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Metastatic Medullary Thyroid Cancer (MTC) in Children

Ilham Midhat[1*], Hanan Boualam[1], Sana Rafi[1], Sara Ijdda[1], Ghizlane EL Mghari Tabib[1], Nawal EL Ansari[1]

[1]Department of Endocrinology, Diabetology, Metabolic Diseases and Nutrition CHU Mohammed VI, Marrakech, Morocco

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***Corresponding author:** Ilham Midhat
Department of Endocrinology, Diabetology, Metabolic Diseases and Nutrition CHU Mohammed VI, Marrakech, Morocco

Abstract | **Case Report**

Medullary thyroid carcinoma (MTC) in children is a rare tumour, accounting for approximately 5% of paediatric thyroid cancers. In more than 95% of cases, it occurs in a hereditary context related to a germline mutation of the RET gene, observed in MEN 2A, MEN 2B syndromes or in familial forms of MTC. We report a rare case of metastatic MTC in a 13-year-old child, revealed by a compressive goitre. The initial assessment showed a very high preoperative calcitonin level. The patient underwent a total thyroidectomy with targeted removal of the most suspicious lymph nodes, as a complete cervical lymph node dissection could not be performed due to significant adhesions. Pathological examination confirmed the diagnosis of MTC. Staging revealed distant metastases. Genetic analysis, however, did not find any RET proto-oncogene mutations. Treatment will be discussed at a multidisciplinary meeting in order to define the most appropriate and personalised strategy for this patient.

Keywords: Medullary Throid Carcinome (MTC), Children, Multiple Endocrine Neoplasia (MEN), RET Mutation, Calcitonin – Thyroidectomy, Metastatic Disease, Targeted Therapy, Prognosis.

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumour originating from the parafollicular C cells of the thyroid gland. It accounts for approximately 5% of thyroid cancers in children [1, 2]. Though MTC may be either sporadic or inherited, in children, over 95% of MTC is hereditary, as part of the multiple endocrine neoplasia (MEN) syndromes MEN 2A and 2B, and the related variant familial MTC. Early identification and treatment of CMT in these hereditary syndromes, before extrathyroidal extension, determines the prognosis [3].

This article presents a rare case of metastatic MTC in a child revealed by a compressive goitre, illustrating the challenges of diagnosis and, more particularly, management of this condition.

CASE REPORT

A 13-year-old patient with no significant medical history, presented with dyspnoea, associated with dysphagia and dysphonia, with a rapidly progressing goitre over the previous four months, which became life-threatening one day before admission to the emergency department, without flush syndrome, developing in the context of a deterioration in general health.

A cervical CT scan **(Figure 1)** with ultrasound revealed a goitre due to compressive thyroiditis with reduction of the tracheal lumen and probable circumferential subglottic oedema and jugular carotid and submandibular lymph nodes. Calcitonin was 2000 pg/ml and thyroid function tests were normal.

The patient was rushed to the operating room for a total decompressive thyroidectomy with lymph node dissection of the most accessible adenopathies, due to the difficulty of cervical lymph node dissection caused by diffuse adhesions in the cervical region, followed by a tracheotomy.

The extemporaneous pathological examination revealed a tumour focus with cell clusters and cytonuclear atypia suggestive of solid papillary carcinoma or medullary carcinoma, and the histopathological study revealed malignant tumour proliferation infiltrating the thyroid parenchyma, with a morphological appearance suggestive of medullary carcinoma of the thyroid, with vascular emboli, perineural involvement, extra-thyroid extension and lymph node metastasis with capsular breach, with anti-

cacitonin antibodies; anti-TTF1 and anti-CK19 positive on immunohistochemical complement.

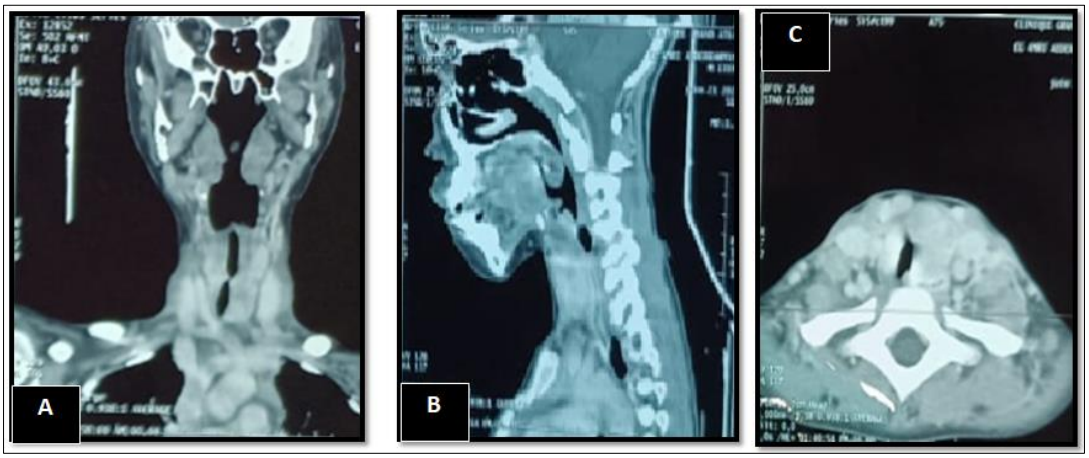

Figure 1: Cervical CT scan with frontal (A), sagittal (B) and axial (C) slices showing a goitre on thyroiditis with reduction of the tracheal lumen and probable subglottic oedema with jugular carotid and submandibular lymph nodes

A thoraco-abdominal-pelvic computed tomography CT scan was performed as part of the staging assessment, revealing multiple suspicious intraparenchymal nodules that may be secondary in origin, complemented by an 18-FDG PET (positron emission tomography) scan **(Figure 2)** showing moderate diffuse hypermetabolism in the ENT region, more pronounced in the left paramedian cervical region, consistent with post-surgical inflammatory changes. However, residual disease cannot be ruled out, associated with bilateral lateral cervical microlymph nodes, moderately hypermetabolic, suspicious in this context; to be monitored, and multiple bilateral pulmonary micronodules, non-hypermetabolic, suspected of secondary involvement, with no other suspicious hypermetabolic foci in the rest of the explored volume. The MEN's work-up was normal.

Genetic analysis did not reveal the C634 mutation of the RET proto-oncogene in exon 11, and a family investigation is underway.

Therapeutic management will be discussed at a multidisciplinary consultation meeting (MCM) attended by specialists in endocrinology, nuclear medicine, oncology and ENT, in order to determine the most appropriate and personalised strategy for the patient.

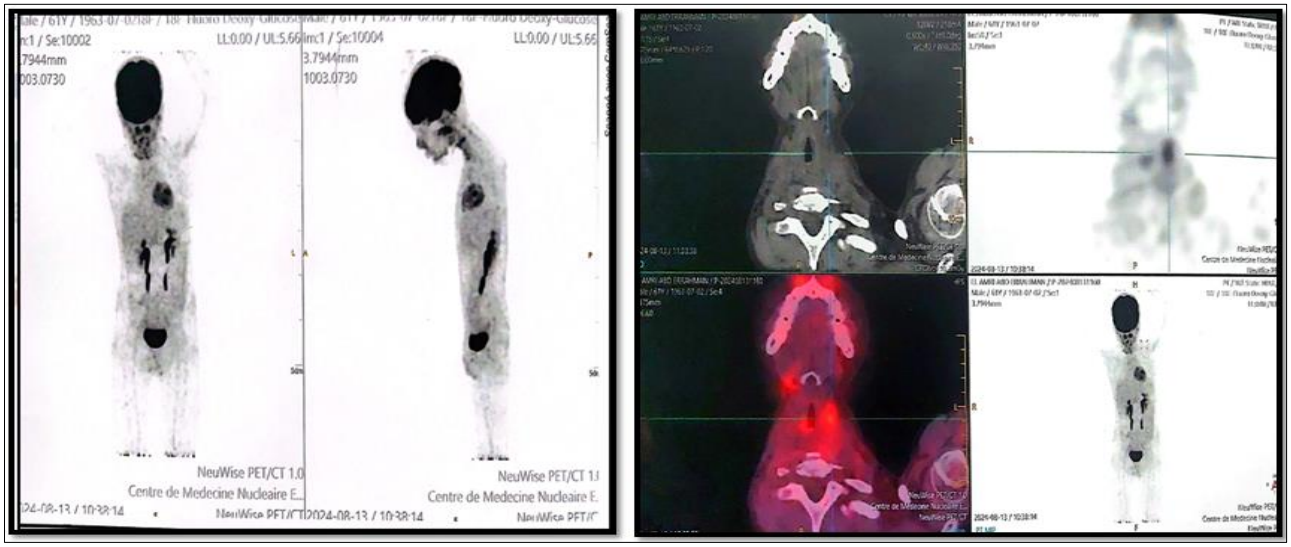

Figure 2: 18-FDG PET (positron emission tomography) scan showing moderate diffuse hypermetabolism in the ENT region, more pronounced in the left paramedian cervical region, consistent with post-surgical inflammatory changes. However, residual disease cannot be ruled out, associated with bilateral lateral cervical microlymph nodes, moderately hypermetabolic, suspicious in this context, and multiple bilateral pulmonary micronodules, non-hypermetabolic, suspected of secondary involvement

DISCUSSION

Thyroid cancer is the most common endocrine malignancy in children, accounting for approximately 1.5% of all malignant thyroid tumours, with an incidence in children under 15 years of age of 2 per 1 million people, and the incidence of MTC accounts for 2–8%. These data are consistent with our clinical case, the age of the patient was 13 years old [3].

MTC is rarely detected at the clinical stage, as it mainly involves hereditary forms that are diagnosed at the preclinical stage. Cases diagnosed at the clinical stage are generally RET gene mutations, and are revealed by a thyroid nodule with euthyroidism or a multinodular goitre, most often associated with cervical lymph node involvement (70%), and some (15%) may even present with symptoms of upper aerodigestive tract compression [4, 5].

Approximately 5-10% of patients with MTC develop distant metastases to the liver, lung, bone, brain and skin [6, 7]. Patients with familial MTC may experience systemic symptoms resulting from excessive secretion of hormones by the tumour, including calcitonin and its associated peptides, leading to flushing and diarrhoea [4 - 5]. Patients may also present with manifestations of MEN syndrome [8, 9]. In the case of our patient, metastases were detected in the lymph nodes and liver, which is consistent with the results reported in the published literature.

Initial evaluation of thyroid nodules should include ultrasound, as certain images are associated with different risks of malignancy and, in addition to the size of the nodule, determine the need for thyroid puncture (FNA) [10, 11].

The American Thyroid Association (ATA) strongly recommends FNA for nodules of 1 cm or more that are highly suspicious or moderately suspicious on ultrasound [7, 8]. Preoperatively, ultrasound can determine the need for and nature of lymph node dissection. Our patient did not undergo FNA, because he was admitted in a critical respiratory distress state.

When serum calcitonin levels exceed 500 pg/mL, the probability of metastasis increases significantly, warranting additional imaging tests. These include cervical ultrasound thoracic CT, abdominal CT or magnetic resonance imaging (MRI), and bone scintigraphy [5-12].

The main treatment of MTC is primarily based on complete surgical resection with lymph node dissection. However, patients with extensive metastatic disease that cannot be treated curatively by surgery or radiotherapy, targeted systemic therapies are becoming a major treatment option. Targeted therapies and immunotherapy are emerging approaches in metastatic MTC and have been shown to significantly improve progression-free survival. Nevertheless, their efficacy remains partial, highlighting the need for complementary therapeutic approaches [13,14].

Immunotherapy is another promising strategy, aimed at enhancing the anti-tumour immune response through the administration of therapeutic antibodies. Patients who do not respond to RET pathway inhibitors or other molecular therapies may be candidates for cytotoxic chemotherapy or biological agents [13, 14]. Furthermore, according to ATA recommendations, adjuvant external radiotherapy may be considered in patients at high risk of local recurrence or who have had incomplete resection [15, 16].

Finally, precision medicine, based on advanced genetic and transcriptomic analyses, could transform the management of CMT. For example, the identification of biomarkers predictive of response to targeted therapies or immunotherapy would make it possible to personalise treatments and optimise clinical outcomes.

In the diagnostic workup of MTC, germline RET testing is mandatory for all patients. When a RET mutation is identified, or when genetic results are expected to be delayed, it is crucial to exclude pheochromocytoma and primary hyperparathyroidism (PHPT) prior to surgery [6].

MTC shows exceptionally high penetrance in MEN 2 syndromes, with 70–100% of mutation carriers developing the disease before the age of 70. The strong genotype–phenotype correlation characteristic of these syndromes allows clinicians to anticipate the likely age of onset based on the specific RET mutation involved. Accordingly, the ATA risk classification system stratifies mutations according to the expected timing of MTC development. In MEN 3, MTC represents the primary cause of mortality and is marked by a highly aggressive course. Survival outcomes at 10 years are significantly poorer than in MEN2, largely due to its very early onset and the advanced stage at which it is often diagnosed.

Nowadays RET genetic screening allows the identification of RET mutated gene carriers shortly after birth or during pregnancy, and an early prophylactic thyroidec tomy can definitively cure the patient. This is less likely for children affected by MEN2B since these cases are usually caused by de novo RET mutations and no familial history of MTC is present. The MEN2B children still arrive late at diagnosis, often with distant metastases already present but, fortunately, it has recently been demonstrated that vandetanib can be successfully used also in children as well as in adults [6].

CONCLUSION

Metastatic MTC in children is an extremely rare condition, most often identified in a familial context, particularly in the MEN syndrome. It remains a complex condition to manage, characterised by a reserved prognosis and limited treatment options. Targeted therapies have prolonged progression-free survival, but their efficacy is hampered by the emergence of resistance mechanisms and sometimes restrictive tolerance. Future prospects are based on the development of innovative strategies, including immunotherapy, combination approaches and the integration of precision medicine, in order to optimise therapeutic response and improve clinical outcomes.

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