

# An Interesting Case of Familial Medullary Carcinoma Thyroid – Seldom Seen by Surgeons

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## Abstract

Medullary thyroid carcinoma (MTC) constitutes around 5% of all thyroid cancers with a worse prognosis. It accounts for 13% of thyroid cancer-related deaths. A 23-year-old male presented with a 4-year history of progressively increasing thyroid swelling with similar family history. On examination, butterfly-shaped firm swelling of size 7 × 3 cm in the right and 7 × 4 cm in the left seen on the anterior aspect of neck with regular margins and nodular surface moving with deglutition extending from the thyroid cartilage to clavicle head and laterally beyond the sternocleidomastoid into the posterior triangle muscle. Pemberton's sign was negative. Computed tomography neck showed enlarged both thyroid lobes with areas of cystic degeneration and 15 mm retrosternal extension of the left lobe of thyroid with bilateral IB, II, and V lymphadenopathy. Serum calcitonin level was 4435 pg/ml. Fine-needle aspiration cytology favored features of MTC. Total thyroidectomy with central compartment neck dissection was done. Intraoperative frozen sections of bilateral level III were found to be tumor free, so proceeded with thyroid excision and central compartment neck dissection. Histopathology revealed MTC with bilateral multifocal capsular and lymphovascular invasion and metastatic foci in the right central compartment lymph node. Hence, early diagnosis in family members offers a higher likelihood of cure and long-term survival.

**Key words:** Familial medullary thyroid carcinoma, Medullary thyroid carcinoma, Medullary thyroid carcinoma, MTC

## INTRODUCTION

Medullary thyroid carcinoma (MTC) constitutes around 5% of all thyroid cancers<sup>[1]</sup> with a worse prognosis. It accounts for 13% of thyroid cancer-related deaths. MTC usually arises from parafollicular cells that normally secrete a number of peptide hormones such as calcitonin, serotonin, and vasoactive intestinal peptide.<sup>[2]</sup> Thus, it is widely accepted as neuroendocrine tumor. Both sporadic and familial forms are seen, with 70% and 30% incidence, respectively.<sup>[3]</sup> The hereditary form of MTC accounts for 5%–10% of all malignancies of thyroid; hence, early detection in family members offers a long-term survival. Here, we present a case report of familial MTC (FMTC).

## CASE REPORT

A 25-year-old male presented with progressively increasing swelling in the thyroid region for the past 4 years, with a history of neck swelling in the family. No history of associated complaints such as pain, dysphagia, breathlessness, change in voice, palpitations, weight gain or loss, and restlessness. The patient is a known smoker and alcoholic. There was a history of similar complaints in the family for sister who is on treatment and uncle who was expired.

On examination, the patient was found to be thin built and moderately nourished. Vitals were normal. Inspection findings showed swelling seen on the anterior aspect of neck which is butterfly shaped with regular margins. Size was 7 × 3 cm in the right side and 7 × 4 cm in the left side. The swelling moved with deglutition and the surface appeared nodular and skin over the swelling appeared normal. Veins over the swelling were visible and there were no scars and sinuses. Trachea appeared to be in midline.

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Month of Submission : 09-2019  
Month of Peer Review : 10-2019  
Month of Acceptance : 11-2019  
Month of Publishing : 11-2019

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Palpatory findings showed the swelling extended superiorly from the thyroid cartilage and inferiorly up to clavicle head. Lateral border was not applicable and extended beyond the sternocleidomastoid into the posterior triangle muscle. Medially it extended up to 1 cm lateral to midline on the right side. Swelling was firm and nodular. Trachea was deviated to the right. Swelling was situated deep to the deep fascia. Cervical lymph nodes were not palpable. Pemberton's sign was negative. Examination of other systems showed eye signs as negative, skull, and oral cavity normal. Cardiovascular system, respiratory system, and central nervous system appeared normal.

Ultrasonography of the neck revealed enlarged right and left lobes of thyroid with retrosternal extension of the left lobe of thyroid. Ultrasonography features were suggestive of multinodular goiter (MNG) with bilateral level IB, II, and V subcentric lymph nodes. Computed tomography (CT) neck – showed enlarged both thyroid lobes with areas of cystic degeneration and retrosternal extension of the left lobe of thyroid for a distance of 15 mm. Bilateral level IB, II, and V subcentimetric enlarged lymph nodes were seen.

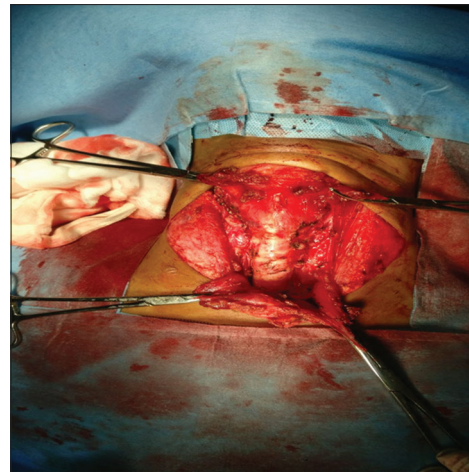
Serum calcitonin level was 4435 pg/ml and serum calcium level was 9.6 mg/dl. Thyroid function tests and routine blood investigations were done and are within normal limits. Antithyroid peroxidase level was found to be 1.26 IU/ml. CT chest and abdomen were normal and no signs of metastasis noted.

Fine-needle aspiration (FNA) cytology was done in the swelling over neck. Cellular smears studied show cells arranged in clusters of varying sizes and in dispersion in a hemorrhagic background. The cellular smears studied showed round to oval to polygonal to many spindle-shaped cells and plasmacytoid cells, many with cytoplasm showing coarse granularity.

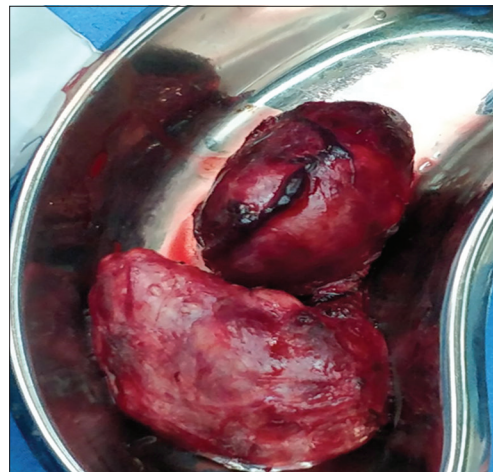
Moderate anisonucleosis noted with few binucleate and trinucleate forms and occasional bizarre cells, the nuclei showing uniform stippled, finely dispersed chromatin to mildly hyperchromatic nuclei. Occasional areas show cells arranged in follicular pattern. Occasional cells show intranuclear cytoplasmic inclusions. Cyst macrophages also noted.

## RESULTS

Pre-operative workup was done and the patient was taken up for surgery. Total thyroidectomy with central compartment neck dissection was done. Intraoperatively, frozen sections of bilateral level III were found to be free of tumor and hence proceeded with thyroid excision and central compartment neck dissection [Figures 1 and 2].



**Figure 1: Picture after total thyroidectomy and central compartment node dissection**



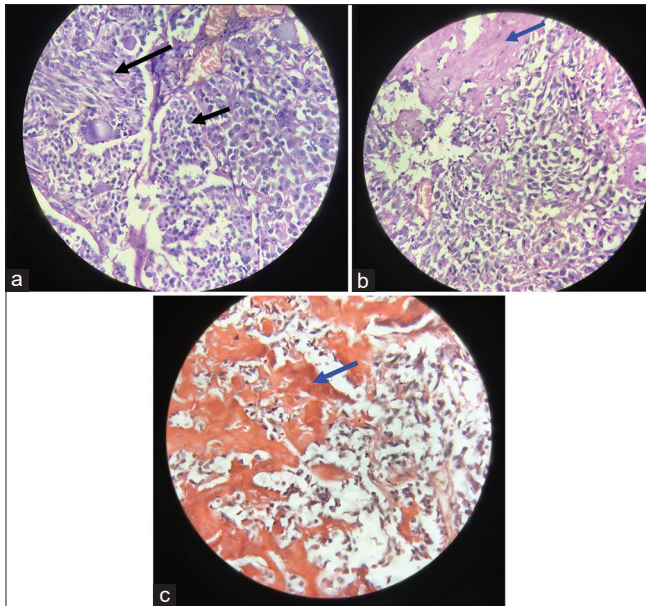
**Figure 2: Excised thyroid gland**

Histopathology revealed MTC with bilateral multifocal capsular and lymphovascular invasion and metastatic foci in the right central compartment lymph node [Figure 3a-c].

After 2 months, a repeat serum calcitonin showed 5 pg/ml.

## DISCUSSION

MTC originates from the parafollicular or C-cells of the thyroid gland, which produce calcitonin as well as other secretory products such as carcinoembryonic antigen (CEA), adrenocorticotrophic hormone (ACTH), chromogranin, histaminases, neurotensin, somatostatin, and B-melanocyte-stimulating hormone.<sup>[4]</sup> Most MTCs occur sporadically (75–80%), but they are also found in hereditary syndromes such as multiple endocrine neoplasia (MEN 2A) (Sipple syndrome), MEN 2B (Wagenmann–Froboese syndrome), and FMTC.<sup>[4]</sup> MEN 2A that accounts for 95% of MEN 2 cases is characterized by MTC, primary hyperparathyroidism (HPT), and pheochromocytoma.<sup>[5,6]</sup> There are four variants



**Figure 3: Histopathological images: (a) Round cells (short arrow) and spindle-shaped cells (long arrow), (b) pink amorphous deposition depicting amyloid deposition (blue arrow), (c) amyloid deposition confirmed by Congo red stain (blue arrow)**

of the MEN 2A syndrome: Classical MEN 2A, MEN 2A with cutaneous lichen amyloidosis, MEN 2A with Hirschsprung disease, and FMTC, in which the families or individuals have MTC but not pheochromocytomas or HPT.<sup>[7]</sup> The hereditary forms are characterized by germline mutations in the rearranged during transfection (RET) proto-oncogene located on chromosome 10q11.2.<sup>[5,7,8]</sup> This oncogene encodes a transmembrane protein receptor kinase and is usually expressed in the cells of the neural crest, branchial arches, and the urogenital system. Approximately 50% of sporadic MTCs harbor RET mutations and up to 80% of the remaining carry RAS (HRAS, KRAS, or NRAS) mutations.<sup>[9-11]</sup> Sporadic MTC typically occurs between the fourth to sixth decades of life; however, patients with hereditary disease present earlier like our patient. Patients often have a thyroid nodule, which may be associated with palpable cervical lymphadenopathy (15–20% of the cases).<sup>[12]</sup>

Approximately 2–4% of patients develop Cushing syndrome as a result of ectopic production of ACTH. FNA biopsy is used to make the diagnosis of MTC in patients with a solitary thyroid nodule (or a dominant nodule within an MNG).<sup>[12]</sup> The sensitivity of FNA for the diagnosis of MTC is 50%–80%, though a higher sensitivity can be achieved by adding the immunohistochemical staining for calcitonin.<sup>[13-15]</sup> When the suspicion for MTC is high (patient with flushing, diarrhea, and in the context of a thyroid nodule), calcitonin can be measured in the washout of the FNA biopsy needle.<sup>[14]</sup> The FNA cytology report often displays discohesive or weakly cohesive cells

that may be spindle shaped, plasmacytoid, or epithelioid in appearance.<sup>[12,16]</sup> Furthermore, giant cells, oncocytic clear cells, and small carcinoma-like cells may also be present. The nuclei are generally eccentric, and chromatin granularity is seen as a salt and pepper appearance similar to other neuroendocrine tumors.<sup>[12]</sup> The presence of amyloid is helpful but not by itself diagnostic.<sup>[17]</sup> The diagnosis is confirmed by immunostaining for calcitonin, chromogranin, or CEA.<sup>[12]</sup> Thyroglobulin staining is usually negative. As it is not possible to distinguish sporadic from familial disease at initial presentation, all new patients with MTC should be screened for RET point mutations, pheochromocytoma, and HPT. Pre-operative calcitonin levels may correlate with tumor size in both sporadic and familial cases of MTC.<sup>[18]</sup> Pre-operative calcitonin level of cutoff 50 pg/mL may help predict who will have a biochemical complete response after surgery. Our patient calcitonin was 4435 pg/ml prior to surgery which decreased to 5 pg/ml in the post-operative period. Machens *et al.*<sup>[19]</sup> reported that 62% of the patients with MTC without nodal metastases had normal calcitonin postoperatively, while 10% of patients with nodal metastasis had normal post-operative calcitonin levels. Contrast-enhanced CT of the neck and chest, three-phase contrast-enhanced multidetector liver CT, or contrast-enhanced magnetic resonance imaging (MRI) of the liver, and axial MRI and bone scintigraphy are recommended in patients with extensive neck disease and signs or symptoms of regional or distant metastases and in all patients with a serum calcitonin >500 pg/mL.<sup>[4]</sup> 18F-Fluorodeoxyglucose-positron emission tomography (PET)/CT nor F-DOPA-PET/CT is recommended to detect the presence of distant metastases.<sup>[5]</sup> MTC can only be cured by complete resection of the thyroid tumor and any local and regional metastases.<sup>[20,21]</sup> Total thyroidectomy is the treatment of choice for patients with MTC due to the high incidence of multicentricity, the more aggressive course compared with differentiated thyroid cancer, and the fact that 131I therapy is usually not effective.<sup>[20]</sup> For MTC limited to the neck and no evidence of involved cervical lymph nodes on pre-operative ultrasound, total thyroidectomy with prophylactic bilateral central compartment lymph node dissection is the desired initial treatment and this was the recommended management that we offered our patient. Roughly, 10% of patients with sporadic MTC and all patients with FMTC have bilateral or multifocal disease; likewise, the latter all have premalignant diffuse C-cell hyperplasia.<sup>[4]</sup> Therefore, total thyroidectomy rather than unilateral lobectomy is the preferred surgical approach.<sup>[4]</sup> MTC patients with unilateral intrathyroidal tumors are reported to have lymph node metastases in 81% of central compartment (Level VI) dissections, 81% of ipsilateral lateral compartment (Levels II–V) dissections, and 44% of contralateral lateral compartment (Levels II–V)

dissections.<sup>[22]</sup> Very similar numbers are reported for patients with bilateral tumors. In addition, the incidence of lateral compartment nodal disease depends on the frequency of metastases in the central compartment. Pre-operative neck ultrasonography and basal calcitonin/CEA levels may be helpful to define the extent of nodal metastases and hence guide surgery, although this is debatable. Patients with basal calcitonin levels  $>20$  pg/mL are unlikely to have nodal metastases.<sup>[19]</sup> Increasing calcitonin levels ( $>20$  pg/mL) are associated with metastases to the ipsilateral central and ipsilateral lateral compartment, contralateral central compartment ( $>50$  pg/mL), contralateral lateral compartment ( $>200$  pg/mL), and upper mediastinum ( $>500$  pg/mL).<sup>[22]</sup> As such, biochemical cure can be achieved in patients with pre-operative calcitonin levels  $<1000$  pg/mL but is unlikely in patients with levels  $>10,000$  pg/mL.<sup>[19]</sup> The current American Thyroid Association (ATA) guidelines recommend that patients without nodal metastases on ultrasonography and no distant disease undergo total thyroidectomy and bilateral level VI node dissection.<sup>[4]</sup> In this scenario, no consensus was reached regarding the optimal management of the lateral compartments, and the guidelines indicate that a prophylactic lateral neck dissection may be considered based on calcitonin levels.<sup>[4]</sup> The ATA guidelines could not attain a consensus agreement on this topic but did recommend that prophylactic lateral neck dissections may be considered based on serum calcitonin levels.<sup>[4]</sup> In contrast, the NCCN guidelines suggest considering a prophylactic ipsilateral modified neck dissection for high-volume or gross disease in the adjacent central compartment if the tumor is  $\geq 1$  cm in size or the disease is bilateral.<sup>[20]</sup> In patients with diagnosed lymph node metastases (but no distant disease), total thyroidectomy, bilateral level VI dissection, and dissection of Levels II–V in the involved compartment are recommended.<sup>[20]</sup> Prophylactic dissection of the contralateral neck can be considered if the calcitonin level is  $>200$  pg/mL.<sup>[20]</sup> Some authors have suggested that prophylactic central compartment neck dissection is not required in patients with small intrathyroidal MTCs with a pre-operative calcitonin  $<20$  pg/mL, as metastatic lymph nodes are exceedingly rare in these circumstances.<sup>[19]</sup> Patients with MTC limited to the neck and cervical lymph nodes should have a total thyroidectomy, dissection of the central compartment lymph nodes (Level VI), and dissection of the involved lateral neck compartments (Levels II–V). When pre-operative imaging is positive in the ipsilateral lateral neck compartment but negative in the contralateral neck compartment, contralateral neck dissection should be considered if the basal serum calcitonin level is  $>200$  pg/mL.<sup>[4]</sup>

External beam radiation therapy (EBRT) as adjuvant therapy to the neck and mediastinum is not routinely indicated

but should be considered in patients with incompletely resected disease and those considered at high risk for locally recurrent disease.<sup>[20]</sup> This includes patients with microscopic residual disease, the presence of extrathyroidal extension, or extensive lymph node metastases.<sup>[4]</sup> The potential benefits must be weighed against the acute and chronic toxicity linked with this treatment modality.<sup>[12]</sup> EBRT appears to be effective for local tumor control.<sup>[23,24]</sup> As a general rule, patients should no longer be candidates for repeat neck surgery, as the operation becomes more technically challenging after EBRT.<sup>[12]</sup> If recommended, 60–66 Gy is delivered to the thyroid bed over a 6-week period, although higher doses are needed for gross residual disease.<sup>[25]</sup>

Intensity-modulated radiation therapy is recommended for disease adjacent to the spinal cord to reduce toxicity. Patients in the post-operative period are risk stratified based on their risk of recurrence into low-risk disease and high-risk tumors. Serum calcitonin and CEA levels are measured at 3 months after surgery and if undetectable or within the normal range, the NCCN guidelines recommend annual serum calcitonin and CEA testing.<sup>[20]</sup> However, the ATA guidelines diverge somewhat and recommend measurement at 6-month intervals for 1 year and then once yearly, provided physical examination is also normal. We are performing the ATA recommended follow-up and surveillance strategy. Patients with elevated calcitonin levels, as our patient was found to have 3 months after surgery, need additional imaging.<sup>[20]</sup> If calcitonin is  $<150$  pg/mL, ultrasound is recommended and if no disease is identified and the physical examination is unremarkable, these patients can be followed at 6-month intervals with examination, laboratories, and neck ultrasonography.<sup>[4]</sup> If post-operative calcitonin is  $>150$  pg/mL, the patients need evaluation by neck ultrasonography, chest CT, contrast-enhanced MRI, or triple-phase contrast-enhanced CT of the liver, bone scintigraphy, and MRI of the axial skeleton and pelvis to evaluate for metastatic disease.<sup>[20]</sup> The liver is the most common site of distant metastases in patients with MTC, occurring roughly in 45% of patients with advanced disease.<sup>[4]</sup> Other sites of distant metastasis include bone, brain, and lung.<sup>[12]</sup> If imaging work-up is negative, monitoring with history and physical examination, calcitonin and CEA levels, and evaluation of the neck with ultrasonography should continue. Brain imaging is indicated only if patients have neurological symptoms.<sup>[20]</sup> Measurement of calcitonin and CEA doubling times can also be used to determine the rate of progression of MTC.<sup>[26,27]</sup> The frequency of repeating imaging studies will be dependent on the magnitude and rate of rise of the calcitonin and CEA levels. Patients with stable post-operative calcitonin levels in 150 pg/mL–300 pg/mL range are usually followed with yearly neck ultrasound for several years, reserving repeat cross-sectional imaging (neck,

chest, abdomen, and pelvis) looking for distant metastases in those patients with rising calcitonin or CEA levels. PET/CT scans are considered only when the calcitonin concentrations are higher than 500 pg/mL–1000 pg/mL.<sup>[28]</sup> Radionuclide bone scan can be helpful in selected cases when cross-sectional imaging fails to identify the source of the elevated calcitonin levels.<sup>[29-31]</sup>

## CONCLUSION

MTC being an uncommon thyroid malignancy, genetic screening for evaluation of FMTC, MEN2A, and MEN2B should always be considered in pre-operative workup. Early diagnosis in family members offers a higher likelihood of cure and long-term survival.

Total thyroidectomy with central compartment neck dissection is the mainstay of treatment and regular follow-up is a must to prevent recurrence. Family counseling and screening of family members are a prerequisite in cases of familial medullary carcinoma.

## ACKNOWLEDGMENT

On behalf of the author team, I would like to wholeheartedly thank our HOD Prof. Jeyakumar S. for his encouragement and support and also Prof. Dhalapathi Sadacharan (Surgical Endocrinologist, MMC) for his guidance intraoperatively.

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**How to cite this article:** Mustafa M, Daniel R, Bharadwaj RA, Aravindan SP, Kiran YS, Reddy ML. An Interesting Case of Familial Medullary Carcinoma Thyroid – Seldom Seen by Surgeons. Int J Sci Stud 2019;7(8):8-13.

**Source of Support:** Nil, **Conflict of Interest:** None declared.