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Management of Medullary Thyroid Carcinoma

Mumtaz A. Ansari, Rohan Kumar Gupta, and Vivek Srivastava*

Department of General Surgery, Institute of Medical Sciences, BHU, Varanasi, India.
mumtazbhu@gmail.com, rohan926@gmail.com, vivekims97@gmail.com*

Abstract: **Thyroid cancer is the most common malignancy of the endocrine system, representing 3.8% of all new cancer cases. Medullary thyroid cancer (MTC) accounts for about 5% of thyroid malignancies and arises from the parafollicular or C cells of the thyroid. Medullary carcinomas arise sporadically in about 70% of cases. The remaining 30% are familial, occurring in the setting of multiple endocrine neoplasia (MEN) syndrome 2A or 2B, or familial medullary thyroid carcinoma without an associated MEN syndrome. After a diagnosis of MTC on FNAB, next steps should be measurement of serum calcitonin and CEA, analysis for a RET germline mutation. Awareness regarding diagnosis and management of both sporadic and hereditary MTC is essential. Hence we summarize the recommendations for diagnosis and management of MTC according to current clinical guidelines.**

Index Terms: **Medullary thyroid cancer, Fine needle aspiration, Calcitonin, Multiple endocrine neoplesia.**

I. INCIDENCE

In normal population, the prevalence of palpable thyroid nodules ranges from 1% (in male) to 5% (in female), and the detection of thyroid nodules by ultrasonography increases from 19% to 68%, higher in female and elderly patients (Dean et al, 2008). The incidence of thyroid cancer in the United States is 7.7 per 100,000, which has been increasing due to availability of newer modalities of screening (Pacini et al, 2012; British Thyroid Association, 2007).

Medullary thyroid carcinoma (MTC) accounted for 5%–8% of all thyroid malignancies (Pacini et al, 2012), but according to recent analysis of the U.S. Surveillance, Epidemiology, and End Results program database revealed that a lower incidence rate of 1%–2% of all thyroid cancers in the United States (Hegedus et al, 2004).

II. INTRODUCTION

MTC accounts for about 5% of thyroid malignancies and arises from the parafollicular or C cells of the thyroid mostly situated superolaterally in the thyroid lobe, which, in turn, are derived from the ultimobranchial bodies (from fourth pharyngeal pouch).Most MTCs occur sporadically. However, approximately 25% are associated with several inherited syndromes such as familial MTC, MEN2A, and MEN2B. All these variants are known to result secondary to germline mutations in the RET proto-oncogene.

III. GENETIC FEATURES OF MEDULLARY THYROID CANCER SYNDROMES

Medullary carcinomas arise sporadically in about 70% of cases. The remaining 30% are familial, or associated with multiple endocrine neoplasia (MEN) syndrome 2A or 2B, or familial medullary thyroid carcinoma without an associated MEN syndrome.

Both familial and sporadic medullary forms are associated with gain-of-function driver mutations in the RET receptor tyrosine kinase.

Multiple Endocrine Neoplasia (MEN) Syndromes:

The MEN syndromes are a group of inherited diseases caused by proliferative lesions (hyperplasia, adenomas, and carcinomas) of multiple endocrine organs.

Have some distinctive features:-

- younger age in onset than sporadic
- occur in multiple endocrine organs, either synchronously or metachronously
- often multifocal
- more aggressive and more recurrence

MEN II A: (Sipple syndrome)

- Gain of function mutation of RET

Components:

- Pheochromocytoma, MCT & parathyroid hyperplasia
- Loss of function mutation of RET
- Hirschsprung disease

* Corresponding Author

MEN II B: Components:

MCT, Multiple neuromas and marfanoid features:

Familial medullary thyroid cancer can be seen as variant of MEN-2A, without the other characteristic manifestations. In comparison with MEN-2, familial medullary carcinoma typically presents at an older age and follows a more indolent course.

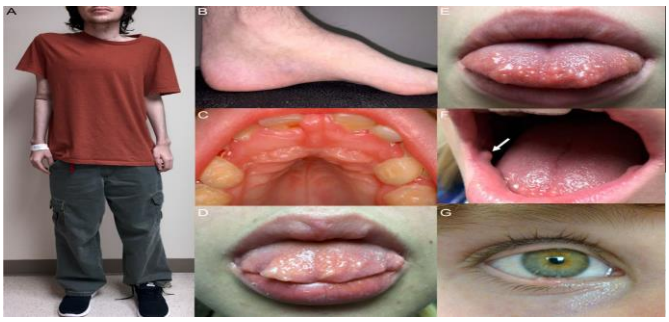

Fig. 1. Image showing charaterestics of MEN2B (A) marfenoid feature rest with mucocutaneous neuroma

IV. Clinical Features

Often present with a neck mass with or without palpable cervical lymphadenopathy (15% to 20%). Pain or aching, dysphagia, dyspnoea, or dysphonia are characterisitc of local invasion of tumor. Distant blood-borne metastases usually uncommon at the time of presentation. Metastasis occurs to the liver, bone (frequently osteoblastic), and lung sign of advanced disease.MTC is usually more aggressive than the other more common types of thyroid cancer. TSH usually remains normal when MTC is present most of the time.

Paraneoplastic feature like Diarrhea, flushing, pruritus or features of cushing syndrome (Due to 5HT, histamine, VIP, ACTH, PGF2alpha, PGE2).

V. Diagnosis

Usually presents as neck mass either associated with pain of change in voice or difficulty in swallowing.

Whenever a patient present approach should be clinical examination the initial evaluation of a thyroid nodule must include detailed clinical examination and history and ultrasonography assessment, because certain sonographic patterns are key to diagnose the chances of malignancy and, in addition to nodule size, drive the decision for FNAC (Brito et al, 2014).

High-suspicion nodules—those that are hypoechoic with irregular borders, microcalcifications, taller-than-wide morphology,firm, increase vascularity or obvious extrathyroidal extension—have a risk of malignancy of 70%–90%. Hypoechoic nodules that are solid with a regular border considered as intermediate-suspicion nodules with a malignancy risk of 10%–20% (Smith-Bindman et al, 2013).

The American Thyroid Association (ATA) guideline makes a strong recommendation for FNAC of those nodules which is 1 cm or greater in size and have a high- suspicion (moderate-quality evidence) or intermediate- suspicion (low-quality evidence) sonographic pattern (Smith-Bindman et al, 2013).

A. On FNAC

The cytologic feature of MTC on FNAC can be variable, leading MTC to be misdiagnosed as a follicular neoplasm, sarcoma, or a plasmacytoma (Haugen et al 2015).

Chang et. al. 26 examined 34 cases of MTC on FNAC and found that the diagnosis was correct in 82.4% of the cases (Wells et al, 2015).

Another study found that 89.0% of MTC cases on cytological examination (81 of 91) were diagnosed correctly on cytology (Chang et al, 2005).

However, a meta-analysis of fifteen studies involving 641 cases of FNA for MTC found out a detection rate of only 56.4% on cytology (Papaparaskeva et al, 2000).

The revised ATA guideline for MTC now recommends that in case of inconclusive cytological result measurement of calcitonin in FNA specimens and immunohistochemistry for calcitonin, CEA, and chromogranin should be done (grade B recommendation based on fair evidence); however, the guideline does not recommend a threshold value for calcitonin (Haugen et al, 2016).

Once MTC is diagnosed on FNA, measurement of serum calcitonin and CEA, analysis for a RET germline mutation, and a staging workup should follow.

Ultrasound examination of the neck must be performed in all patients with MTC. In case of advanced disease Contrast-enhanced CT of neck and chest, three-phase contrast-enhanced multi-detector liver CT, or contrast-enhanced MRI of the liver, and axial MRI and bone scintigraphy are recommended, and in all patients with a serum Calcitonin level greater than 500pg/mL. Grade C Recommendation (Trimboli et al, 2015).

B. Pathological feature

Medullary carcinomas may arise as a solitary nodule or manifest as multiple lesions involving both lobes of the thyroid. Multicentricity is common in familial cases. Larger lesions often contain foci of necrosis and hemorrhage and may extend through the capsule of the thyroid.

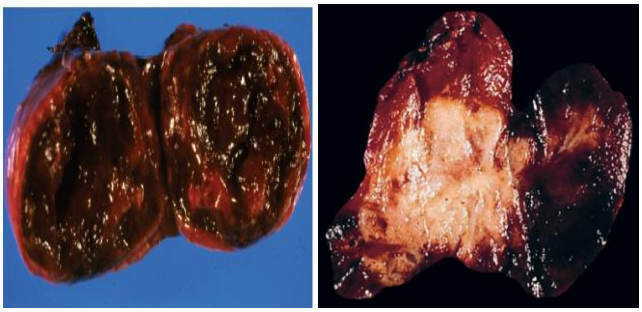

Fig. 2. Gross pathology of MTC

C. On microscopy

Medullary carcinomas are composed of polygonal to spindle-shaped cells, which may form nests, trabeculae, and even

follicles. Amyloid deposits presence in adjacent stroma as altered calcitonin molecule is a distinctive feature. Calcitonin demonstrable both within the cytoplasm of the tumor cells and in the stromal amyloid by immunohistochemical methods. One of the characteristic features of familial medullary carcinomas is presence of multiple site of C cell hyperplasia involving both lobes among them on of act as precursor lesion for malignancy (Wells et al, 2015).

VI. Surgical management

Preoperative assessment of calcitonin contribute for extension of MTC and nodal involvement. In a study of 300 consecutive patients with MTC managed by total thyroidectomy and compartment-oriented lymph node dissections there was virtually no risk of nodal involvement when s.ctn was less than 20 (N <10).

When Basal serum CTN levels exceeding 20, 50, 200, and 500pg/mL it was associated, with metastases to lymph nodes in the ipsilateral central and lateral neck, and the contralateral central and contralateral lateral neck, and the upper mediastinum (Wells et al, 2015).

VII. Recommendation

- Patients with MTC with no evidence of nodal metastases by US examination and no any evidence of distant metastases should have a total thyroidectomy with central group of lymph node dissection (level VI). Grade B Recommendation (Wells et al, 2015).
- In patients with MTC with no evidence of nodal metastases on US, and no distant metastases, dissection of lymph nodes in the lateral compartments (levels II–V) can be considered on the basis of basal calcitonin level Grade I Recommendation (Wells et al, 2015).
- Patients with MTC with involved cervical nodes should have a total thyroidectomy with central and ipsilateral neck node dissection when imaging shows no involvement of contralateral nodes contralateral node dissection should be considered when basal calcitonin level more than 200 (Wells et al, 2015).

A. Prophylactic thyroidectomy for children

- Highest risk: In patients with MEN2B and a RET codon M918T mutation
  Recommendation: Should undergo total thyroidectomy within 1 year of life or may within first month of life. Central node dissection should be considered when parathyroid is identified during procedure or planned for autotransplant (Wells et al, 2015).
- High risk:-Children with MEN2A and RET codon 634 mutation
  Recommendation: Children in the ATA-H category : total thyroidectomy to be done within 5 yr or in case of rising calcitonin level earlier .central neck dissection to be done when there is imaging evidence of node involvement or calcitonion level more than 40 pg/ml (Wells et al, 2015).
- Moderate risk: rest other RET mutation
  Recommendation: Children in the ATA-MOD category clinical examination with s.calcitonin level measurement to be done 6 month or yearly follow up to be done thyroidectomy to be considered when there is rising ctn level or any evidence of nodule on examination or on sonography (Wells et al, 2015).

B. If associated parathyroid hyperplasia present

Recommendation: In case of MTC with men 2A patients with HPTH only visibly enlarged parathyroid glands should be resected. If all four glands are enlarged then subtotal parathyroidectomy to be done or one parathyroid to be left on vascular pedicle or autotransplanted. Grade C Recommendation (Wells et al, 2015).

VIII. Follow up

- Patients with elevated postoperative serum CTN levels less than 150pg/mL physical examination and regular sonographic evaluation to be done at 6 month interval . Grade C Recommendation (Wells et al, 2015).
- If the postoperative serum CTN level exceeds 150pg/mL evaluation of distant metastases to be done with CT/MRI/bone scintigraphy or radiactive scan (Wells et al, 2015).

Conclusion

The initial diagnosis of a suspicious thyroid nodule is the same in DTC and MTc, but the remainder of the workup for a diagnosis of MTC is distinct. After a diagnosis of MTC on FNA, next steps should be measurement of serum calcitonin and CEA, analysis for a RET germline mutation, the appropriate workup for pheochromocytoma and hyperparathyroidism as indicated based on RET mutation status, and assessment for metastatic disease. Total thyroidectomy is recommended for all cases due to multicentricity in inherited cases follow up is done by interval USG and serum calcitonin and CEA level. Central group of lymph node dissection recommended in all cases. Prophylactic thyroidectomy in children is strongly recommended on the basis of RET and codon mutation status.

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