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Medullary Thyroid Carcinoma

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Abstract **Original Research Article**

Medullary thyroid carcinoma is a rare malignant tumor of the thyroid. An early diagnosis is associated with a better prognosis. Calcitonin is the cornerstone of diagnosis. In this study, we will discuss the clinical and evolutionary characteristics of this condition through a retrospective study of thirty-three patients over a period of seven years between January 2013 and December 2019. Our study includes 33 patients, comprising 12 men and 21 women with a sex ratio of 0.57. The average age of our patients is 45 years. A family history of similar cases was present in six patients (18%). As for the circumstances of discovery in our study, all our patients consulted for a cervical swelling (100%). Seven patients (20%) presented with signs suggestive of malignancy (dysphonia), and fourteen patients (40%) had lymphadenopathy at the time of diagnosis. Calcitonin levels were measured preoperatively in eighteen patients with a very high recurrence rate (60%). Cervical lymph node metastases were present in 40% of cases (fourteen patients). Total thyroidectomy was performed in all patients in our series. It was performed initially in 70% of cases. For patients who initially underwent partial thyroidectomy, we performed totalization regarding the other thyroid lobe. Lymph node dissection was performed in 60% of cases. Radiotherapy was indicated for all patients in our series except for the two patients with normal postoperative calcitonin levels. Close surveillance was the therapeutic choice for these patients. MTC remains a relatively rare tumor. It mainly affects young adults and mainly manifests as an isolated thyroid nodule. It is a lymphophilic tumor, and lymph node involvement is very early. Calcitonin is the basis of preoperative diagnosis. It guides the stage of the disease, helps to guide surgery, constitutes a key element of follow-up, and is considered an important prognostic factor for survival. Despite advances in targeted therapy, complete surgical resection remains the only curative treatment.

Keywords: Tumeur Rare, Traitement Chirurgicale, Calcitonine.

INTRODUCTION

Medullary Thyroid Carcinoma (MTC) is a rare malignant tumor that accounts for 5 to 10% of thyroid cancers [1]. It is a neuroendocrine tumor that develops from the parafollicular C cells responsible for calcitonin secretion. It presents in two forms, sporadic and familial, either isolated or as part of multiple endocrine neoplasia type 2 (MEN2). Early diagnosis is associated with a better prognosis. In this study, we will explore the clinical and evolutionary characteristics of this condition through a retrospective analysis of thirty-three patients over a period of seven years from January 2013 to December 2019.

RESULTS

Our study includes 33 patients, comprising 12 men and 21 women, with a sex ratio of 0.57. The average age of our patients is 45 years. A family history of similar cases was present in six patients (18%). Thirty-six percent of patients in our series underwent surgery for pheochromocytoma. As for the circumstances of discovery in our study, all our patients consulted for a cervical swelling (100%). Twenty-one percent of patients presented with signs suggestive of malignancy (dysphonia), and forty-two percent presented with cervical swelling with lymphadenopathy. Cervical ultrasound was performed in thirty-two patients. A cervical CT scan was performed initially in one patient presenting with a plunging goiter. Fifty-three percent had nodules classified as TIRADS 5, twenty-eight percent had TIRADS 4 nodules, ten nodules were classified as TIRADS 4, and nineteen percent of patients had nodules classified as most likely benign lesions (TIRADS 3). Calcitonin levels were measured preoperatively in twenty patients, showing very high levels in sixty percent of cases. To assess tumor extension, cervical ultrasound, thoracic CT scan, and abdominal ultrasound/MRI were

systematically performed in all patients, revealing cervical lymph node metastases in 60% of cases, mediastinal lymph node metastases in 20% of cases, two patients with pulmonary metastases, and hepatic metastases observed in only one case. Total thyroidectomy was performed in all patients in our series, with 60% performed initially. For patients who initially underwent total thyroidectomy, totalization regarding the other lobe was performed. Lymph node dissection was performed in 60% of cases whenever cervical lymphadenopathy was detected clinically or radiologically. In 40% of cases, the postoperative calcitonin level was normal after total thyroidectomy; therefore, no surgical reoperation for lymph node dissection was performed, and monitoring of calcitonin levels was proposed. Radiotherapy was indicated for all patients in our series except for those with normal postoperative calcitonin levels. Close surveillance was the therapeutic choice for these patients. Over a five-year follow-up, cure was observed in 70% of cases, partial response in 26% of cases, and death occurred in 4% of cases.

DISCUSSION

MTC is a rare neuroendocrine tumor that presents in two forms, sporadic and familial, either isolated or as part of multiple endocrine neoplasia type 2 (MEN2).

Patient history is a crucial step in the diagnosis. It seeks evidence supporting the malignancy of the nodule and the familial nature of the tumor. Specific signs of medullary carcinoma and paraneoplastic syndrome are also investigated during history taking (flush, motor diarrhea). Cervical examination helps characterize the thyroid tumor and search for lymph node metastases. Medullary thyroid carcinoma is highly lymphophilic, with lymph node invasion being very common and early. Lateral lymph nodes seem to represent the barrier between local and systemic disease, with contralateral involvement indicating systemic disease [1]. In our series, lymphadenopathy is present at the time of diagnosis in 30% of cases.

A general examination searches for distant metastases. They reveal MTC in less than 10% of cases and are mainly located in the lung, liver, bones, and less frequently in the brain and skin. They almost never occur in the absence of lymph node metastases. They are correlated with calcitonin and CEA values. Diagnosis is often guided by a significant elevation in baseline calcitonin. Rare metastatic sites have been described in the literature. Kazakai *et al*., [2], reported a case of breast metastasis. In our series, metastases are present in the initial clinical presentation in 40% of cases.

Calcitonin measurement is a cornerstone in the management of medullary thyroid carcinoma (MTC), serving three key purposes: screening, diagnosis, and therapy. [2].Calcitonin plays a pivotal role in MTC screening. A recent 2020 Cochrane review assessed calcitonin screening rates in over 72,000 patients with thyroid nodules. The prevalence of MTC was found to be 0.32%, with calcitonin demonstrating a sensitivity of 83-100% and a specificity of 94-100% in detecting MTC [3]. Additionally, a study by Francesca Torresan *et al*., compared outcomes before and after the implementation of routine preoperative serum calcitonin screening in patients with sporadic MTC. They observed a significant decrease in tumors with lymph node involvement and a notable increase in the cure rate following the introduction of serum calcitonin screening [4]. Thus, systematic calcitonin screening proves sufficiently sensitive for MTC detection, enabling early diagnosis, superior therapeutic outcomes compared to symptomatic cases, and a more favorable prognosis.

However, it's important to acknowledge potential drawbacks of a screening program, such as numerous false positives and unnecessary surgeries. In 2009, the European Thyroid Association (ETA) appeared to revise its stance from 2006 and now recommends calcitonin screening only in the presence of clinical risk factors. Similarly, the American Thyroid Association (ATA) no longer advocates for routine testing, suggesting it only for suspicious lesions.These guidelines reflect a balanced approach, weighing the benefits of early detection against the risks of overdiagnosis and overtreatment, underscoring the importance of individualized risk assessment in MTC management.

Calcitonin constitutes a highly sensitive tumor marker for MTC (medullary thyroid carcinoma); it is more sensitive than cytology in the diagnosis of this pathology, but its specificity is not absolute. Hypercalcitoninemia may be observed in other pathologies (renal failure, prostate, breast, lung cancers, and bronchial and digestive endocrine tumors). Stimulation tests have been used for differentiation between MTC and other etiologies. The usefulness of these stimulation tests is questioned as they did not improve diagnostic accuracy [1-5]. However, Fugazzola *et al*., still advocate for the use of stimulated calcitonin in patients with nodular thyroid disease and basal calcitonin of 10 to 100 pg/mL [6].

The value of basal calcitonin may be correlated with the stage of the disease. Values <10 pg/mL are reassuring for the absence of C-cell pathology. Patients with homolateral cervical metastatic disease have a basal calcitonin of at least 20 pg/mL. The involvement of contralateral central lymph nodes is correlated with a basal calcitonin level of at least 50 pg/mL, while contralateral lateral lymph nodes are found in patients with a calcitonin level of at least 200 pg/mL [3]. A basal calcitonin above 500 pg/mL suggests metastatic disease [5]. Calcitonin also has prognostic value. In addition to its sensitivity to MTC, calcitonin can also be considered a prognostic factor. Statistical analyses have revealed a

correlation between baseline calcitonin levels, tumor size, stage, and tumor morbidity. A recent follow-up study of 1026 patients with MTC showed that when calcitonin levels are ≥500 pg/mL, only 50% of patients achieve biochemical cure; all distant metastases were observed in patients with baseline calcitonin at this level or higher. No patient was cured at a preoperative calcitonin level >10,000 pg/mL [5-9]. Calcitonin doubling time allows monitoring of recurrence, progression, and prediction of MTC survival. Barbet et al. found in a multivariate analysis that calcitonin doubling time and carcinoembryonic antigen (CEA) are independent risk factors for survival. When calcitonin doubling time was <0.5 years, 5-year survival was 25%. However, when calcitonin doubling time was >2 years, 100% of patients were alive at 10 years [7].

The medullary thyroid carcinoma (MTC) is also accompanied by an elevation of carcinoembryonic antigen (CEA) in more than half of cases. It is a tumor marker that primarily has prognostic significance in the management of this pathology. The ATA recommends measuring CEA at baseline and at least every 6 months [8]. CEA measurement also helps determine the stage of the disease. According to Machens *et al*., an increase in CEA indicates an advanced stage of the disease. CEA values above 30 micrograms/mL were associated with contralateral lymph node metastases. A CEA level above 100 micrograms/mL was correlated with distant metastases [5-9]. CEA measurement also has prognostic value. A meta-analysis revealed that CEA doubling time had a higher predictive value than calcitonin doubling time, and measuring both is recommended in MTC follow-up [3].

Ultrasound is the imaging modality of choice for patients suspected of MTC and is associated with a sensitivity of 75.3%, specificity of 93.1%, and overall accuracy of 80.4% [3]. The ultrasound criteria from the 2015 ATA guidelines on thyroid nodules to predict malignancy work well in MTC and may also have prognostic implications [10-12]. However, 28% of MTC cases may present with low-risk ultrasound characteristics [13]. On the other hand, a study by Matrone *et al*., suggests that MTC may have a different ultrasound appearance from that of differentiated thyroid cancer and that current risk stratification systems may not identify MTC. The suggestive characteristics of MTC are limited due to the relative rarity of the disease [5-14].

The PET scan, although its role in initial surgery is not established, has been well studied for assessing recurrence. The ATA and NCCN guidelines do not recommend it for detecting distant metastases due to reduced sensitivity [8-15]. The 2020 guidelines from the European Association of Nuclear Medicine (EANM) recommend the use of 18F-DOPA PET/CT in the context of persistent/recurrent MTC and in cases of suspected distant metastases [5]. The ESMO guidelines recommend F-DOPA-PET/CT, if available, in patients with elevated serum calcitonin levels (≥ 500 pg/mL) [16].

Thyroid fine-needle aspiration cytology can provide a preoperative diagnosis. However, its sensitivity in detecting MTC was only 56.4% in a meta-analysis of 15 studies involving 6411 MTC cases [17]. If fine-needle aspiration is inconclusive and there is doubt about MTC, measuring calcitonin in the aspirate washout samples and performing immunohistochemistry for calcitonin, CEA, and chromogranin (positive in MTC) and thyroglobulin (negative in MTC) can also be performed, increasing the cytology sensitivity to 89.2%. Despite these tests, a significant failure to make a correct diagnosis could still occur in nearly 44% of cases because the initial suspicion of MTC on cytology is not present. However, all these procedures remain cumbersome compared to the efficacy of serum calcitonin measurement, which is necessary anyway and has shown its superiority to cytology in suggesting the diagnosis [3].

RET gene analysis in MTC allows for the diagnosis of familial forms, presymptomatic diagnosis, and specific and early management of genetically at-risk relatives. ATA guidelines propose a mutation-based approach to choose the timing of prophylactic thyroidectomy [18-19]. However, it is not common practice to analyze M918T mutations in patients with sporadic MTC (ATA) [8]. The 2019 ESMO recommends optional somatic RET mutation testing for individualized targeted therapy if selective treatment with a RET inhibitor is planned for advanced MTC patients [16].

Intraoperative frozen section examination allows for a correct diagnosis in 88% to 100% of cases. Perioperative evaluation of frozen sections determines if the tumor exhibits desmoplastic stromal reaction (DSR) to guide surgical treatment. Medullary thyroid carcinomas with negative DSR typically do not have lymph node metastases, while DSR-positive tumors potentially have lymphatic spread. If a patient's intrathyroidal MTC is DSR-negative on frozen section, prophylactic lateral neck dissection is avoided. Therefore, in DSR-positive tumors with calcitonin levels >85 pg/ml (female) or >100 pg/ml (male), respectively, and/or clinically/radiologically positive lymph nodes, functional lateral neck dissection (levels II to IV) is recommended [1].

Surgical treatment is the cornerstone of managing medullary thyroid carcinoma (MTC). Complete surgical resection of the thyroid mass and locoregional metastases is the only curative option for locoregional MTC [16]. Surgery is scheduled only after ruling out associated pheochromocytoma, even in sporadic forms. Total thyroidectomy is necessary due to the constant bilaterality of lesions in familial forms and in 30% of sporadic cases. Total thyroidectomy is

accompanied by lymph node dissection, the specifics of which may vary among teams but are generally accepted due to MTC's particular lymphophilic nature.

In cases where the tumor is confined to the thyroid, the standard surgical treatment involves total thyroidectomy and bilateral central compartment neck dissection. Central compartment dissection in MTC patients has a higher cure rate than thyroidectomy alone [15]. Current guidelines from the ATA and NCCN recommend that patients with sporadic MTC confined to the thyroid gland, and without evidence of cervical or distant metastases by ultrasound examination and no distant metastases, undergo total thyroidectomy and bilateral central compartment dissection [8-15]. This may not be performed solely in patients with small intrathyroidal MTC and a preoperative calcitonin level below 20 pg/ml, as the risk of metastasis remains very low [16-20]. For lateral compartment dissection, in the presence of lymph node metastasis on ultrasound, total thyroidectomy with bilateral central compartment dissection and dissection of involved lymph node compartments is recommended [20]. In the absence of lymph node or distant metastases, there is no consensus on prophylactic lateral compartment dissection, as aggressive prophylactic lateral compartment dissection may lead to postoperative morbidity without benefiting survival [18].

Prophylactic homolateral compartmental neck dissection may be considered for tumors smaller than 1 cm if metastases are found in the central compartment or if calcitonin levels are higher than 20 pg/ml (ATA) [19]. The 2016 NCCN guidelines recommend that selective prophylactic neck dissection on the homolateral side be considered for patients with high-volume disease and positive central lymph nodes [15]. ESMO generally recommends total thyroidectomy with bilateral central compartment dissection and homolateral neck dissection at least at levels IIA, III, and IV if serum calcitonin levels are between 50 and 200 pg/mL in patients with negative cervical ultrasound. Prophylactic contralateral neck dissection may be considered in the presence of positive homolateral lymph nodes or a basal calcitonin level above 200 pg/mL (ATA and ESMO) [8-16].

In cases of locoregional disease without distant metastasis, surgical resection is the first therapeutic option with or without postoperative radiotherapy [16]. Total thyroidectomy with dissection of involved nodal compartments is recommended, but surgery should be palliative, aiming to preserve speech, swallowing function, and parathyroid gland function [15]. It's crucial that individualized surgical decisions are made based on life expectancy, underlying comorbidities, and patient preferences [20].

In cases of localized persistent or recurrent MTC in the neck, surgical re-intervention is recommended. Totalization of MTC diagnosed postoperatively after lobectomy is not systematically performed in all patients. It is indicated in cases of MTC with germline mutation or sporadic MTC with detectable postoperative calcitonin or abnormal ultrasound with residual MTC [16]. Totalization with imaging-positive or biopsy-positive lymph node dissection is recommended. If lateral cervical dissection was not performed during initial surgery, lateral compartment-oriented dissection should be performed if the preoperative serum calcitonin level is less than 1000 pg/mL, and at least five metastatic lymph nodes are removed during the initial operation according to ATA guidelines [8]. Limited surgical procedures, such as resection of grossly metastatic lymph nodes, should be avoided. Surgical re-intervention for locoregional lesions can achieve long-term biochemical cure in up to one-third of patients [15]. However, in the presence of significant regional or metastatic disease, extensive surgical intervention is not associated with a higher cure rate, and less aggressive procedures should be considered.

The role of surgery in disseminated disease is more limited and controversial. In most cases, surgery is considered a means to reduce tumor size, alleviate symptoms, and prevent complications.

For adjuvant treatment, MTC is relatively resistant to radiotherapy, and scientific evidence for the use of external beam radiotherapy in this context is limited. It might be indicated locally in inoperable patients or postoperatively. Postoperative external beam radiotherapy has not shown a significant improvement in overall survival [21]. The objective of postoperative external beam radiotherapy in treating patients with MTC is to achieve local control in individuals at high risk of regional recurrence (microscopic or macroscopic residual MTC, extrathyroidal extension, or extensive lymph node metastases) and those at risk of airway obstruction [3-15]. A meta-analysis revealed that MTC patients who underwent adjuvant radiotherapy showed a 38% reduction in the risk of locoregional recurrence, with a trend towards better local control with doses exceeding 60 Gy [3]. However, there are no clear recommendations on this adjuvant treatment, and it should be used selectively as it could limit the possibility of subsequent necessary intervention due to fibrosis induction [20].

Systemic treatment (chemotherapy, targeted therapies) may be initiated in patients with MTC with lesions at critical sites (brain and lung metastases), in the presence of symptomatic metastases, hormonal secretion, or bone fractures. It should not be offered to patients with high calcitonin levels without any detected macroscopic structural disease, in the presence of low tumor burden, and in the absence of macroscopic progression on imaging [20-22]. Its objectives include ensuring control of locoregional disease, controlling distant metastases, relieving symptoms of metastasis

(pain), and addressing symptoms of hormonal excess. Most guidelines (ATA, ESMO) do not recommend the use of simple or combination chemotherapy regimens as first-line systemic treatment in patients with persistent or recurrent MTC due to low response rates and the emergence of promising new treatment options [16]. First-line systemic treatment should be considered in unresectable locoregional diseases and distant metastases with symptomatic or progressive MTC [16-21].

Treatment with multi-tyrosine kinase inhibitors (TKIs) is also considered systemic treatment. It is not curative, shows no evidence of benefit on overall survival, and its impact is limited over time by frequent tumor escape and multiple side effects [3-23]. Primarily, vandetanib or cabozantinib can be used as first-line systemic treatment monotherapy in patients with advanced progressive MTC [23].

The toxicity of TKIs is mainly attributed to "off-target" effects, and selective RET inhibitors are highly attractive for MTC treatment. The latest NCCN and FDA guidelines have introduced highly selective RET inhibitors into the management of MTC: selpercatinib and pralsetinib [16].

Due to the lack of improvement in overall survival with targeted systemic therapies, the search for additional adjunct therapies to target recurrent or metastatic MTC continues. Indeed, MTC also expresses somatostatin receptors in vitro and in vivo, as well as cholecystokinin 2 receptors (CCK2R). There is currently growing interest in PRRT (targeting somatostatin receptors) for the treatment of advanced, progressive, or metastatic MTC [3-24]. Immunotherapeutic concepts have not yielded encouraging responses so far, probably because MTC is immunologically cold [16].

The surveillance of medullary thyroid carcinoma aims to monitor treatment efficacy, detect local recurrences, and screen for distant metastases. It is mainly done through the measurement of calcitonin and CEA. The timing of measurement after surgery is crucial [8]. ATA recommendations suggest measuring serum calcitonin and CEA levels three months after the operation. ESMO and NCCN recommendations also suggest measuring them approximately 30 to 60 days and 2 or 3 months after surgery, respectively [16].

If the ACE level is normal and calcitonin is undetectable, they should be measured every 6 months during the first year and then annually. Patients with normal ACE and undetectable calcitonin are considered biochemically cured and have an excellent prognosis [18]. Postoperatively, basal calcitonin levels can determine if the surgical procedure was complete; a value lower than 10pg/ml confirms biological remission [25].

Patients with calcitonin levels below 150 pg/ml should undergo a clinical examination with cervical ultrasound. In the absence of lesions, patients should be monitored every six months with a clinical examination, ultrasound, measurement of serum calcitonin and ACE levels, and evaluation of doubling time, but surgery is not recommended in the absence of structural disease [15]. Patients with incomplete biochemical responses without structural disease are followed with conservative monitoring. Therapeutic interventions based on increased biochemical markers are not recommended [26]. If ultrasound shows a positive result with persistent or recurrent CMT, management includes surveillance, surgical resection, radiotherapy, and systemic treatment, depending on symptoms, location, tumor volume, and likelihood of significant structural progression [20]. Mitra Niafar reported increased calcitonin and ACE levels in a patient with CMT who underwent total thyroidectomy and central lymph node dissection. Ectopic lesions secreting calcitonin and ACE were found in the right side of the upper and anterior mediastinum [9].

If postoperative calcitonin is higher than 150 pg/ml, metastatic disease is suspected. Patients should be evaluated with imaging procedures including cervical ultrasound, thoracic CT scan, MRI or CT of the liver, as well as bone scintigraphy and MRI of the pelvis and axial skeleton [8-15].

The prognosis of CMT is generally favorable with a 5-year survival rate of 78.2% and a 10-year survival rate of 61.4%. Several prognostic factors have been established for CMT, including tumor size, presence and extent of invasion of surrounding tissues, cervical lymph node metastases, and distant metastatic disease, which combine to predict survival [27]. According to Ana *et al*., the main prognostic factors are advanced age, significant tumor volume, local and distant metastases, presence of the somatic mutation M918T, and decreased calcitonin and ACE doubling time. Calcitonin and ACE levels remain the main prognostic factors in CMT [19]. Persistent hypercalcitoninemia postoperatively and rapid increases in ACE levels in a stable calcitonin state are important prognostic factors [16]. Calcitonin and ACE doubling times are correlated with tumor recurrence rate and survival [22-28]. The quality of initial surgery is also an important prognostic factor; adequate surgical treatment and complete resection through total thyroidectomy with lymph node dissection reduce the risk of lymph node recurrence and subsequently decrease the rate of surgical re-intervention after initially poor surgical outcomes.

CONCLUSION

CMT remains a relatively rare tumor, mainly affecting young adults and typically presenting as an isolated thyroid nodule. It is a lymphophilic tumor, and lymph node involvement occurs very early. Calcitonin plays a crucial role in preoperative diagnosis, staging of

the disease, surgical guidance, surveillance, and is considered an important prognostic factor predictive of survival. However, its systematic preoperative measurement remains a subject of controversy.

Despite advancements in targeted therapy, complete surgical resection remains the only curative treatment. Chemotherapy has not yet proven effective in CMT. Radiotherapy has been proposed to delay relapses and stabilize the disease. Furthermore, personalized medicine in terms of next-generation sequencing (NGS) holds academic interest, but NGS analyses have not yet resulted in therapeutic targets beyond RET.

Competing Interests: The authors declare no competing interests.

Authors' Contributions:

MAH described the case, conducted literature research, and drafted the initial version of the manuscript. AM and OM revised the manuscript and made substantial contributions. AO and MNEE reviewed the case description and conducted simultaneous literature research. All authors read and approved the final manuscript.

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