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Bilateral Medullary Thyroid Carcinoma in a 3-Year-Old Female Patient with Multiple Endocrine Neoplasia 2A Syndrome Undergoing Prophylactic Thyroidectomy: Should Current Guidelines Be Revised?

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What Is Known about This Topic?

- The American Thyroid Association recommends the performance of prophylactic thyroidectomy for multiple endocrine neoplasia (MEN) 2A patients with a codon 634 mutation at or before the age of 5 years. However, to date, the literature reports only a few cases in which thyroidectomy performed prophylactically has revealed the presence of already developed medullary thyroid carcinoma (MTC).

What Does This Case Report Add?

- The present report describes a case of incidentally discovered bilateral MTC in a 3-year-old MEN 2A female patient undergoing prophylactic thyroidectomy, with no preoperative ultrasonographic features suggestive of such a pathology. It is likely that the current guidelines should be revised to recommend calcitonin screening and prophylactic thyroidectomy at an earlier age in such patients. Due to the rarity of these patients, cumulative literature on the topic is essential, and, therefore, reports such as the present one add greatly to the available literature.

Keywords
Multiple endocrine neoplasia 2A · Medullary thyroid carcinoma · Prophylactic thyroidectomy · Age · Incidental carcinoma · Guidelines

Abstract
Background: Multiple endocrine neoplasia (MEN) 2A is an autosomal dominant disorder that results from a mutation in the *RET* proto-oncogene on chromosome 10. Almost all of the affected patients develop medullary thyroid carcinoma (MTC). The American Thyroid Association recommends pro-

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phylactic thyroidectomy in MEN 2A pediatric patients, with the age of the recommended thyroidectomy varying according to the codon mutation present. ***Objectives:*** This report questions the reliability of the currently placed guidelines and whether the age threshold for prophylactic thyroidectomy in patients with known codon 634 mutations should be lowered, in parallel with an earlier evaluation of calcitonin levels in the serum. ***Methods:*** We report the preoperative diagnosis as well as operative and postoperative course of a 3-year-old female patient with MEN 2A (codon 634 mutation) who underwent prophylactic thyroidectomy. The postoperative histopathologic findings are presented and discussed. ***Results:*** Despite the prophylactic nature of the operation, in parallel with a borderline calcitonin increase in the serum, bilateral MTC was discovered on pathology. ***Conclusion:*** It is likely that the current guidelines should be revised to recommend calcitonin screening and prophylactic thyroidectomy at an earlier age for MEN 2A patients with known codon 634 mutations.

Introduction

Multiple endocrine neoplasia (MEN) 2A is an autosomal dominant disorder that results from a mutation in the *RET* proto-oncogene on chromosome 10 [1, 2]. Almost 100% of affected patients develop medullary thyroid carcinoma (MTC), while pheochromocytoma occurs in 50% and hyperparathyroidism in 25% [3]. The American Thyroid Association recommends prophylactic thyroidectomy in genetically diagnosed MEN 2A pediatric patients, with the age of the recommended thyroidectomy varying according to the codon mutation present (Table 1) [4]. We present a patient who underwent prophylactic thyroidectomy well within the timeline of the recommended guidelines; however, final pathology demonstrated bilateral MTC. This report questions the reliability of the currently placed guidelines and whether the age threshold for prophylactic thyroidectomy in this particular codon mutation should be lowered, in parallel with an earlier evaluation of calcitonin levels in the serum.

Case Report

We report the case of a 3-year-old female patient with known family history of MEN 2A. Two years ago, the patient's father was diagnosed with bilateral pheochromocytoma and MTC and eventually underwent genetic testing which demonstrated a de novo mutation in the *RET* proto-oncogene (*RET* Cys634Arg c.1900T>C). His daughter, our current patient, underwent genetic testing at 1 year of age and was found to be a carrier of the same mutation (*RET* Cys634Arg c.1900T>C). It was advised that the patient should undergo prophylactic thyroidectomy before the age of 5 years, as recommended by the current guidelines for this particular codon mutation [4]. Until the time of thyroidectomy, yearly screening with serum calcitonin was performed, although the current guidelines recommend initiation of such screening at the age of 3 years [4]. At the age of 2 years and 10 months, serum calcitonin was demonstrated to be slightly elevated (18.9 ng/L, normal range 0.0–13.0 ng/L). Carcinoembryonic antigen was normal (2.0 ng/mL, normal <5.5 ng/mL), and serum calcium was normal as well, approaching a level of 10.39 mg/dL (normal range 8.8–10.8 mg/dL). A neck ultrasound (US) showed no thyroid masses and no enlarged cervical lymph nodes. The level of plasma metanephrine was slightly elevated (97.5 pg/mL, normal <65 pg/mL), and that of plasma normetanephrine was normal (81.4 pg/mL, normal <196 pg/mL). Abdominal US showed no adrenal masses. Repeated calcitonin levels 4 months later demonstrated a further elevation from the previous value (23.9 ng/L). The patient's case was discussed at our institution's multidisciplinary neuroendocrine tumor board meeting, and it was decided to recommend prophylactic thyroidectomy at her current age (3 years and 4 months).

The patient underwent total thyroidectomy with an uneventful operative and postoperative course. Four normal parathyroid glands and both recurrent laryngeal nerves were identified and preserved. Postoperative serum calcium and parathyroid hormone levels were normal, and the patient was discharged 24 h following the operation.

Table 1. Recommended timing for prophylactic thyroidectomy according to *RET* codon mutation

ATA risk group for MTC	*RET* codon mutation	Recommended timing for prophylactic thyroidectomy
Highest	918	First months of life to first year
High	634, 883	At or before the age of 5 years, according to calcitonin levels
Moderate	533, 609, 611, 618, 620, 630, 631, 666, 768, 790, 804, 891, 912	Upon elevation of calcitonin levels, or during childhood if parents prefer not to be under lengthy follow-up

ATA, American Thyroid Association; MTC, medullary thyroid carcinoma.

On the histopathology report, the thyroid gland weighed 3.1 g, with the right lobe measuring 2.2 × 1.3 × 1.6 cm, the left lobe 2.3 × 0.7 × 0.8 cm, and the isthmus 2.0 × 0.6 × 0.5 cm. Macroscopically, a 0.2 × 0.2 × 0.2 cm intracapsular nodule was demonstrated in the left lobe. No other macroscopic nodules were seen. Microscopic examination revealed bilateral medullary microcarcinomas of the thyroid, with the greatest diameter of 0.6 cm, with no extrathyroidal extension, lymphovascular or perineural invasion. Stains for calcitonin and carcinoembryonic antigen were positive (Fig. 1). One unremarkable parathyroid gland was demonstrated adjacent to the right lobe. One month after the operation, calcitonin levels were evaluated again and were found to be undetectable.

Discussion

MTC in childhood is exceedingly rare and is almost always the result of a de novo or inherited activating mutation in the *RET* proto-oncogene [5]. Patients with identified mutations are classified by the American Thyroid Association into risk categories according to the aggressiveness of associated MTC [4]. Patients carrying "highest-risk" mutations are recommended to undergo prophylactic thyroidectomy (and possible central cervical lymph node dissection) within the first year of life. For patients carrying "high-risk" mutations (which include the Cys634Arg mutation present in our patient), prophylactic thyroidectomy is recommended at or before the age of 5 years. Patients carrying "moderate-risk" mutations are recommended to undergo thyroidectomy upon elevation of calcitonin levels or in childhood if the parents prefer not to remain under constant and lengthy follow-up.

MTC is the most common cause of death in MEN 2A patients, and the goal of prophylactic thyroidectomy is to remove thyroid tissue before the development of carcinoma, its lymph node extension, and distant metastases [6]. However, the literature has demonstrated a handful of cases in which prophylactic surgery revealed incidental carcinoma. Sim et al. [7] reported a case of a 4-year-and-8-month-old girl with a codon 634 mutation whose prophylactic thyroidectomy specimen demonstrated incidental MTC. In Machens et al.'s [8] publication, in which 130 patients with mutated codon 634 were reported, the age of the youngest patient found to have MTC was 15 months. Similarly, Sanso et al. [9] reported a case of MTC discovered in a 17-month-old patient with a codon 634 mutation. In Schreinemakers et al.'s [10] publication which included 62 patients with the mutation, the earliest age of MTC was 1.25 years.

Shepet et al. [11] demonstrated a significant difference in disease-free survival among MTC patients who underwent prophylactic thyroidectomy when compared to those who underwent therapeutic thyroidectomy. In addition, patients' probability for cure from MTC has been found to be associated with lymph node status, ranging from 95% when no lymph nodes are involved, 31–57% when 1–10 lymph nodes are involved, and 0–4% when more than 10 lymph nodes are involved with MTC [12–

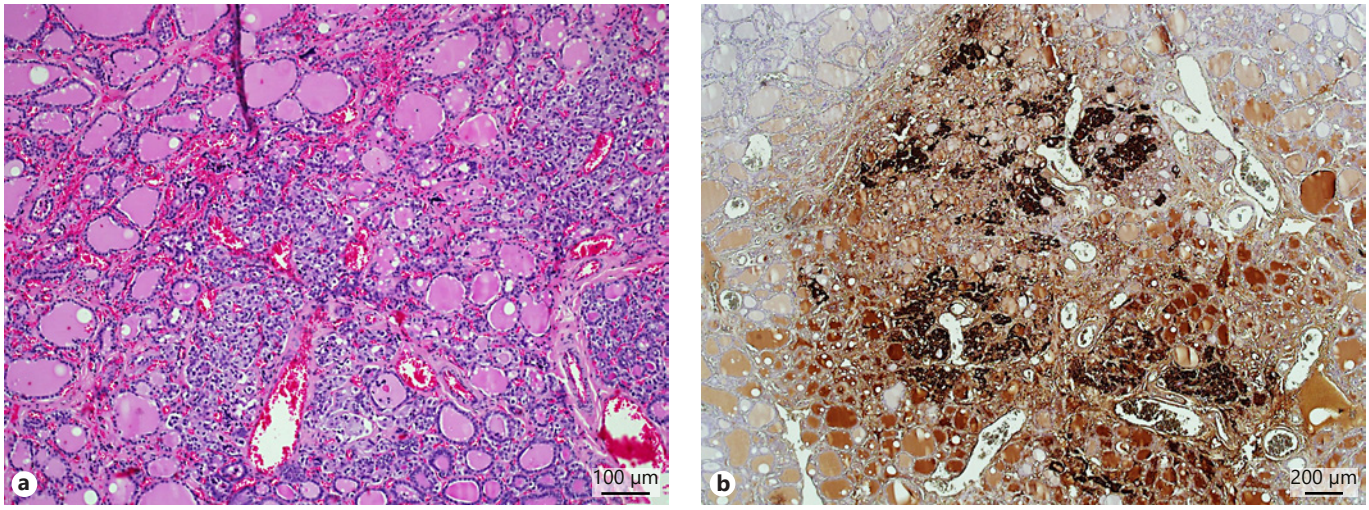

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Fig. 1. a Histopathologic findings. Thyroid gland: medullary thyroid microcarcinoma. The tumor measures <1 cm and exhibits nesting growth pattern. HE, ×100. **b** Immunohistochemistry. Calcitonin positivity is present in cytoplasm of the tumor cells.

14]. Previous publications have demonstrated the possibility of lymph node involvement regardless of the size of the tumor and even in micro-medullary carcinomas of less than 0.5 cm in diameter [15]. The performance of thyroidectomy prior to the development of MTC and definitely prior to the development of lymph node involvement in nearly all cases is a crucial aspect of the prophylactic nature of the procedure. Although thyroidectomy at a younger age may be associated with increased operative risk, due to the fact that the patients of interest are young children with several years of potential survival ahead of them, and the fact that surgical resection is the only definitive therapy for MTC, the authors definitely believe that an earlier operation is worth the risk. However, the importance of performing these operations only in experienced, high-volume centers must be emphasized.

Previous reports have demonstrated elevated calcitonin levels during infancy, possibly leading to difficulty in its utilization for screening in younger MEN 2A patients [16, 17]. Basuyau et al. [16] investigated normal ranges of calcitonin levels in different age groups and genders, recommending the utilization of normal reference values of <40 ng/L for children under 6 months and <15 ng/L for children 6 months to 3 years of age. For children >3 years of age, values indistinguishable from adults were recommended, <5 and <12 ng/L for males and females, respectively. Our current report demonstrates that screening US is not always accurate in demonstrating the presence of MTC, which emphasizes the importance of using calcitonin as a screening method starting from a young age. Due to the possibility of significantly elevated levels in infants under 6 months, along with the unlikelihood that such values would outweigh the risks of an operation at such a young age in 634 patients, we find it unreasonable to recommend calcitonin screening under the age of 1 year. After that age, however, it seems logical to recommend such screening, while utilizing reference values similar to those proposed by Basuyau et al. [16].

The currently reported case, along with the few others present in the literature, demonstrates that in MEN 2A patients carrying a codon 634 mutation, the development of MTC is possible long before the recommended age of prophylactic thyroidectomy. Given the fact that surgical excision of the thyroid gland prior to development of MTC provides patients with the best chance for long-term survival, it is possible that the current guidelines should be revised to recommend prophylactic thyroidectomy at an earlier age. The authors believe that such a decision regarding recommended timing of prophylactic thyroidectomy should only be made in the context of a consensus meeting hosted by the European or American Thyroid Association, following a multidisciplinary discussion of the available literature, to which this current report adds. In addition, it may be wise to recommend initiation of screening with serum calcitonin well before the age of 3 years, deciding on surgery when any elevation in calcitonin levels occurs and despite the appearance of a "normal" thyroid gland on neck US.

Conclusion

In MEN 2A patients carrying a codon 634 mutation, the development of MTC can occur long before the recommended age for prophylactic thyroidectomy (5 years). To prevent such cancers and the related morbidity and mortality, it is likely that the current guidelines should be revised to recommend calcitonin screening and prophylactic thyroidectomy at an earlier age.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no financial conflicts of interest to declare.

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