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Cytology of medullary thyroid carcinoma – report of 4 cases

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ABSTRACT

Medullary thyroid carcinoma (MTC) is an uncommon thyroid tumor which derives from the parafollicular or C cells of the gland and is associated with specific supportive diagnostic markers. Despite this, its cytological diagnosis is often difficult owing to variable patterns of growth and cytologic features. We report here with four cases of MTC. The diagnosis was established on fine-needle aspiration cytology (FNAC) followed by surgical resection and confirmed on histopathology. Preoperative serum calcitonin (CT) levels were also done in all the four cases.

Keywords: Medullary thyroid carcinoma, Calcitonin, Fine needle aspiration cytology

INTRODUCTION

Medullary thyroid carcinoma is a rare calcitonin-producing neuroendocrine tumor, which accounts for less than 10% of all the thyroid carcinomas. Sporadic and familial forms occur, with the sporadic form accounting for 70% of cases and familial form 10-20%. Hereditary MTC is transmitted as an autosomal dominant trait either alone as familial medullary thyroid carcinoma (FMTC) or as 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 (RET), mainly in exons 10–15[2].

This is one of the rare 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 four cases of MTC, which were diagnosed on cytology along with discussion of the differential diagnosis and review of literature.

Case 1

A 16-year-old female patient presented with a progressively increasing midline neck swelling for the past 3 months. Physical examination revealed an oval, firm to hard swelling measuring 2 cm in diameter in the right lobe of thyroid, moving with deglutition and an enlarged right-sided cervical lymph node.

Case 2

The second patient was a 30-year-old female with a swelling on left of midline of the neck since few years, not associated with any other complaints. Clinical examination showed a firm neck mass 2 cm in diameter, on left of midline and moving with deglutition.

Case 3

A 50 years old female presented with long-standing thyroid swelling since 12 years. Clinical examination revealed hard right-sided thyroid swelling 4 cms in diameter, moves with deglutition. Not associated with any other complaints. CT scan neck showed large heterogenous irregular mass lesion with foci of

calcification involving right lobe and isthmus of thyroid gland. Medially the mass was compressing and displacing trachea. Laterally mass was partially encasing right common carotid artery. There were multiple enlarged cervical, upper and lower paratracheal lymph node suggestive of metastasis.

Case 4

A 49-year-old male presented with a left-sided neck mass since 1 year, not associated with any complaints. On examination, swelling was noted on the left side, measuring 4 cm, firm to hard and moved with deglutition. No cervical lymph node was palpable.

There was no family history of similar tumors in any of the 4 patients and none had any other endocrine disorders. Also all the four patients were euthyroid.

FNAC from the thyroid lesions was done with 23-gauge needle and 10ml syringe. In first case FNAC from right cervical lymph node was also done. The smears were prepared and stained by Papanicolaou (Pap) and May-Grunwald Giemsa (MGG) stains. Congo red stain was also done.

Microscopic examination of the smears in the first 3 cases showed cellular smears with dispersed as well as few clusters of plasmacytoid cells of variable sizes. The cells had eccentric nuclei with coarse chromatin and abundant amphophilic cytoplasm (**Fig.1**). Anisonucleosis, bi-nucleation and multi-nucleation was also noted. Small clumps of amyloid-like amorphous material were seen in the background, in Pap stained smears. Congo-red staining confirms the material as amyloid (**Fig. 3**). A diagnosis of the MTC was made on the basis of these cytological findings. Aspirates from the fourth case were also cellular, showed several small and large clusters of elongated spindle-shaped cells with scant cytoplasm and hyperchromatic, pleomorphic nuclei (**Fig.2**). Amorphous amyloid-like material was present in this case as well based on these cytological features, a diagnosis suggestive of MTC was rendered.

Smears from cervical lymph node in the first case showed infiltration of lymphoid tissue with spindle-shaped cells establishing the presence of metastasis. However, cells seen in the primary tumor aspirates were plasmacytoid type.

Preoperative serum calcitonin levels were done in all four cases. In first case CT levels were 755pg/ml while in second case CT levels were 1080pg/ml. In third and fourth cases CT levels were >20,000pg/ml and 15,000pg/ml respectively.

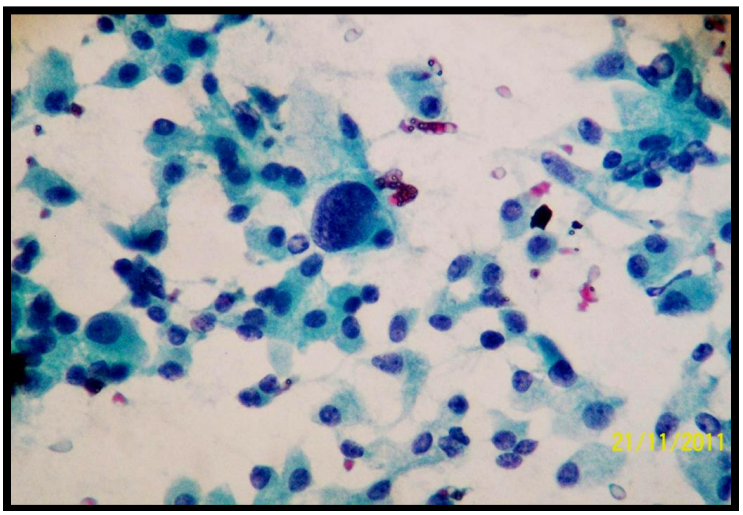

Figure 1 Medullary thyroid carcinoma.
Dispersed cells with a 'plasmacytoid' cell type, with sudden anisonucleosis (Pap 400x)

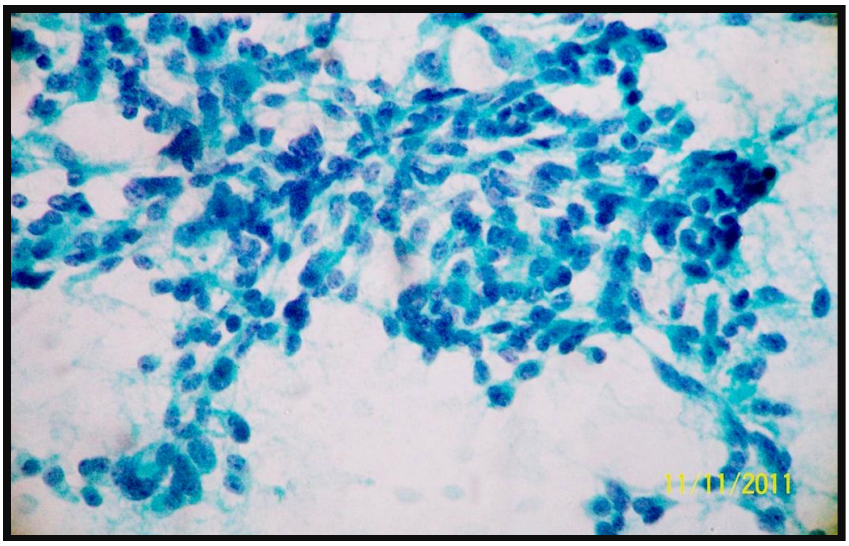

Figure 2 Medullary thyroid carcinoma. Spindle cell variant.
Clusters of spindle cells with elongated nuclei and speckled nuclear chromatin (Pap, 400x)

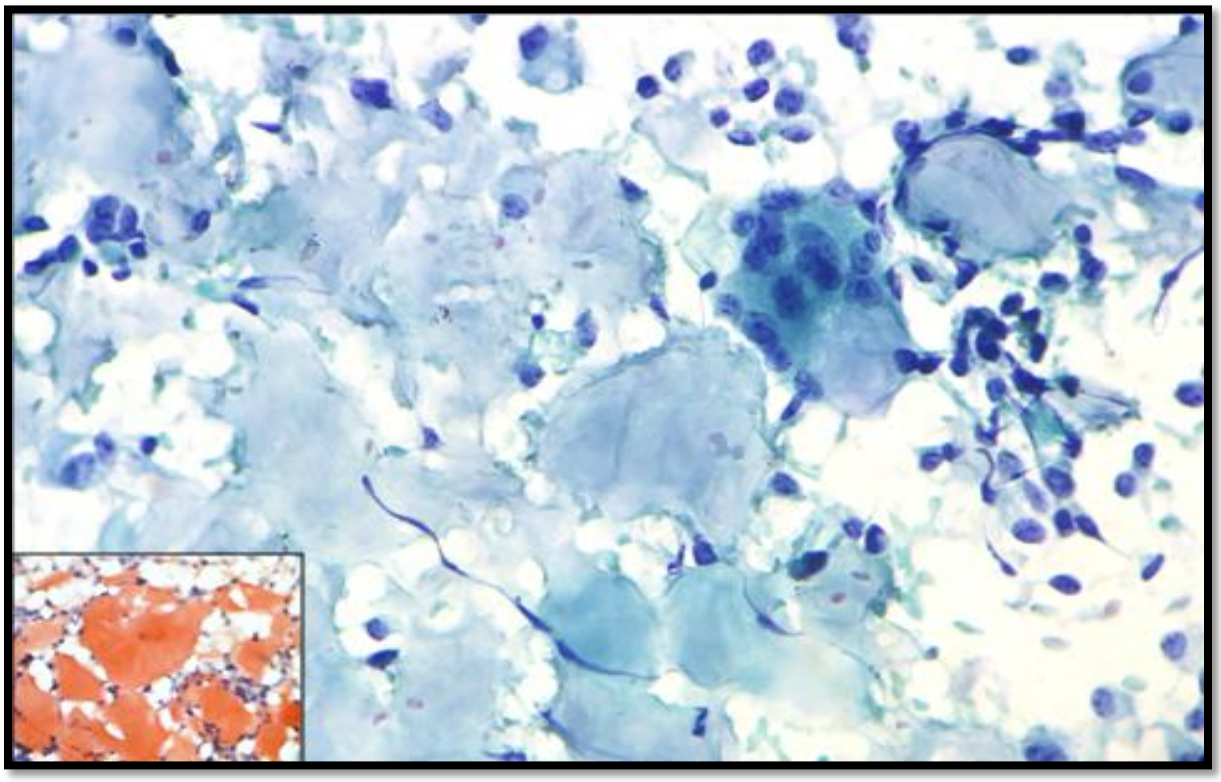

Figure 3 Medullary thyroid carcinoma. Dense amorphous clumps of amyloid stained greenish with PAP. (Pap 400x) Inset – Congo-red stain showing orange-red amorphous clumps confirming it as amyloid

DISCUSSION

The recognition of the pathological features of MTC by Horn[4] and Hazzard et al[5] in the 1950s and demonstrated that is derived from the calcitonin producing parafollicular cells allowed the distinction of such a tumor type from the more common follicular cells[6,7]. 70% - 80% of MTC are sporadic, most of them are unilateral and 20% - 30% are bilateral.

FNAC is considered a first line diagnostic test for evaluation of thyroid lesions along with immunocytochemistry. Also accurate preoperative diagnosis of MCT has important implications for clinical management. Cytologic criteria for the diagnosis of MCT are well described[8,9]. However, variable patterns of growth and cytologic presentation may cause diagnostic difficulty.

This tumor has a range of different cytologic patterns plasmacytoid, spindle cell, small cell, follicular, tubular and giant cell variants. The commonest is plasmacytoid cell type[10]. In our study out of four, in three cases we observed plasmacytoid cell type. FNAC smears from the plasmacytoid MTC are usually cellular, yielding tumor cells that are dispersed and are characterized by eccentric nuclei, "neuroendocrine type" chromatin moderately abundant dense cytoplasm, binucleated and multinucleated cells and a relatively clean background[11]. 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[10].

Apart from the classic plasmacytoid cell pattern, the neoplastic cells may resemble spindle cells as in our fourth case[10]. In such cases, the detection of amyloid is a valuable pointer to the diagnosis. 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[10].

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 a melanoma[10]. In such problematic cases, measurement of serum calcitonin levels are very helpful in resolving the dilemma.

Other differential diagnosis of medullary carcinoma in FNA specimens includes: Hurthle-cell neoplasm, papillary carcinoma, metastatic neuroendocrine tumors, and plasmacytoma. Hurthle cells usually show prominent nucleoli, lack a neuroendocrine chromatin pattern and cytoplasmic granules. Papillary carcinoma cells exhibit classic nuclear features and are negative for calcitonin and positive for thyroglobulin. A detailed family and clinical history is helpful in the diagnosis of MTC, as this diagnosis has implications for other members of the family[12,13].

MTC invades locally and gives rise to metastasis in cervical and mediastinal lymph nodes and distant organs, particularly lung, liver, and skeletal system. They appear to be more common in sporadic and MEN-IIb-associated tumors than in MEN-IIa-associated neoplasms. These metastases may be the first manifestation of the disease and be a source of confusion to the pathologist[3]. In literature it is mentioned that microscopically, they tend to resemble the primary tumor[3]. On the contrarily, in our first case primary tumor revealed plasmacytoid cell morphology while cervical lymph node from the same case showed spindle cell morphology.

The biological behavior of MTC is much less favorable than other well-differentiated thyroid carcinomas. A 10-year survival of about 50% of MTC patients is reported in several series. Early diagnosis may result in higher probability of cure and long-term survival[14,15].

Calcitonin is the most reliable tumor marker because it is highly specific and sensitive[16]. A variety of diseases, other than MTC, including nodular thyroid disease, autoimmune thyroiditis and neuroendocrine tumors, may also cause elevation of CT[17,18,19] 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[20].

An interesting new technique has been described, which is based on the measurement of calcitonin

levels in FNAC washout fluid[21]. 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.

CONCLUSION

FNAC is simple, OPD based procedure can greatly help in definitive preoperative diagnosis of MTC. In our experience, in spite of cytologic variability we were able to diagnose all cases of MTC accurately on FNAC. So 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.

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