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# Medullary thyroid carcinoma in ethnic Chinese with MEN2A: A case report and literature review ☆

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**Abstract** Medullary Thyroid Carcinoma (MTC) is the most common cause of death in MEN patients.

It is curative by prophylactic total thyroidectomy, but controversies remain as to the optimal timing for prophylactic thyroidectomy. The current recommendation is for prophylactic total thyroidectomy before age 5, but a recent study suggested that in the ethnic Chinese, even "high risk" mutations did not result in early malignant change, and it was suggested that prophylactic thyroidectomy may be performed at a later age. We report a case of an ethnic Chinese girl with MEN2A codon 634 (C634R) mutation, whose operative specimen at prophylactic thyroidectomy at 4 years 8 months showed MTC. We advocate that management of MEN2A patients should be codon-directed, regardless of ethnicity.


In patients with MEN-2A syndrome, the risk of developing medullary thyroid carcinoma (MTC) is 90%–100%. Generally the first neoplasm to develop in these patients [1], MTC is also the most common cause of death in MEN patients. Early prophylactic total thyroidectomy, i.e. before the development of MTC, is currently the only curative treatment [2,3] and significantly improves long-term outcomes [1]. In children with the known inherited mutated RET protooncogene, the current treatment recommendation is prophylactic total thyroidectomy before age 5 [1,4], on the basis that MTC rarely develops earlier. The issue of optimal timing for surgery is, however, still unresolved. Certain "high risk" mutations have been shown to be associated with development of MTC as early as one year of age [3,4], but some authors have also suggested that ethnicity may play a role in clinical manifestation [5]. It has been suggested that in the ethnic Chinese, MTC may develop later and that prophylactic total thyroidectomy may possibly be safely delayed [5].

We present a case of an ethnic Chinese girl with MEN2A codon 634 mutation who was found to harbour medullary thyroid carcinoma at age 4 years 8 months, highlighting the potential risk of delaying prophylactic thyroidectomy.

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## 1. Case report

Our patient was referred to the surgical clinic at age 4 years 4 months. She had been diagnosed with MEN2A (mutation) on the basis of a strong family history for MTC. Her mother was known to have MEN2A (codon 634, exon 11, TGC-CGC mutation), diagnosed at age 20 with a phaeochromocytoma, and subsequently developed MTC. The patient's maternal uncle had phaeochromocytoma and thyroid carcinoma and her maternal grandmother had metastatic thyroid cancer at age 40. Genetic testing of our patient revealed heterozygosity for the same mutation at codon 634 (C634R). There is no known history of Hirschsprung's Disease, either in the patient or in other family members.

Pre-operatively, she was clinically and biochemically euthyroid. Serum calcitonin level was slightly elevated (18 ng/L) but urinalysis showed that vanillylmandelic acid, epinephrine, norepinephrine, dopamine and 5-OH Indole Acetic Acid levels were within normal range. Prophylactic total thyroidectomy with clearance of bilateral trachea-oesophageal grooves was performed at age 4 years 8 months.

Intraoperatively, the thyroid gland was normal on palpation. Post-operative recovery was unremarkable, with no functional injury to the bilateral recurrent laryngeal nerves and parathyroid glands. She was discharged on the second post-operative day. Histopathology of the thyroid revealed multifocal C cell hyperplasia (focal, diffuse and nodular) with two foci of micro medullary thyroid carcinomas — 2 mm and 1 mm in maximum dimensions (Fig. 1). The resection margins had no tumour involvement, and there was no evidence of lymphovascular or perineural invasion or lymph node metastasis. Postoperative calcitonin levels normalised to 6.0 ng/L.

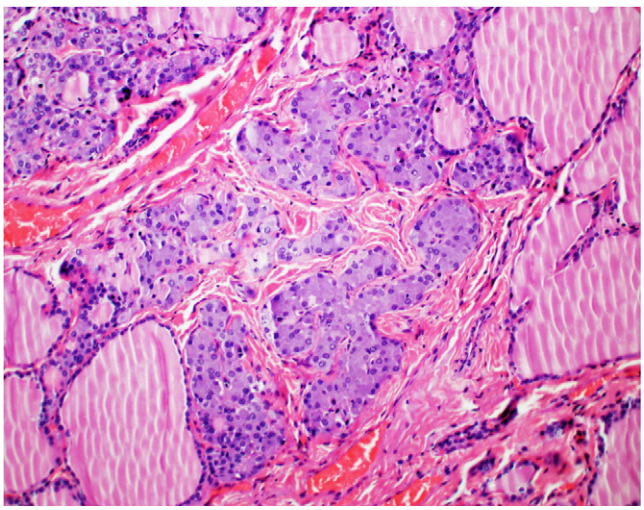

**Fig. 1** Hematoxylin and eosin-stained photomicrograph showing a focus of medullary thyroid carcinoma featuring nests and trabeculae of polygonal tumour cells with cytologically bland round to oval nuclei and abundant amphophilic cytoplasm; surrounding thyroid follicles are present.

## 2. Discussion

The development of MTC in MEN2A is almost certain [1], with metastases early in the course of the disease, even with microscopic MTC [6]. Lymph node metastases decrease the patient's prospects of cure from 95% (with 0 metastases) to 31% to 57% (with 1–10 lymph node metastases) to 0%–4% (with more than 10 lymph node metastases) [7]. MTC is chemo- and radio-resistant, although targeted drug therapy with tyrosine kinase inhibitors, such as Vandetanib, has shown promise in the treatment of advanced MTC [8]. Nonetheless, total thyroidectomy before the development of MTC is still the only curative option to date [2,3].

Thyroidectomies carry known surgical risks, including vocal cord paresis/paralysis, permanent hypoparathyroidism and hypocalcaemia [9]. Complication rates for cervical endocrine surgery are higher in children than adults, partly due to a later presentation of endocrine disease secondary to the hesitation to operate on children when asymptomatic or with benign disease [10]. Nonetheless, these risks can be minimised when surgeries are performed by high volume surgeons [11].

In addition to increased surgical morbidity, premature or overly aggressive surgical treatment may lead to issues related to difficulties with long-term drug compliance [11,12]. Postoperative management of hypocalcaemia in the paediatric patient can be challenging. Ensuring compliance with oral calcium/vitamin D supplementation is difficult; treatment may require intravenous calcium supplementation, resulting in extended hospitalisation [11]. In addition, the labile requirement of thyroxine during growth and development, as well as long-term compliance with thyroxine replacement, poses a challenge to both the physician and patient [5]. Detailed and evidence-based guidelines for the proper titration of levothyroxine and the frequency of monitoring blood tests, especially in later childhood and adolescence still remain to be established [13].

Current recommendation for patients with MEN2A is prophylactic total thyroidectomy before the age of 5 [4], but with the increasing recognition that the risk of MTC development is codon-specific and mutation-specific, this has led to calls for codon-directed management [4], to better balance the risk and benefit to the individual patient.

The RET (Rearranged during transfection) proto-oncogene encodes a tyrosine kinase receptor involved in both multiple endocrine neoplasia type 2 (MEN 2) [14] and Hirschsprung disease (HSCR) [15]. The MEN-2A phenotype includes a diverse array of genotypic makeup, with mutations of the RET proto-oncogene found in either exons 10, 11, 13, 14, 15 or 16 [16]. Based on the age of onset of disease and genotype, codon 634 and 618 mutations