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INSIGHTS INTO MEDULLARY CARCINOMA THYROID: A CASE SERIES AND REVIEW OF THE LITERATURE.

Oncology

Durgesh Kumar Associate Professor Surgical Oncology (KSSSCI)
Priyank Agarwal Senior Resident, Department of Surgical Oncology (KSSSCI)
Neharika Associate Professor Department of General Surgery Hind Institute of Medical Sciences
Tanvi Singhvi Associate Professor Department of Pathology Hind Institute of Medical Sciences
Ankur Verma* Associate Professor Surgical Oncology (KSSSCI) *Corresponding Author

ABSTRACT

Objective: To study the mode of clinical presentation, the role of tumor markers serum calcitonin and CEA in diagnosis and follow-up, and Surgery as a "curative" modality in treatment. **Methods:** In a retrospective analysis, 12 patients with medullary carcinoma thyroid who underwent surgical intervention between 2012 and 2015 at a tertiary care institute were included. Their medical records were retrieved and their follow-up records were analysed. **Results:** Surgical management with more of a radical approach than conservative gives better results and low recurrence in patients with medullary carcinoma thyroid. Tumor markers serum calcitonin and CEA were found to be reliable markers in the diagnosis and follow-up of patients with MTC. **Conclusion:** Medullary carcinoma thyroid, though rare and aggressive thyroid carcinoma can be cured with appropriate surgical management. The most common mode of clinical presentation in a case of medullary carcinoma thyroid is goiter. Serum calcitonin and CEA are reliable markers in establishing the diagnosis and during follow-up. Adjuvant radiotherapy can be offered for high-risk diseases.

KEYWORDS

Medullary Thyroid Cancer (MTC), Prophylactic surgery in MTC

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor that can produce calcitonin from parafollicular cells(1). MTC constitutes 5–10% of all thyroid carcinomas and 0.4–1.4% of all thyroid nodules. MTC arises from C cells or parafollicular cells in the thyroid gland that secrete calcitonin (CT); C cells are distributed throughout the thyroid's stroma, mostly in the upper poles, in between thyroid follicles(2). Approximately 80% of cases are sporadic while the remaining 20% cases are familial, secondary to a germline rearranged during transfection (RET) mutation(3), which is seen in Multiple endocrine neoplasia type 2 (MEN 2) syndrome(4). Extensive careful surgery is the only curative option for localized MTC(5). Calcitonin is the primary secretory product of MTC, a particular and extremely sensitive biomarker that is generated by both normal and malignant C cells. Carcinoembryonic antigen (CEA) is also produced by neoplastic C cells. These chemicals are commonly utilized as markers for MTC patient diagnosis, prognosis, and follow-up(6). Approximately half of patients with sporadic MTC appear with a thyroid nodule, which is linked to lymph node metastases in the neck region. Distant metastasis are mostly present in liver lungs and bones, although they are rarely present(7,8).

MATERIAL AND METHODS

A Retrospective Cohort Study at a tertiary care institute in India which comprised of all diagnosed and operated cases of medullary carcinoma thyroid. All patients of medullary carcinoma thyroid who underwent surgery at the institute were include in the study. Patients who didn't consent, those who were lost to follow-up, or if medical records were not available, were excluded from the study. Candidates underwent surgery by a single experienced Onco-surgeon. Informed consent was taken from parents/ guardians of all subjects. This study fulfilled the ethical consideration and started after the approval of the Institution Ethics Committee (IEC).

All candidates underwent extensive pre-operative evaluation which included their clinical history and examination. The preoperative radiological and biochemical evaluation included Ultrasonography neck, a computed tomography scan of the chest abdomen and pelvis, Serum calcitonin, serum CEA, serum calcium, and 24-hour urine metanephrines. Definitive diagnoses of medullary carcinoma thyroid were done using tissue diagnosis including fine needle aspiration cytology, slide reviews, and post-operative histopathology reports of patients who underwent hemithyroidectomy for benign pathology.

All patients underwent Total thyroidectomy along with additional procedures (central lymph node dissection and functional neck dissection) based on the extent of the disease. In cases of recurrences wide excision, neck dissection and tracheal ring resection were carried out accordingly. Adjuvant radiotherapy was considered in patients with positive margins, microscopic disease on histopathological reports, patients with positive lymph nodes, and detectable serum calcitonin levels.

Patients were followed up every 3 months for 2 years, and then 6 months afterwards. During each visit, patients were evaluated clinically, radiologically (ultrasonography neck, chest x-ray), and biochemically (Serum calcitonin, serum CEA, serum calcium).

The Statistical Package for Social Sciences (SPSS) IBM software version 26 (IBM SPSS Advanced Statistics, Chicago, IL, USA) was used to analyze the data collected after tabulating it in an Excel spreadsheet. The results of the categorical measurements were presented in numbers or ratios. Using the Pearson correlation coefficient, the results of quantitative variables were presented as median (95% confidence interval) or mean ± SD. A p-value of 0.05 or less was used to determine the level of significance, which was set at 5%.

RESULTS

Out of 12 patients 9 patients belong to age group of more than 45 years while remaining belongs to less than 45 years. Approximately two-third of patients were females and one-third were males. 7 out of 12 patients presents with neck swelling as their chief complaint, while only 2 patients were asymptomatic and were discovered incidentally. 8 out of 12 patients presented to OPD within 1 year of developing the symptoms. 10 out of 12 patients were diagnosed with MTC preoperatively by FNAC while rest were diagnosed with postoperative histopathology following thyroidectomy. Tumor Markers Serum calcitonin and CEA were elevated in all 12 patients.

Total thyroidectomy was done in 10 out of 12 patients, remaining 2 patients underwent hemithyroidectomy. 6 out of 12 patients underwent additional central compartment lymph node dissection and functional neck dissection, other 2 patients underwent only central compartment lymph node dissection. One patient required a sternotomy due to an enlarged thymus and underwent an additional thymectomy. 2 of the patients who underwent hemithyroidectomy earlier, underwent completion thyroidectomy and central compartment lymph node dissection after definite diagnoses of MTC were made on histopathology. 1 patient with multinodular goiter who underwent total thyroidectomy was planned for additional Central compartment and functional neck dissection in the second sitting. (Fig-1)

In the postoperative histopathology report of thyroid gland 8 out of 12 patients had nodule size in the range of 2 to 4 cm, while 3 patients had

nodules with size more than 4 cm, while only 1 patient had nodule that was less than 2 cm in size.

In the final histopathology staging almost half of patients belong to stage IV a, while the remaining half belong to stage III or less. In stage IV a patient 4 out of 6 patients had T3N1b disease, while the remaining 2 patients had T4a disease.

7 out 12 patients had loco-regional disease while remaining had regional disease. 7 out of 12 patients showed perineural invasion, 5 patients showed lympho-vascular space invasion, 2 patients showed extra capsular spread. On average 15-20 lymph nodes were identified in all cases but in one case thymoma was found with 13/35 lymph nodes and the patient underwent additional thymectomy. None of the patients had any systemic or pressure symptoms. All patients were followed up at regular intervals. There was no evidence of recurrence clinically or radiologically. Serum calcitonin and serum CEA were within normal ranges in all 12 patients during the follow-up. Adjuvant radiotherapy was given in 2 patients whose post-operative histopathology was suggestive of stage IV B. (Table -1)

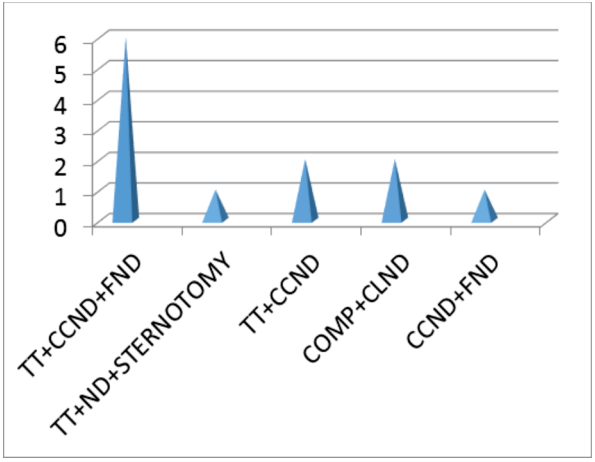

Figure 1: Procedure Done

Table 1: Results

AGE	>45 years	9
	<45 years	3
SEX	Male	4
	Female	8
COMPLAINTS AT PRESENTATION	Neck swelling	7
	Assymptomatic	2
	Diagnosed from routine thyroidectomy HPE reports	3
DURATION OF SYMPTOMS	<1 year	8
	>1 year	4
DIAGNOSIS ESTABLISHMENT	Pre operative FNAC	10
	Post operative HPE	2
TUMOR MARKER Serum Calcitonin	<100 pg/ml	4
	100 – 300 pg/ml	3
	>300 pg/ml	5
TUMOR MARKER Serum CEA	<30 ng/ml	3
	30 – 50 ng/ml	1
	>50 ng/ml	8
SURGICAL INTERVENTION FOR PRIMARY	Total Thyroidectomy	10
	Hemithyroidectomy	2
SURGICAL INTERVENTION FOR NECK SECONDARIES	Central compartment lymph node dissection (CCND) + functional neck dissection (FND)	6 +1
	Only central compartment lymph node dissection (CCND)	2
	Completion thyroidectomy + Central compartment lymph node dissection (CCND)	2
	Sternotomy	1
POSTOPERATIVE HPE PRIMARY NODULE SIZE	<2 CM	1
	2-4 CM	8
	>4 CM	3
POSTOPERATIVE HPE TUMOR STAGING	Stage I	1
	Stage II	4
	Stage III	1
	Stage IVA- T3 N1b	4
	Stage IVA- T4a Any N	2
	Stage IVB	0
POSTOPERATIVE HPE DISEASE EXTENSION	LOCO- REGIONAL	7
	REGIONAL	5
POSTOPERATIVE HPE ADDITIONAL INFORMATION	Perineural invasion	7
	Lympho-vascular space invasion	5
	Extracapsular spread	2

DISCUSSION

Medullary carcinoma thyroid is a rare neuroendocrine tumor which mostly presents in 4th to 5th decade of age. Even though MTC's are rare but a large number of studies have been done and are ongoing related to it, which over time have shaped the current guidelines for management of differentiated thyroid cancers.

Although most common presentation of medullary carcinoma thyroid is solitary thyroid nodule, but it may also be asymptomatic or may be diagnosed following routine thyroidectomies.

Risk factors for Lymph node involvement and distant metastasis are 1) Tumor size more than 2 cm, 2) Lympho-vascular space invasion, 3) Extracellular spread, 4) Age less than 40 years.

Surgical management is an important modality for locoregional control. Total Thyroidectomy along with Central compartment neck dissection (CCND) should at least be done in all patients of MTC with surgically resectable disease.

In accordance with the impairment shown by the preoperative ultrasonography, the ATA (American thyroid association) advises carrying out Total thyroidectomy with CCND and finishing the lateral lymph node dissection. The ATA recommends finishing the lymph node dissection in the contralateral lateral compartment in instances with basal CT, or 200 pg/mL (9). Juez et al recommended performing central compartment lymph node dissection ipsilateral and ipsilateral lateral to the tumor if the basal calcitonin was 20–50 pg/mL, bilateral central and ipsilateral lateral lymph node dissection to the tumor if the basal calcitonin was 50–200 pg/mL, and completing the contralateral side if the basal calcitonin was 200 pg/mL (10).

In this study the histopathological profile of patients suggests that majority of patients had nodule size less than 2 cm and lympho-vascular space invasion and perineural spread are found in majority of the cases along with lymph nodes involvement in few. All patient underwent total thyroidectomy and CCND, functional neck dissection (FND) was considered in patients with positive lymph nodes in level II, III, IV of neck. In patients who were diagnosed with MTC following routine hemithyroidectomy were considered for completion thyroidectomy and additional CCND and FND based on lymph node status. One patient in this study underwent additional thymectomy.

Serum Calcitonin and CEA are very important tumor markers in MTC. Many studies have been done in past which suggested the role of serum calcitonin in diagnoses of MTC (11). In this study all patients had raised levels of Serum calcitonin and CEA preoperatively which was comparable to other studies, thus measuring serum calcitonin and CEA preoperatively in all patients of thyroid swelling is must. All patients in this study show drop in the levels of serum calcitonin and CEA postoperatively over long duration follow-up. Although routine postoperative follow-up included serum calcitonin level measurement, our study suggest measurement of serum CEA in addition to serum calcitonin gives better follow-up results, which was comparable with other studies like Costante et al reported that the survival of patients with MTC correlates strongly with the doubling times for their levels of calcitonin and carcinoembryonic antigen (CEA) (12).

Post operative rise in serum calcitonin and CEA is suggestive of distant metastasis or local recurrence, but none of the patients in our study showed raised levels at any postoperative follow-up.

Thus, radical surgical resection in compare to conservative surgery gives better results in cases of MTC's on long term follow-up.

Prophylactic thyroidectomy may wait until after 5 years of age in 2

conditions, first there is no aggressive family history of disease, second is normal ultrasonography report and calcitonin levels. Any patient with a thyroid nodule >5mm or calcitonin >40 pg/ml should undergo total thyroidectomy (13). More the size of nodule and calcitonin levels higher is the risk of disease and metastasis.

There are few drawbacks of our study, first of them is patients who presented with surgically curable disease were included in the study which caused the selection bias. Second drawback was that the patients who were lost to follow-up were excluded from the study which lowers the sample size of this study. Third drawback was that RET mutation testing was not offered to the patients, as role of RET mutation is associated with MTC(14).

For patients who are very susceptible to locoregional relapse, particularly those who have nodal involvement, extrathyroidal extension, or residual illness, radiotherapy should be taken into consideration(15). Role of External beam Radiotherapy (EBRT) in MTC was inadequately studied as only two patients in this study who were having T4a disease were being considered for EBRT, but to comment on effective role of EBRT in MTC a study with larger sample size is needed.

CONCLUSION

Medullary Carcinoma Thyroid, though rare and aggressive thyroid carcinoma can be cured with appropriate surgical management. Surgery is the primary treatment to remove all possible diseases. The most common mode of presentation is Solitary thyroid nodule. Serum Calcitonin and CEA are reliable markers in establishing the diagnosis and during follow up. The preoperative Serum Calcitonin values correlated with the final histopathological stage of the disease. (Statistically not proven- inadequately powered). Adjuvant radiotherapy can be offered for high-risk disease.

REFERENCES

1. Treglia G, Rufini V, Piccardo A, Imperiale A. Update on Management of Medullary Thyroid Carcinoma: Focus on Nuclear Medicine. Semin Nucl Med. 2023 Jul;53(4):481–9.
2. Pelizzo MR, Mazza EI, Mian C, Merante Boschin I. Medullary thyroid carcinoma. Expert Rev Anticancer Ther. 2023 Sep 2;23(9):943–57.
3. Bai Y, Niu D, Yao Q, Lin D, Kakudo K. Updates in the advances of sporadic medullary thyroid carcinoma: from the molecules to the clinic. Gland Surg. 2020 Oct;9(5):1847–56.
4. Jayasinghe R, Basnayake O, Jayarajah U, Seneviratne S. Management of medullary carcinoma of the thyroid: a review. J Int Med Res. 2022 Jul;50(7):030006052211106.
5. Kim M, Kim BH. Current Guidelines for Management of Medullary Thyroid Carcinoma. Endocrinol Metab. 2021 Jun 30;36(3):514–24.
6. Ceolin L, Duval MADS, Benini AF, Ferreira CV, Maia AL. Medullary thyroid carcinoma beyond surgery: advances, challenges, and perspectives. Endocr Relat Cancer. 2019 Aug;26(9):R499–518.
7. Kazaure HS, Roman SA, Sosa JA. Medullary thyroid microcarcinoma: A population level analysis of 310 patients. Cancer. 2012 Feb;118(3):620–7.
8. Zhang D, Colombo C, Sun H, Kim HY, Pino A, De Leo S, et al. Unilateral Surgery for Medullary Thyroid Carcinoma: Seeking for Clinical Practice Guidelines. Front Endocrinol. 2022 Jul 11;13:875875.
9. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan;26(1):1–133.
10. Juez LD, Mercader E, Amunategui I, Febrero B, Rodríguez JM, Gómez Ramírez J, et al. Extension of Prophylactic Surgery in Medullary Thyroid Carcinoma. Differences Between Sporadic and Hereditary Tumours According to Calcitonin Levels and Lymph Node Involvement. World J Surg. 2022 Apr;46(4):820–8.
11. Vardarli I, Weber M, Weidemann F, Führer D, Herrmann K, Görges R. Diagnostic accuracy of routine calcitonin measurement for the detection of medullary thyroid carcinoma in the management of patients with nodular thyroid disease: a meta-analysis. Endocr Connect. 2021 Mar;10(3):358–70.
12. Costante G, Durante C, Francis Z, Schlumberger M, Filetti S. Determination of calcitonin levels in C-cell disease: clinical interest and potential pitfalls. Nat Clin Pract Endocrinol Metab. 2009 Jan;5(1):35–44.
13. Tavares MR, Toledo SPA, Montenegro FLM, Moyses RA, Toledo RA, Sekyia T, et al. Surgical approach to medullary thyroid carcinoma associated with multiple endocrine neoplasia type 2. Clinics. 2012 Apr;67:149–54.
14. Xu JY, Grubbs EG, Waguespack SG, Jimenez C, Gagel RF, Sosa JA, et al. Medullary Thyroid Carcinoma Associated with Germline RET ^{K666N} Mutation. Thyroid. 2016 Dec;26(12):1744–51.
15. Rowell NP. The role of external beam radiotherapy in the management of medullary carcinoma of the thyroid: A systematic review. Radiother Oncol. 2019 Jul;136:113–20.