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Medullary Thyroid Carcinoma in a 13-Year-Old Boy: A Rare Pediatric Presentation with Pulmonary Metastases

Sara. BOUMEIZ[1*], Samir. Barkiche[1], Zakariya. Benoumrhar[1], S. Laatitioui[1], M. Saadoune[1], N. Oumghar[1], M. Darfaoui[1], A. El Omrani[1], M. Khouchani[1]

[1]Radiation Oncology Department, Oncology and Haematology Hospital; Mohammed VI University Hospital, Marrakech, Morocco

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***Corresponding author:** Sara. BOUMEIZ
Radiation Oncology Department, Oncology and Haematology Hospital; Mohammed VI University Hospital, Marrakech, Morocco

Abstract **Case Report**

Medullary thyroid carcinoma (MTC) is an uncommon thyroid malignancy in the pediatric population, accounting for a small proportion of thyroid cancers in children. We report the case of a 13-year-old boy who presented with progressive respiratory symptoms and was ultimately diagnosed with sporadic MTC with pulmonary metastases. Initial imaging suggested a compressive thyroiditis, but worsening symptoms led to emergency total thyroidectomy, tracheostomy, and lymph node dissection. Histopathological examination cofirmed MTC with extracapsular spread and lymph node involvement. Interestingly, the child exhibited thickened lips, raising suspicion of a dysmorphic syndrome. Genetic testing for RET mutations, including exon 11, returned negative, supporting a sporadic form of the disease. The patient was started on selpercatinib (40 mg twice daily) and levothyroxine (125 µg per day), with clinical stability observed over the subsequent six months. This case highlights the importance of early diagnosis and comprehensive management of pediatric MTC, especially in cases with atypical features.

Keywords: Medullary thyroid carcinoma, pediatric oncology, pulmonary metastases, RET gene, dysmorphic features.

1. INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor originating from the parafollicular C cells of the thyroid gland and accounts for 5% of all thyroid cancers in children. The epidemiology of pediatric MTC differs significantly from that observed in adults, with hereditary forms predominating in younger patients.

MTC is inherited in approximately 95% of cases. The sporadic form is extremely rare in the paediatric population [1,2]. Inherited forms are most often associated with multiple endocrine neoplasia (MEN) syndromes, particularly MEN 2A and MEN 2B, which involve mutation in Rearranged during Transfection (RET) proto-oncogene. MEN2A is much more common (95% of MEN2 cases) and presents with four variants. Classical MEN2A is characterized by MTC in nearly all patients and low penetrance of pheochromocytoma and HPTH, depending on the specific RET mutation involved [3].

MEN2B, which is associated with a germline point mutation in codon M918T in the RET kinase domain in more than 95% of patients, accounts for only 5% of MEN2 cases [4]. In MEN2B, patients experience a very aggressive course of MTC, with presentation in infancy and early lymph node and distant metastases. Pheochromocytomas occur in approximately half of patients with MEN2B, and the syndrome is also associated with characteristic physical features, such as marfanoid habitus, ocular abnormalities, and generalized ganglioneuromatosis [5]. Approximately 75% of MEN2B cases are sporadic, making early recognition, diagnosis, and prophylactic thyroidectomy challenging[6].

Sporadic MTC is not linked to germline RET pathogenic variants. Instead, it frequently exhibits somatic RET pathogenic variants, primarily the p.M918T variant, as well as pathogenic variants in rat sarcoma (RAS) genes, particularly HRAS [7]. Recent large-scale studies have shown that sporadic pediatric MTC patients tend to be older at presentation, have larger primary tumors, and present with more advanced disease stages[8].

Early diagnosis is crucial, given the tumor's potential for local invasion, early lung, liver, and bone metastases, which, together with airway obstruction, are the most common causes of death [9].

2. CASE PRESENTATION

A 13-year-old boy, the youngest of three siblings born from a first-degree consanguineous union, presented in March 2024 with a dry cough. No family history of thyroid carcinoma, MEN, pheochromocytoma, or hyperparathyroidism was found in any family members across three generations.

Over time, the patient's clinical condition progressively deteriorated. The initially benign cough evolved into dyspnea and dysphagia, accompanied by moderate but unquantified weight loss. Notably, classical symptoms associated with MTC such as episodic flushing or chronic diarrhea were absent.

Initial cervical computed tomography (CT) imaging suggested a diagnosis of thyroiditis, and the patient received conservative symptomatic management. However, follow-up CT imaging revealed the development of a compressive goiter with significant airway narrowing. Despite intensified medical treatment, the patient's respiratory symptoms continued to worsen, ultimately necessitating urgent surgical intervention.

On July 29, 2024, the patient underwent emergency total thyroidectomy, tracheostomy placement, and left cervical lymph node dissection. Intraoperative frozen section analysis suggested either papillary or medullary carcinoma, prompting comprehensive lymph node sampling. Definitive histopathological examination confirmed medullary thyroid carcinoma with extracapsular extension, and involvement of cervical lymph nodes. Immunohistochemical staining were consistent with MTC, including positive staining for calcitonin and chromogranin A.

Postsurgical clinical examination revealed a stable patient with WHO performance status 0, functioning tracheostomy, and two palpable jugulocarotid lymph nodes. Of particular clinical significance, the patient exhibited markedly thickened lips, a distinctive dysmorphic feature that raised concern for an underlying genetic syndrome.

Postoperative biochemical evaluation showed markedly elevated serum calcitonin levels (>5000 pg/mL) and elevated carcinoembryonic antigen (CEA: 25.8 ng/mL; normal <3.0 ng/mL), while thyroid hormone levels remained within normal ranges following thyroid hormone replacement therapy.

Thoraco-abdominopelvic CT identified multiple bilateral pulmonary nodules highly suspicious for metastatic disease. Subsequent positron emission tomography-computed tomography (PET-CT) confirmed moderate postoperative hypermetabolism in the cervical operative region, while the pulmonary micronodules appeared non-hypermetabolic but remained morphologically suspicious for metastases, based on size and distribution patterns. Brain magnetic resonance imaging (MRI) was normal.

Genetic testing specifically targeting RET exon 11 mutations was performed and returned negative, arguing against MEN 2A. However, this targeted analysis did not rule out MEN 2B or other potential RET mutations in alternative exons. Biochemical evaluation successfully excluded pheochromocytoma (normal plasma and urinary metanephrines) and hyperparathyroidism (normal serum calcium and parathyroid hormone levels), further supporting a sporadic MTC diagnosis rather than a hereditary MEN syndrome.

Treatment and Follow-Up

Following the confirmation of metastatic MTC, systemic therapy was indicated. Given that conventional chemotherapy has limited efficacy in MTC and considering the advanced stage of the disease, the multidisciplinary tumor board decided to initiate targeted therapy with selpercatinib, a selective RET inhibitor, at a dose of 40 mg twice daily (80 mg/day total), in accordance with recent pediatric guidelines for advanced or metastatic RET-mutant MTC. The patient also received levothyroxine at 125 µg per day for thyroid hormone replacement. The patient tolerated both treatments well, and his clinical condition has remained stable over a follow-up period of six months. At each control visit, there have been no new symptoms or evidence of clinical deterioration.

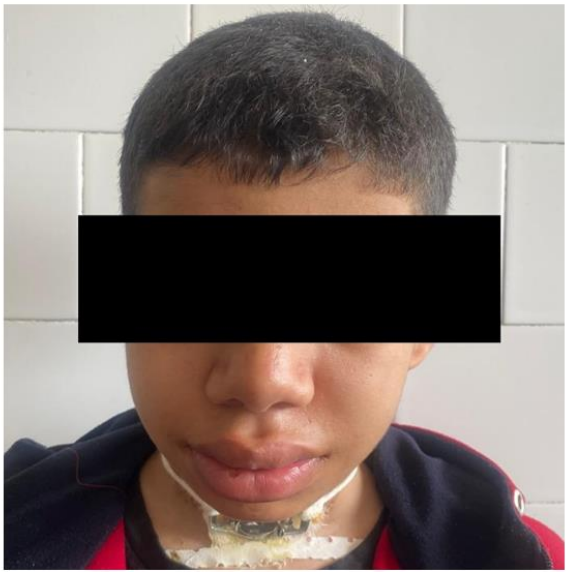

Figure 1: Thick lips in the context of multiple endocrine neoplasia type

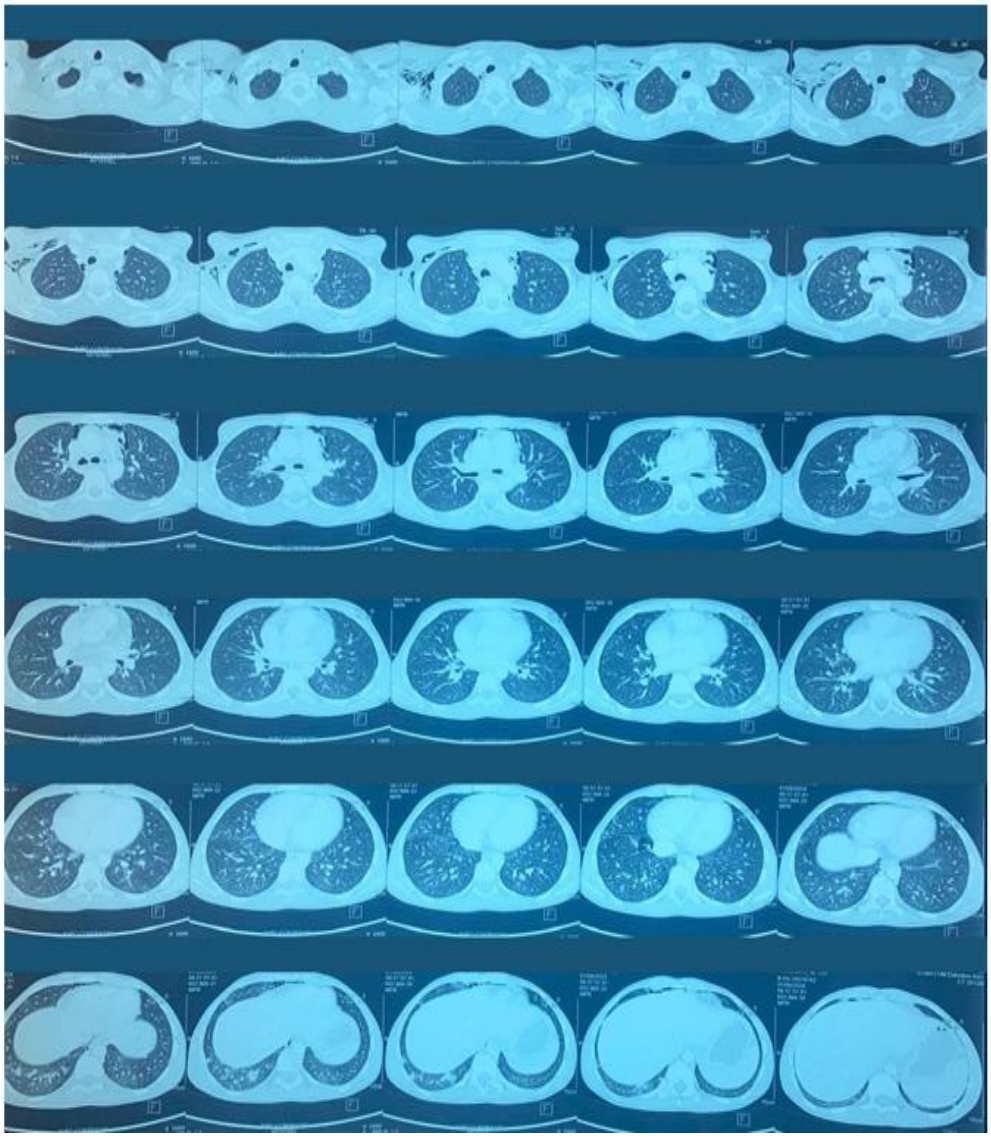

Figure 2: Chest CT scan: presence of pulmonary metastases at the time of diagnosis

3. DISCUSSION

MTC in children is uncommon and is usually linked to genetic syndromes, particularly MEN 2A and MEN 2B. These forms are typically caused by activating mutations in the RET proto-oncogene. Sporadic MTC is less frequent in the pediatric population and tends to present at a more advanced stage with a poorer prognosis. The absence of family history across three generations, combined with negative RET exon 11 testing, strongly suggests a sporadic form of MTC in our patient.

RET mutations are most commonly found in exons 10, 11, 13, 14, 15, and 16. Mutations in exon 11, especially at codon 634, are commonly related to MEN 2A, whereas MEN 2B is predominantly associated with mutations in exon 16 (codon 918) (3,10). In our case, RET exon 11 was negative, arguing against MEN 2A; however, this does not exclude MEN 2B or rare mutations in other exons. The presence of thickened lips raised suspicion for MEN 2B, which is characterized by mucosal neuromas, marfanoid habitus, and early-onset MTC. Therefore, expanded genetic analysis remains advisable.

Endocrine assessment ruled out pheochromocytoma and hyperparathyroidism, further supporting a sporadic diagnosis. Still, periodic screening of at-risk family members should be considered.

The clinical course in our patient illustrates several important aspects of pediatric sporadic MTC. The initial presentation with respiratory symptoms rather than a palpable thyroid nodule is not uncommon in advanced cases, where local invasion and compression can predominate over discrete mass effects. The progression from cough to dyspnea and dysphagia over several months reflects the aggressive nature of sporadic MTC in children, who typically present with larger

tumors and more advanced disease stages compared to hereditary cases[8].

Serum calcitonin and CEA are sensitive markers for MTC diagnosis and monitoring [11]. Our patient had very high calcitonin levels postoperatively, consistent with metastatic disease.

The imaging findings in the present case illustrate key diagnostic challenges in pediatric MTC. While PET-CT demonstrated postoperative hypermetabolism in the neck, the pulmonary metastases appeared non-hypermetabolic despite being morphologically suspicious. This observation underscores the limitation of FDG-PET in detecting all MTC metastases, as these tumors may exhibit variable glucose metabolism. The reliance on morphological characteristics rather than metabolic activity for identifying pulmonary metastases emphasizes the need for comprehensive follow-up imaging protocols, even in the absence of significant FDG uptake.

Surgery remains the primary treatment for MTC, and complete resection offers the only potential for cure [9]. In our case, the emergency nature of the procedure, necessitated by airway compromise, may have limited the extent of surgical resection, as evidenced by the persistently elevated tumor markers postoperatively.

In metastatic cases, surgery is rarely curative, and systemic therapy may be required. Traditional chemotherapy offers limited benefit. Recent trials support the use of tyrosine kinase inhibitors (TKIs) such as vandetanib and cabozantinib, which target RET and VEGFR. These two oral agents are now approved by the U.S. Food and Drug Administration (FDA) for patients with progressive advanced MTC, following phase III studies that demonstrated a prolongation of progression-free survival of adult patients. Nonetheless, it is important to highlight that these therapies do not significantly improve overall survival, and the response to therapy varies significantly[12–14]. More recently, selpercatinib received full FDA approval for use in both adults and children (aged ≥2 years) with advanced or metastatic RET-mutant medullary thyroid carcinoma (MTC). This approval was supported by results from the phase III LIBRETTO-531 trial, which demonstrated a notable improvement in progression-free survival compared to conventional therapies[15].

Although EBRT is not commonly recommended for the treatment of MTC, it has been shown to improve locoregional control in patients with unfavorable prognostic factors that indicate a high likelihood of recurrence after surgery. EBRT may also play a role in palliation or local control of unresectable disease, and it can be considered in cases of locoregional recurrence or symptomatic bone metastases [16,17]. In the context of our patient's presentation with local invasion and airway compromise, adjuvant radiation therapy might be considered as part of a comprehensive treatment approach.

The management of pediatric sporadic MTC requires a multidisciplinary approach, involving pediatric endocrinologists, oncologists, surgeons, and genetic counselors. Despite the absence of family history, genetic counseling remains important for the patient and family, particularly given the phenotypic features suggestive of MEN 2B. If expanded genetic testing reveals a RET mutation, family screening protocols would need to be implemented.

Long-term surveillance should include regular biochemical monitoring with serum calcitonin and CEA levels, cross-sectional imaging to assess for disease progression, and monitoring for potential late effects of treatment. The relatively favorable long-term outcomes reported for pediatric sporadic MTC, with 10-year overall survival rates of 93%, provide cautious optimism, although individual outcomes depend heavily on disease stage at presentation and response to treatment.

4. CONCLUSION

This case illustrates a rare presentation of sporadic MTC in a child with pulmonary metastases and atypical clinical features. It emphasizes the need for early clinical suspicion, the role of tumor markers and imaging in disease staging, and the importance of genetic testing even in seemingly sporadic cases. Long-term follow-up and genetic counseling are recommended for the patient and family.

5. Ethical Considerations

Written informed consent was obtained from the patient's parents for the publication of this case report, including the use of any accompanying images. The authors affirm that they have respected the patient's right to privacy and confidentiality.

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