dissection in some patients with MEN 2B who we assess to have undergone a suboptimal initial surgery, have persistent elevations in calcitonin, yet no definitive metastatic disease in cervical lymph nodes on imaging studies. However, such cases are uncommon in the current era of high-quality transcutaneous ultrasound and four-dimensional computed tomography imaging.

In our practice, when evaluating a newly diagnosed patient with MEN 2B, we first determine the presence or absence of pheochromocytoma. The 21-year-old patient in our case report self-palpated her own MTC and underwent thyroidectomy in the setting of a pheochromocytoma due to the failure to recognize her underlying MEN 2B. All newly diagnosed MEN 2B patients should be screened for the presence of pheochromocytoma before surgery (and regularly thereafter) to avoid a potential life-threatening hypertensive crisis. If plasma or urine metanephrines are elevated in the setting of a unilateral or bilateral adrenal mass, the patient should be appropriately prepared for surgery with alpha and beta blockade.²⁶ We often perform both the adrenal and the neck surgery at the time of a single anesthesia induction. The adrenal surgery is performed first, usually with a minimally invasive technique for a unilateral adrenalectomy and an open operation for bilateral (cortical sparing) adrenalectomy.^{27,28} The patient is then repositioned for neck surgery.

In the future, it is possible that novel tyrosine kinase inhibitors may play a role in the systemic treatment of MTC.²⁹ However, at present, surgical resection of both the thyroid gland and the central and lateral cervical lymph nodes remains the standard treatment of MEN 2B-associated MTC. To achieve long-term cure of MTC, successful treatment is dependent on a prompt diagnosis early in life and a thorough initial operation performed by an experi-

enced surgeon. Our data would suggest that achieving these two goals may be a continued challenge in patients with this rare disease.

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