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Metastatic Medullary Thyroid Carcinoma: Current Situation and Outlook

F-Z. El Jaafari[1*], S. Ijdda[1], S. Rafi[1], G. El Mghari[1], N. El Ansari[1]

[1]Department of Endocrinology, Diabetology, Metabolic Diseases, and Nutrition Mohammed VI University Hospital, Marrakech

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***Corresponding author:** F-Z. El Jaafari
Department of Endocrinology, Diabetology, Metabolic Diseases, and Nutrition Mohammed VI University Hospital, Marrakech

Abstract **Original Research Article**

***Introduction*:** Medullary thyroid carcinoma (MTC) is a rare thyroid cancer, accounting for 1-2% of cases. While localized MTC has a good prognosis, metastatic MTC presents significant treatment challenges. This study explores diagnostic approaches, treatment options, and future perspectives for managing metastatic MTC. ***Materials and Methods*:** A retrospective study was conducted on 7 patients with metastatic MTC diagnosed between 2020 and 2024 at the Mohammed VI University Hospital. Diagnosis was confirmed through elevated calcitonin levels and histopathology. Imaging and biopsies identified metastases. Treatments included surgery, radiotherapy, chemotherapy, and targeted therapy. ***Results*:** The mean age of patients was 52 years, with lymph node (71.4%) and lung (71.4%) metastases being most common. Treatment involved surgery, with adjuvant therapies in select cases. Two recurrences were noted. ***Discussion*:** MTC is primarily sporadic but can be familial, often linked to MEN syndromes. Early diagnosis is based on elevated calcitonin and imaging. Targeted therapies and immunotherapy show promise but face challenges like resistance. Precision medicine offers future potential for personalized treatment. ***Conclusion*:** Metastatic MTC remains difficult to treat, but targeted therapies and emerging treatments like immunotherapy and precision medicine offer hope for better outcomes.

Keywords: Medullary Thyroid Carcinoma, Metastatic MTC, Targeted Therapy, Calcitonin, Surgery, Radiotherapy, Precision Medicine, Immunotherapy.

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumour arising from thyroid parafollicular cells (C cells), which are responsible for the production of calcitonin. It accounts for around 1 to 2% of thyroid cancers and is frequently associated with genetic mutations, particularly in the RET gene. Although the prognosis of localised cases is good, metastatic forms affecting sites such as lymph nodes, liver, lungs and bone present significant therapeutic challenges [1-3].

This article aims to explore diagnostic approaches, therapeutic options and future perspectives for the management of metastatic CMT.

MATERIAL AND METHODS

This is a retrospective study of a cohort of 7 patients diagnosed with metastatic CMT between 2020 and 2024, hospitalised at the endocrinology, diabetology and metabolic diseases department of the Mohammed VI University Hospital in Marrakech. Clinical, biological, radiological and histopathological data were collected from medical records.

The diagnosis of CMT was confirmed by elevated serum levels of calcitonin (>100 pg/mL) and carcinoembryonic antigen (CEA), combined with histopathological findings. Metastases were identified by imaging (CT, MRI, PET scan, Octreoscan, scintigraphy) and/or biopsy.

Treatments included surgical approaches, radiotherapy, chemotherapy and targeted therapy.

RESULTS

Of the 7 patients, 57.14% were female, with a mean age of 52 years (range: 32-78 years). Initial symptoms were mainly compressive signs in 57.14% of patients, with dyspnoea and dysphagia, bone pain in 28.6% of patients and flush syndrome in 14.28% of patients. A nodular goitre was found in 85.7% of patients, and an isolated thyroid nodule in 14.3%. Lymph

node and lung metastases were present in 71.4% of patients, and bone metastases in 28.6%, but liver metastases were not found in our patients.

A pheochromocytoma associated with CMT in the context of NEM 2B was found in only one patient.

Treatment consisted of surgery in all patients, combined with radiotherapy in 3 patients, targeted tyrosine kinase therapy in 2 patients, and chemotherapy in 2 patients because the tumour was unresectable.

Anatomopathological studies showed CMT with lymph node metastases in 5 patients, and vascular emboli in 2 patients.

Genetic studies were not performed in any of our patients, as they were not available at our hospital.

Two cases of recurrence were noted.

DISCUSSION

Medullary thyroid carcinoma (MTC) is a rare tumour that accounts for less than 5% of thyroid cancers, with an estimated annual incidence of around 350 new cases in France [4]. It can occur in two main forms: sporadic, accounting for around 75% of cases, and familial, accounting for around 25% of cases, often associated with syndromes such as multiple endocrine neoplasia type 2 (MEN2) [5]. The male-to-female ratio of CMT is slightly skewed in favour of females, with a ratio of approximately 1.5:1 (female to male) [4]. This is consistent with our research, where we have noted a predominance of females.

The mean age at diagnosis of CMT is approximately 50 years [6]. However, specific information on the mean age at diagnosis of patients with metastatic CMT is limited, making it difficult to determine the exact mean age of patients with metastatic CMT. The mean age in our study was 52 years.

Most patients with sporadic CMT present with solitary thyroid nodules, most often located in the upper lobe because C cells predominate in this region [11, 12]. At the time of presentation, most patients (70%) have cervical lymph node involvement, and some (15%) may even present with symptoms of upper aerodigestive tract compression [11, 12].

Approximately 5-10% of patients with CMT develop distant metastases to the liver, lung, bone, brain and skin [13, 14]. Patients with familial CMT may experience systemic symptoms resulting from excessive secretion of hormones by the tumour, including calcitonin and its associated peptides, leading to flushing and diarrhoea [11, 12]. Patients may also present with manifestations of NEM syndrome [15, 16]. In our study, lymph node and lung metastases were the most common.

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) [7-10].

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 fine aspiration.

If serum calcitonin is greater than 500 pg/mL, metastases are more likely and further imaging is recommended. Recommended imaging studies include cervical ultrasound, thoracic computed tomography (CT), abdominal CT or magnetic resonance imaging, or bone scintigraphy [12-17].

The main treatment for CMT is surgical resection combined with lymph node dissection. However, patients with extensive metastatic disease that cannot be treated by surgery or radiotherapy alone are candidates for targeted therapy. Targeted therapies and immunotherapy are both emerging therapies for patients with metastatic MTC, and have shown significant efficacy in prolonging progression-free survival, but this efficacy remains limited, highlighting the need for complementary treatment strategies [3-19].

Immunotherapy is another promising treatment modality for thyroid cancer patients and involves the use of immunoglobulin-based therapies to boost the patient's immunity to the cancer. Patients who do not respond to targeted therapy are candidates for cytotoxic chemotherapy or biological agents [3-19]. According to the ATA, adjuvant external radiotherapy may be considered in patients at high risk of recurrence or who have undergone incomplete resection of CMT [1-18].

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.

CONCLUSION

Metastatic medullary thyroid carcinoma remains a complex disease with a guarded prognosis and major therapeutic challenges. Targeted therapies, although effective in prolonging progression-free survival, have limitations linked to the emergence of resistance and sometimes difficult tolerance. The future of treatment lies in the development of innovative strategies, such as immunotherapy, combination therapies and the integration of precision medicine.

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