Original Article

Medullary Thyroid Cancer: An Experience from a Tertiary Care Hospital of a Developing Country

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Abstract

Background: Medullary thyroid carcinoma (MTC) is a rare type of thyroid cancer that occasionally occurs as part of MEN2A. The universal treatment of MTC is total thyroidectomy with central lymph node dissection. For disease progression, carcinoembryonic antigen (CEA) and calcitonin (CTN) need to be followed. Our aim was to study the presence and patterns of the above-mentioned characteristics of MTC in our population. **Methodology:** This retrospective study was conducted in a tertiary care hospital of Pakistan in which data of thirty-two medullary thyroid cancer patients over the past 20 years were reviewed and analysed after fulfilment of inclusion criteria. Their clinical, pathological, biochemical and treatment modalities were recorded through a retrospective review of their medical record files. **Results:** The mean age of patients was 42.88 ± 2.67 years in our study, with a male-to-female ratio of 2:1. Patients with sporadic MTC were 68.8%, while 31.2% were familial. The rates of metastasis were highest in bones followed by lungs and liver. Total thyroidectomy was performed in 26 (81.2%) patients and among those chemotherapy and XRT were performed in one and two patients, respectively. Histologically, the mean tumour size was 7.62 ± 3.64 cm. Median pre-surgery calcitonin was 5756 pg/ml that decreased to 29.3 pg/ml post-surgery. Median pre-surgery CEA level was 246.5 ng/ml that decreased to 6.39 ng/ml post-surgery. Two patients were RET positive. **Conclusion:** MTC usually presents in the fourth decade of life with male predominance and mostly sporadic occurrence. Total thyroidectomy with subsequent serial calcitonin and CEA levels thereafter are the mainstay of treatment and follow-up.

Keywords: Clinicopathological characteristics, developing country, medullary thyroid cancer

Introduction

Medullary thyroid carcinomas are rare tumours and account for 5%–8% of all thyroid carcinomas but represent up to 13.4% of thyroid cancer-related mortality.[1] These tumours are derived from the parafollicular C cells of the thyroid gland that produce calcitonin. 75–85% of the cases occur as sporadic, and another 20–25% occur as hereditary form caused by a mutation in RET proto-oncogene.[2] The hereditary form is associated with pheochromocytoma and hyperparathyroidism, and together they are labelled as multiple endocrine neoplasia (MEN2A).[3] MTC may present clinically as neck swelling of thyroid origin or lymphadenopathy. They may also cause local compressive symptoms in the form of dysphagia, hoarseness or stridor.[4,5]

In advanced cases, these tumours may present with metastatic lesions to the lungs, liver, bones and brain. Biochemically, these tumours produce calcitonin (CTN) and carcinoembryonic antigen (CEA), which are used for diagnosis and monitoring of disease progression. High levels of these markers may indicate advanced disease.[6] Total thyroidectomy with neck dissection is the treatment modality of choice, and the extent of neck dissection depends on the number of lymph nodes involved.[7] Post-operatively, patients are followed up with calcitonin and CEA levels at 3–6-month intervals. For metastatic lesions, MRI and CT scans may be considered.[8]

Patients with hereditary MTC are also screened for pheochromocytoma and hyperparathyroidism before the surgery. Patients with high levels of serum metanephrines and

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.ijem_474_21

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Submitted: 17-Nov-2021 **Revised:** 24-Dec-2021
Accepted: 09-Jan-2022 **Published:** 27-Apr-2022

How to cite this article: Khan SA, Aziz A, Esbhani UA, Masood MQ. Medullary thyroid cancer: An experience from a tertiary care hospital of a developing country. Indian J Endocr Metab 2022;26:68-72.

normetanephrines are optimized first with medical treatment to control blood pressure.[9]

There have been only a few studies to assess the clinical characteristics of this disease entity. Timely diagnosis can lead to earlier detection of cases and better therapeutic outcomes. Furthermore, family members can also be screened before they possibly develop the tumour. Hence, we plan to undertake this study so that the characteristics and treatment outcomes could be ascertained in our population.

Materials and Methods

This was a retrospective review of patient records presented to the tertiary care hospital in Karachi, Pakistan, for the diagnosis and management of medullary thyroid cancer. Inpatient and outpatient records were included. Demographic, clinical, laboratory data, information related to treatment pattern and follow-up for medullary thyroid cancer were recorded in pro forma.

Data were collected retrospectively by reviewing patient records for both baseline and subsequent visits post-intervention (surgery and medical therapy). For each patient, we analysed the following data recorded by the primary physician at the diagnosis of medullary thyroid cancer: age and sex, estimated duration since diagnosis, median serum calcitonin and CEA pre- and post-surgery, histopathology and treatment modalities. After the approval from the ethical review committee (ERC) of our centre, we requested the health information and management services (HIMS) to provide the list of patients diagnosed to have thyroid cancer.

A non-probability convenience sampling technique was used to recruit the study participants. A total of 32 patients fulfilled the diagnosis of medullary thyroid cancer based on the clinical characteristics and biochemical markers and were included in the study from 2000 to 2020. These patients were either undergoing treatment with surgery/medical therapy for MTC or being followed up in a tertiary care hospital in Karachi, Pakistan.

Inclusion criteria

The inclusion criteria included confirmed cases of medullary thyroid cancer fulfilling the clinical features and endocrine society diagnostic criteria:

1. Biochemically diagnosed cases of medullary thyroid cancer based on high serum CTN levels either with positive biopsy or with fine-needle aspiration, thyroid nodules and cervical lymphadenopathy, or distant metastases. The diagnosis was confirmed by surgical histological results.
2. Age ≥18 years, either sex.
3. MEN2A will be considered positive if at least one of the family members had a history of hyperparathyroidism or pheochromocytoma, alongside the presence of RET proto-oncogene mutation.

Similarly, MEN2B will be considered if one or more family members had morphological characteristics of the

Table 1: Patients' characteristics

Variables	Results
Age (years)	42.88±2.67
Gender	
Male	21 (65.6%)
Female	11 (34.4%)
Duration of symptoms (years)	0.96±0.29
Age at diagnosis (years)	39.84±2.76
Sporadic or familial disease	
Sporadic	22 (68.8%)
Familial	10 (31.2%)
Familial disease diagnosis (Total=10 patients)	
Familial disease diagnosed by symptoms	6 (60%)
Familial disease diagnosed by screening	4 (40%)

Table 2: Presenting complaints

Variables	Results
Clinical characteristics	
No neck swelling	6 (18.8%)
Neck swelling	26 (81.2%)
History of prior thyroid surgery	
No	30 (93.8%)
Yes	2 (6.2%)
Lymph nodes palpable	
Unknown	13 (40.6%)
Yes	14 (43.8%)
No	5 (15.6%)
Local metastasis	
None	13 (40.6%)
Unilateral lymph node	3 (9.4%)
Bilateral lymph node	16 (50%)
Distant metastasis	
None	24 (75%)
Lungs	3 (9.4%)
Liver	1 (3.1%)
Bone	4 (12.5%)
Metastasis in local structures or in more than two distant sites (other than lymph node)	
None	25 (78.1%)
Local structures	5 (15.6%)
More than two distant sites	2 (6.2%)
Local symptoms	
None	27 (84.4%)
Hoarseness	3 (9.4%)
Dyspnoea	1 (3.1%)
Vocal cord paralysis	1 (3.1%)
Systemic symptoms	
None	30 (93.8%)
Diarrhoea	1 (3.1%)
Other	1 (3.1%)
Family history	
None	22 (68.8%)
MEN 2	8 (25.0%)
RET+	1 (3.1%)
Thyroid Ca	1 (3.1%)

Table 3: Staging of medullary thyroid cancer

Variables	Results
Tumour size (cm)	7.62±3.64
TNM staging (invasion)	
No invasion to surrounding structures	16 (50%)
Local invasion (positive)	10 (31.2%)
Unknown	6 (18.8%)
TNM staging (invasion focality)	
Unifocal	16 (50%)
Bifocal	7 (21.8%)
Multifocal	3 (9.4%)
Not known	6 (18.8%)
TNM staging (laterality)	
Unilateral	14 (43.7%)
Bilateral	12 (37.5%)
Not known	6 (18.8%)
TNM staging (lymph node metastasis)	
No	10 (31.2%)
Yes	18 (56.3%)
Not known	4 (12.5%)
TNM staging (distant metastasis)	
No	21 (65.6%)
Yes	8 (25.0%)
Not known	3 (9.4%)

Table 4: Biochemical markers and FNAC

Variables	Results
Calcitonin (median value) pg/ml	
Pre Surgery	5756
Post Surgery	29.3
CEA (median value) ng/ml	
Pre Surgery	246.5
Post Surgery	6.39
Hyperparathyroidism	
No	30 (93.5%)
Yes	2 (6.5%)
Pheochromocytoma	
No	31 (96.9%)
Yes	1 (3.1%)
TSH pre-surgery	3.21±1.07
Calcium pre-surgery	9.12±0.18
RET	
Positive	2 (6.2%)
Not done/available	30
FNAC	
MTC	12 (37.5%)
Malignant cell	3 (9.4%)
Bethesda Category III	2 (6.2%)
Not Performed	15 (46.9%)

disease with pheochromocytoma and RET proto-oncogene mutation.

Exclusion criteria

Patients with equivocal results of calcitonin and CEA.

Statistical analysis

All analyses were conducted by using the Statistical Package for Social Sciences (Release 19.0, standard version, copyright © SPSS; 1989-02). A descriptive analysis was performed. Proportions were calculated for categorical variables and mean SD for continuous ones.

Results

The mean age of patients with medullary thyroid carcinoma (MTC) was 42.88 ± 2.67 years in our study, with male to female ratio of 2:1. The other demographic features are shown in table 1.

81.2% of patients presented with neck swelling, lymph nodes were palpable in 43.8% of patients and distant metastasis were present in 25% of the patients. The rates of metastasis were highest in bones followed by lungs and liver (12.5%, 9.4%, and 3.1% respectively) [Table 2].

Histologically, the mean tumor size was 7.62 ± 3.64 cm with 8 (25%) patients having distant metastasis. Lymph node metastasis was present in 18 (56.3%) of the patients. 50% of carcinomas in our study were unifocal, followed by bifocal (21.8%) and multifocal (9.4%). The further details of staging of medullary thyroid cancer is mentioned in table 3.

The details of biochemical markers pre and post surgery and FNAC is shown in table 4.

Total thyroidectomy was done in 26 (81.2%) of the patients while one patient had subtotal thyroidectomy followed by complete thyroidectomy as initial fine needle aspiration cytology (FNAC) was Bethesda category 3. Surgery was not performed in 5 patients due to distant metastasis or palliative intent. Chemotherapy was given to only one patient while radiotherapy (XRT) was performed in two patients along with total thyroidectomy and lymph node dissection [Table 5].

Discussion

In our study, the mean age of patients with medullary thyroid carcinoma (MTC) was 42.88 ± 2.67 years, which is almost the same to the study by P.R Manjunath *et al*.[10] where the mean age was 42.07 years (SD 14.5), while a study conducted by Louhibi *et al*.[11] showed that the mean age was approximately 50 years. MTC was predominantly found in males (65.6%) with a male-to-female ratio of 2:1 in our study, which is almost the same as a study by Mehrotra PK *et al*.[12] which showed a male-to-female ratio of 1.7:1, while other studies showed a high prevalence in female patients (65%).[11] 68.8% of MTC cases were sporadic in our study and 31.2% percent were familial, a finding consistent with other studies that showed the majority of MTC cases are sporadic (75%–80%), while 20%–25% are hereditary.[13] The mean duration of symptoms was less than 1 year. Out of 10 patients with familial MTC, four were asymptomatic and diagnosed via screening.

Table 5: Treatment modalities

Variables	Results
Surgery	
No surgery	5 (15.6%)
Subtotal thyroidectomy	1 (3.1%)
Total thyroidectomy	26 (81.2%)
Chemotherapy	
Not given	31 (96.9%)
Given	1 (3.1%)
XRT/RAI	
None	27 (84.4%)
XRT given	2 (6.2%)
RAI given	2 (6.2%)
Both XRT + RAI	1 (3.1%)

81.2% of patients presented with neck swelling, lymph nodes were palpable in 43.8% of the patients, and distant metastasis was present in 25% of the patients, while a study by Finny B *et al*.[14] showed that 67% of the patients had a definite thyroid swelling and 43% had lymphadenopathy at the time of presentation. Rates of metastasis were highest in bones followed by lungs and liver (12.5%, 9.4% and 3.1%, respectively), while a study by Cherian AJ *et al*.[15] showed that the most common site of metastasis is lung, followed by bone and liver. The studies conducted by S. Roman *et al*.[1] and G. Treglia *et al*.[16] showed that MTC is very aggressive; only about half of the patients have localized disease initially, while 35% had regional lymph node metastases, and 13% have distant metastases, especially to the lung, liver or bones. Other study by M. Roy *et al*.[17] showed lymph node involvement in 35–50% and distant metastasis in 10–15%. The prevalence of lymph node metastases at diagnosis has varied between 25% and 62% in several other studies.[18,19] Metastasis from MTC occurs via lympho-vascular pathways, spreading to lymph nodes of neck and mediastinum and then further onwards to the lung, liver and bones.[20] Some patients with advanced MTC can develop obstructive symptoms, e.g., dysphagia, due to local growth, while those with distant metastasis can have flushing and diarrhoea due to high levels of calcitonin.[21] In our study, local symptoms, i.e., hoarseness, dyspnoea and vocal cord paralysis, were present in five patients (15.5%), while systemic symptoms, i.e., diarrhoea, were present in two patients (6.2%).

FNAC sensitivity was known to be 63% vs. 98% for serum calcitonin measurement,[22] and definitive diagnosis may only be made after surgery via histopathology.[23] In our study, FNAC detected MTC in 12 (37.5%) patients.

Histologically, the mean tumour size was 7.62 ± 3.64 cm with 8 (25%) patients showing distant metastasis. Lymph node metastasis was present in 18 (56.3%) of the patients. 50% of carcinomas in our study were unifocal, followed by bifocal (21.8%) and multifocal (9.4%).

An elevated level of serum calcitonin is a highly sensitive marker for post-surgery follow-up of MTC, but it is not especially specific.[24] In advanced tumours, which may be dedifferentiated by decreased calcitonin production, CEA may be a more valuable tumour marker.[25] Median pre-surgery calcitonin was 5756 pg/ml (0.0-18.2) that decreased to 29.3 pg/ml post-surgery. Median pre-surgery CEA level was 246.5 ng/ml (0-10) that decreased to 6.39 ng/ml post-surgery.

Hyperparathyroidism was found in two patients, while pheochromocytoma was found in one patient only. Two patients were positive for RET gene mutations. In our study, it was not possible to screen all the patients, as would have been desirable.[26,27]

The universal treatment of MTC is total thyroidectomy with central lymph node dissection. A number of studies have reported that survival of MTC patients is dependent upon the adequacy of the initial surgical intervention.[28,29] In our study, total thyroidectomy was performed in 26 (81.2%) of the patients, while in other study 92.6% of patients had total thyroidectomy.[12] One patient had subtotal thyroidectomy followed by completion thyroidectomy as initial FNAC was Bethesda category III. Surgery was not performed in five patients due to distant metastasis or palliative intent. Systemic chemotherapy and external radiotherapy are of limited efficacy in MTC.[5,30] This is consistent with treatment of patients in our study, in which chemotherapy was given to only one patient, while XRT was performed in two patients.

Conclusion

Medullary thyroid carcinoma usually presents in the fourth decade of life with male predominance and mostly sporadic occurrence. Total thyroidectomy with subsequent serial calcitonin and CEA levels thereafter are the mainstay of treatment and follow-up.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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