Medullary thyroid carcinoma: Cytological report of two cases

INTRODUCTION
Medullary thyroid carcinoma (MTC) is an uncommon calcitonin (CT)-producing neuroendocrine tumor which accounts for <10% of all the thyroid carcinomas. Both sporadic and familial forms occur, the sporadic form accounting for 70% of cases. Hereditary MTC is transmitted as an autosomal dominant trait either alone as familial MTC or as a part of multiple endocrine neoplasia (MEN) Type 2A or 2B.[1] The pathogenetic mechanism has been associated with germline gain-of-function mutations of the RET proto-oncogene mainly in exons 10–15.[2] This is one of the human cancers where the genetic screening has made it possible to prevent the occurrence of overt disease by performing prophylactic surgery.[2] In specific cases, prevention of this tumor is actually possible by detection of precursor lesion (C-cell hyperplasia)[3] and the hallmark genetic mutation in the RET gene.[2] Monitoring of patients with a positive family history is therefore of great importance. We present two cases of MTC, diagnosed by FNA and subsequently confirmed by histopathological study.

CASE REPORTS

Case 1
A 65-year-old female patient presented with a progressively increasing midline neck swelling for the past 7 years, hoarseness of voice, dysphagia, and generalized weakness for 8 months. Physical examination revealed an oval, firm to hard swelling in the midline of neck measuring 6 cm × 6 cm and moved with deglutition [Figure 1a].

Case 2
A 34-year-old female with a right sided neck swelling since 2 years, not associated with any other complaints. On examination, two lumps were noted; one in the midline measuring 2 cm × 2 cm...
and the other on the right side measuring 1 cm × 1 cm. Both were firm to hard and moved with deglutition [Figure 2a].

Both the patients were in good health, and physical examination was normal with the exception of thyromegaly without lymphadenopathy. There was no history of similar tumors in their families and no evidence of other endocrine abnormalities in both the cases. Hematological parameters, serum urea, serum creatinine, liver function tests, and urinalysis were all normal.

Fine-needle aspiration cytology (FNAC) of thyroid lesions in both cases were done using a 23G needle and 10 mL syringe. The smears thus prepared were stained with hematoxylin and eosin, May-Grunwald-Giemsa (MGG) and Papanicolaou (PAP) stains. Cytosmears in the both the cases showed cells in clusters as well as dispersed singly. Tumor cells were of varied morphology ranging from round cells with central nuclei, plasmacytoid cells with eccentric nuclei and even spindloid. The chromatin was characteristically clumped pattern (salt and pepper like). Cytoplasm varied in amount, mostly abundant and amphophilic in nature. Homogeneous, eosinophilic material was noted in the background was confirmed by Congo red stain as amyloid. Mitotic figures were sparse. [Figures 1b and 2b]. A diagnosis of MTC (plasmacytoid type) was made. Serum Calcitonin levels were assayed in both the cases and were found to be 805 pg/mL and 1210 mg/mL respectively aiding our diagnosis. Histopathology of the resected specimens confirmed the diagnosis.

**DISCUSSION**

MTC is the first human malignancy known to be associated with a tumor marker, the hormone CT. Measurement enables diagnosis as well as prognostication following surgical resection of the primary thyroid tumor. In familial cases, identification of the precursor lesion of this tumor and genetic mutation allows for early diagnosis and therapy. It is also associated with other endocrine abnormalities including parathyroid hyperplasia and pheochromocytoma, as part of the MEN syndromes.[4]

FNAC is considered as a first line diagnostic test for evaluation of thyroid lesions along with immunocytochemistry. An accurate preoperative diagnosis of MTC has important implications for clinical management. Cytological criteria for the diagnosis of MTC are well described. However, variable patterns of growth and cytological presentation may cause diagnostic difficulty.[1] This tumor has a range of cytologic patterns plasmacytoid, spindle cell, small cell, follicular, tubular and giant cell variants, the most common being plasmacytoid cell type.[5] FNAC smears from the plasmacytoid MTC are usually cellular, cells are dispersed and are characterized by eccentric nuclei, “neuroendocrine type” chromatin, moderately abundant dense cytoplasm with some binucleated, and multinucleated cells in a relatively clean background. Intranuclear inclusions can also be seen. The cytoplasm of the tumor cells is faintly granular in fixed material but may show conspicuous red granules in air-dried MGG-stained smears.[6]

Amyloid may be observed as acellular material in the form of strings or as round to oval shaped fragments. It can be seen surrounded by tumor cells or separate from them which stain variable shades of magenta with MGG and grayish-orange with PAP. Congo red staining helps to differentiate amyloid from colloid or hyaline fragments and is diagnostic for MTC.[5][6]

Depending on the specific cytomorphology of the tumor a number of differential diagnoses may arise. The small cell pattern may be mistaken for a malignant lymphoma, poorly differentiated insular carcinoma, or metastatic small cell carcinoma, whereas the spindle cell tumor may mimic a fibroblastic tumor or even melanoma.[6]

In such problematic cases, measurement of serum CT levels is very helpful in resolving the dilemma.

CT is the most reliable tumor marker because of its high specificity and sensitivity. A variety of diseases other than MTC including nodular thyroid disease, autoimmune thyroiditis, and neuroendocrine tumors may also cause elevation of CT, but levels of CT above 100 pg/ml
are reported to be invariably associated with MTC. Stimulatory tests with pentagastrin and calcium infusion can be utilized in suspicious cases with borderline serum levels of CT.\(^7\)

An interesting new technique has been described, which is based on the measurement of CT levels in FNAC wash-out fluid. Another experimental technique has recently been reported in which the tumor cells have been made to fluoresce in vivo. It is proposed that this may help in adequate resection at surgery.\(^8\)

**CONCLUSION**

FNAC is simple outpatient department procedure which can be of great help in the definitive preoperative diagnosis of MTC. In spite of cytological variability we were able to diagnose both the cases of MTC accurately on FNAC. Hence, we highlight here that this rare tumor can be diagnosed with high accuracy if we make use of ancillary studies along with simple procedure such as FNAC. This will help in early diagnosis and may result in higher probability of cure and long-term survival.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**