

REVIEW ARTICLE

A Retrospective Review of Patients with Medullary Thyroid Carcinoma

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Abstract

Introduction: Medullary thyroid cancer (MTC) is a neuroendocrine tumor of the parafollicular or C cells of the thyroid gland. The present study aims to determine the demographic, clinical and pathological characteristics of patients diagnosed with MTC at our surgical centre.

Methodology: We retrospectively reviewed the hospital records of patients who were admitted and operated for MTC at our tertiary level referral hospital from September 2012 till February 2017. Clinical parameters like family history, presenting complaints, presence of metastasis at the time of presentation, site of metastasis and histopathological findings were noted. Duration of hospital stay and drainage was noted as well. Recurrence was defined as the reappearance of high levels of calcitonin or locoregional or distant metastasis after the disease or symptoms disappeared.

Results: During the study period, four males and three females with mean age 56.45 years were operated. At the time of presentation, one patient had liver metastasis and the other had metastasis at multiple sites. All patients in the study underwent total thyroidectomy with central compartment clearance and bilateral neck dissection. On final histopathological examination, four patients had multifocal tumors and three patients had unifocal tumors. Median duration of hospital stay was 7 days and median duration of drain was 5 days. During the follow up period, two patients presented with locoregional recurrences and the two patients with distant metastasis died.

Conclusion: Genetic screening and the evaluation of familial syndromes should always be considered in preoperative workup in MTC patients. Key therapeutic molecular targets in MTC need to be investigated in future studies.

Keywords: Thyroid Carcinoma; Medullary Thyroid Carcinoma; RET

Introduction

Medullary thyroid cancer (MTC) is a neuroendocrine tumor of the parafollicular or C cells of the thyroid gland. MTC accounts for approximately 4% of thyroid carcinomas. The production of calcitonin is a characteristic feature of this tumor. The C cells originate from the embryonic neural crest; as a result, medullary carcinomas often have the clinical and histologic features of other neuroendocrine tumors such as carcinoid and islet-cell tumors. Most medullary thyroid carcinomas are sporadic. However, some are familial as part of the multiple endocrine neoplasia type 2 (MEN2) syndrome. The hereditary forms are linked to a germ line mutation in the rearranged during transfection (RET) oncogene, which are transmitted as an autosomal dominant trait with close to a 100% penetrance of the disease. Diagnosis of most of these tumors relies on fine-needle aspiration cytology (FNAC), which has been associated with a considerable number of false-negative results and may delay the diagnosis [1]. In addition, there is no consensus on the measurement of serum calcitonin levels in nodular thyroid diseases. Surgery is the most effective treatment for these tumors. The overall cause specific mortality of these tumors is 13.3 to 32.6% and 21.6 to 38.6% at 5 and 10 years, respectively [2]. MTC is a unique form of thyroid cancer, which differs in demography, presentation and prognosis from other types of thyroid cancer and thus presents with challenges in its management. The present study aims to determine the demographic, clinical and pathological characteristics of patients diagnosed with MTC at our surgical centre.

Methodology

We retrospectively reviewed the hospital records of patients who were admitted and operated for MTC at our tertiary level referral hospital from September 2012 till February 2017. During this period, 87 patients of thyroid cancers were diagnosed at our centre,

of which seven were operated for MTC. In our hospital, the diagnosis of MTC was based on fine needle aspiration cytology (FNAC) or an elevated serum calcitonin value, or in some cases based on the histopathological report following thyroidectomy. The study was approved by the institutional ethics committee. At the time of admission, patients were enquired about their demographic variables like age and gender. Clinical parameters like family history, presenting complaints, presence of metastasis at the time of presentation, site of metastasis and histopathological findings were noted using a pre-designed semi-structured questionnaire. Duration of hospital stay and drainage was noted as well. All patients were followed for at least one year. Recurrence was defined as the reappearance of high levels of calcitonin or locoregional and or distant metastasis after the disease or symptoms disappeared. Data were analysed descriptively and summarised using mean/median (minimum and maximum) for continuous variables and frequency with percentage for categorical variables (Figure 1).



Figure 1: Postoperative image of the patient

Results

In our study, there were four males and three females, and mean age was 56.45 years, ranging between 38 and 75 years (Table 1). Only one patient had a strong family history. Most common presentation was goitre and one patient was diagnosed after screening. Two of the seven patients had distant metastases at the time of presentation, one had liver metastasis and the other patient had metastasis at multiple sites (lungs, liver, bones, kidneys and prostate). All patients in the study underwent total thyroidectomy with central compartment clearance and bilateral neck dissection. One patient had undergone left hemithyroidectomy 15 years ago, details of which were not available. He presented to us with left submandibular swelling which came as metastasis of medullary carcinoma on biopsy. On final histopathological examination, four patients had multifocal tumors and three patients had unifocal tumors. Median duration of hospital stay was 7 days, ranging from 5 to 8 days and median duration of drain was 5 days, ranging from 4 to 6 days (Table 2). One patient who had metastasis to multiple sites underwent radiation therapy followed by targeted therapy. The other patient with liver metastases at presentation also underwent targeted therapy. All patients had an uneventful recovery in the immediate post-operative period. All patients were followed for at least one year, after which one patient was lost to follow-up. During the follow up period, two patients presented with locoregional recurrences and the two patients with distant metastasis died (Figure 2).

Variables	
Mean age (standard deviation)	46.45 (7.32)
Gender	
Females	3
Males	4
Positive family history	1
Presenting complaints	
Goitre	4
Goitre with lymph node enlargement	2
On screening	1
Metastasis at presentation	2
Site of metastasis	
Liver	1
Multiple sites (≥ 2)	1
Histopathological findings	
Unifocal	3
Multifocal	4

Table 1: Demographic and clinical profile of the patients

Variables	
Median stay in hospital (in days)	7 (5 to 8)
Median duration of drain (in days)	5 (4 to 6)

Table 2: Postoperative variables of the patients



Figure 2: Postoperative image of the thyroid gland

Discussion

The present study describes our experience of diagnosing and treating patients with MTC at our centre. Sporadic MTC accounts for about 80% of all cases of the disease and the typical age of presentation is in the fifth or sixth decade, and there may be a slight female preponderance [3]. In our study, mean age was 56 years, with almost equal male female distribution. The most common presentation in our study was thyroid swelling. A solitary thyroid nodule has been reported by 75 to 95% of patients [4]. Most tumours are located in the upper portion of thyroid gland because the C cells are predominantly located in this region. Furthermore, at the time of presentation, two patients in our study had already metastasized. Though not reported by our patients, up to 15% of the patients have symptoms of upper aerodigestive tract compression or invasion such as dysphagia or hoarseness [5]. One patient in our study had multiple sites of metastasis like lung, liver, bone, kidney and prostate. Nodal metastases, which are seen more commonly in patients with multifocal disease, were not present in our study. Furthermore, systemic symptoms may occur due to hormonal secretion by the tumor. Secretion of calcitonin, calcitonin-gene related peptide, or other substances by the tumor can cause diarrhoea or facial flushing in patients with advanced disease. In addition, occasional tumors secrete corticotropin (ACTH), causing ectopic Cushing's syndrome. Though inherited MTC may have other symptoms due to associated conditions, the clinical presentation and manifestations of the index case may be similar to that of the sporadic MTC case. One advantage is that inherited MTC can be detected early by screening of at-risk family and thus can be cured or prevented by early thyroidectomy.

In the present study, patients were diagnosed on the basis of histopathological testing, which is the gold standard for diagnosis. Though attempted by a few authors, there are no ultrasound features that are pathognomonic for thyroid cancer. Furthermore, the majority of studies evaluating suspicious ultrasound characteristics of nodules focused on papillary thyroid cancer. In a small retrospective study examining the ultrasound characteristic of nodules that were histologically proven to be medullary and papillary thyroid cancer, 50% of MTC were solid and hypoechoic and 16% showed microcalcifications compared with 69.2 and 69.2%, respectively, for papillary thyroid cancer [6]. In other series, hypoechoic was present in 50 to 89% and microcalcifications in 30 to 70%, and there was no difference in echogenicity or the presence or type of calcifications between MTC and papillary thyroid cancer [7,8].

Though not performed in the present study, testing germline mutations in the RET proto-oncogene and, therefore, have a heritable disease is required. The frequency of germline RET mutations have been variable across studies. In one report, 7.3% with apparently sporadic MTC had mutations, and in 18 of these 35, gene carriers were identified in relatives and Seventy-five percent of the familial medullary cases had no prior family history [9]. Based upon these observations, germline RET testing is recommended in all patients. Initial germline testing in patients with C cell hyperplasia or apparently sporadic MTC should include sequencing of exons 10, 11, and 13 through 16 of the RET gene. Sequencing of the remaining exons in the RET gene should be considered in patients with clinical features or family history highly suggestive of hereditary medullary syndromes who demonstrate no mutations in exons 10, 11, or 13 through 16 [10]. A much higher percentage (approximately 60%) of patients with sporadic MTC have somatic (acquired) mutations in the RET gene within the tumor cells [11].

Conclusion

Medullary thyroid carcinomas are rare tumors. Its management is different than that for differentiated thyroid cancers. Genetic screening and the evaluation of familial syndromes should always be considered in preoperative workup in MTC patients. Early diagnosis offers a high likelihood of cure and long term survival, while metastatic disease has a poor prognosis, partly due to limited response to conventional chemotherapy and radiotherapy. Total thyroidectomy with neck dissection remains the gold

standard in the treatment of medullary carcinoma. Key therapeutic molecular targets in MTC need to be identified and future studies should evaluate their efficacy and safety. In the recent years, several emerging treatment options targeting the RET receptor tyrosine kinase have been reported. Among those Vandetanib and Cabozantinib are recommended for the treatment of progressive and metastatic MTC.

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Figure 5: Resumption of Normal duty