Case Report

Hyalinizing trabecular tumor of the thyroid gland: A puzzling entity on fine needle aspiration cytology

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ABSTRACT

Hyalinizing trabecular tumor (HTT) is a rare unique but controversial thyroid neoplasm, characterized by prominent trabecular growth pattern and stromal hyalinization. Whether HTT is a benign tumor or a variant of papillary thyroid carcinoma (PTC) is still unclear. Cytology findings of HTT have been described in few reports. Cytological features of HTT frequently overlap with those of PTC and medullary thyroid carcinoma, which can lead to frequent misdiagnosis. In order to avoid overtreatment like total thyroidectomy, pathologist should be aware of cytological features of HTT. We present a case of 35-year-old female with a right-side thyroid swelling for three years. Fine needle aspiration cytology was performed. According to The Bethesda System for Reporting Thyroid Cytopathology, cytological diagnosis of benign thyroid neoplasm was made. Histopathology of the right thyroidectomy specimen showed HTT. Accurate preoperative diagnosis of HTT requires a very meticulous and cautious approach in the evaluation of cytological features. Trabecular pattern of cells, vague curved nuclear palisading, radiating arrangement of cells around hyaline material, spindled to elongated cells, filamentous cytoplasmic processes with ill-defined cell border and yellow bodies are important diagnostic features of HTT. Nuclear features alone are insufficient for the diagnosis of HTT. Any suspicious cytology of thyroid lesion should follow hemithyroidectomy and histopathological evaluation.

Key words: Fine needle aspiration cytology, hyalinizing trabecular tumor, papillary thyroid carcinoma, medullary thyroid carcinoma

INTRODUCTION

Hyalinizing trabecular tumor (HTT) is a rare controversial thyroid neoplasm.[1-6] Whether HTT is a benign tumor or a variant of papillary thyroid carcinoma (PTC) is still controversy.[4-6] Many cytological and histological features of HTT are similar to those of PTC and medullary thyroid carcinoma (MTC).[1-4,7-10] Accurate preoperative cytological diagnosis has been rarely achieved.[1,2,4,7,8,11,12] Cytological features of HTT are frequently misinterpreted as malignant lesion, which can lead to overtreatment like total thyroidectomy and lymphnodes dissection.[1,6,8,12] Here, we present a case of HTT in a 35-year-old female. This article highlights the cytological features of HTT, in comparison with PTC and MTC, which may help to reduce over diagnosis and guide proper management.

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CASE REPORT

A 35-year-old female presented with a slowly enlarging swelling in front of neck since 3 years. Examination revealed a 5.0 × 4.0 cm sized well-demarcated, firm, non-tender swelling in the right lobe of thyroid. Cervical lymphadenopathy was not evident. Thyroid hormone profile revealed a euthyroid state. Ultrasonography showed a 4.5 × 4.0 cm sized well-defined nodule in the right lobe of the thyroid, without cystic changes and calcification.

Fine needle aspiration cytology (FNAC) was performed using a 22-G needle attached with 10 cc disposable syringe. Methanol fixed smears were stained with

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Hematoxylin and Eosin (H and E) stain. Cellular smears showed small clusters, follicles, loose cohesive groups, overcrowded clusters and many dispersed thyroid follicular cells. Trabecular pattern of cells with nuclear palisading was observed in overcrowded clusters. Cells were round to ovoid in shape with mildly pleomorphic eccentrically located nuclei, fine dispersed pale chromatin, occasional small but conspicuous nucleoli and abundant ill-defined eosinophilic cytoplasm. Occasional cells showed intranuclear inclusion and groove. Many elongated to spindle cells were also seen. Significant number of nuclear crowding, overlapping, intranuclear inclusions and grooves were not evident. Few clumps of eosinophilic hyaline material were seen in cellular clusters. Scanty blood mixed colloid was observed in background [Figure 1]. According to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), cytological diagnosis of benign thyroid neoplasm (category II) (without specification) was made.

The right hemithyroidectomy was done. A well-circumscribed, whitish solid nodule, measured 4.2 × 3.7 × 3.5 cm was found. Histologically, tumor composed of closely packed nests and trabeculae of tumor cells, separated from each other by hyalinized stroma rich in blood vessels. Tumor cells were large oval to elongated in shape with round to oval mildly pleomorphic nuclei, fine granular pale chromatin and abundant pink granular cytoplasm with indistinct cell borders. Occasional nuclei showed intranuclear inclusion and groove. Papillary structures, psammoma bodies and follicular pattern were not found [Figure 2]. Final diagnosis of HTT was made. Patient is under regular follow-up without tumor recurrence or metastasis.

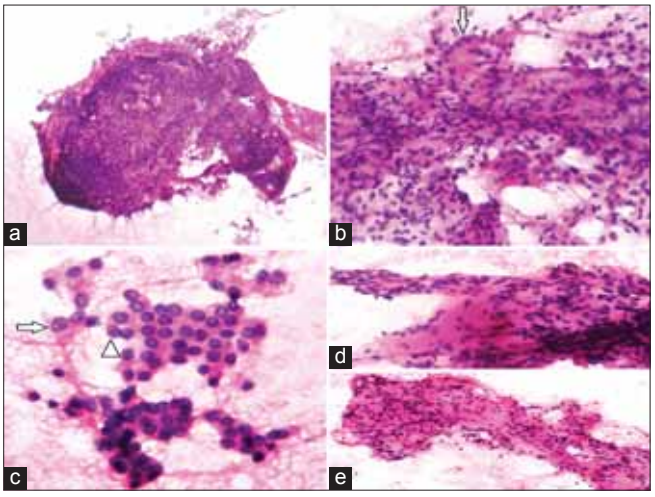

Figure 1: H and E stain: (a) Overcrowded cluster with trabecular arrangement of cells (×200). (b) Nuclear palisading (arrow mark), overcrowding and few spindle cells in cellular cluster (×400). (c) Cells are round to ovoid with eccentrically located nuclei, fine dispersed pale nuclear chromatin, occasional small conspicuous nucleoli, intranuclear inclusion (arrow mark) and groove (triangle mark) and abundant ill-defined eosinophilic cytoplasm (×600). (d, e) Hyaline material is seen within cellular cluster (×400)

DISCUSSION

HTT is a rare thyroid neoplasm of follicular derivation.[1-3,5,6,8,10] HTT generally presents as a asymptomatic well-circumscribed solitary thyroid nodule, a prominent nodule in a multinodular goiter or as an incidental finding in a thyroidectomy specimen.[3,4,6,12] It is common in middle-aged women.[4,9] Few HTT are associated with chronic lymphocytic thyroiditis, Hashimoto's thyroiditis, follicular neoplasm, multinodular goiter and PTC.[2,6,9,12]

The most recent controversial debate is that whether HTT is a benign tumor or a variant of PTC.[4-6] HTT might be a variant of PTC as both have similar nuclear cytology, immunoprofile and RET/PTC oncogene rearrangements.[4-6,9] In contrast, BRAF (heterozygous V600E) and NRAS mutations, which are common in PTC, are constantly absent in HTT.[5,6,8] However, absence of BRAF mutation does not confirm the benign nature of HTT. Galectin-3 is initially thought to be only expressed in PTC, now it is variably (40% of cases) expressed in HTT.[4,6] In contrast to PTC, HTT shows negative immunostaining for cytokeratin 19 and high molecular weight (HMW) cytokeratin.[4,6,9] HTT shows characteristic strong cytoplasmic and membranous immunostaining of tumor cells with MIB-1, which is not seen in any other thyroid neoplasm.[2,3,6,8,9] These results are against HTT as a variant of PTC. The low Ki-67 index and absence of p53 immunostaining are consistent with the benign behavior of HTT.[3] Some authors have also suggested that HTT is not a distinct entity because trabecular growth pattern can be seen in follicular adenoma, PTC, MTC, and metastatic neuroendocrine tumors to the thyroid gland.[4-6]

The pre-operative diagnosis of HTT may be difficult as clinical and ultrasonographic features are non-specific.[6] In such instances FNAC is strongly indicated for exact categorization of lesion, which determine subsequent management.[6] However, the diagnosis of HTT even on FNAC remains challenging.[1,2,4,7,8,11,12] HTT may be misinterpreted as either suspicious or positive for malignancy (TBSRTC, category V or VI).[1-4,7-10] Majority of HTT are misdiagnosed as PTC

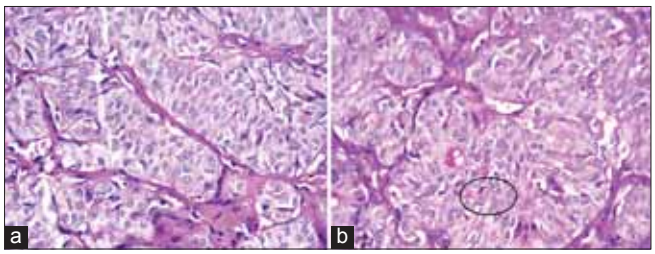

Figure 2: H and E stain: (a) Predominant trabecular arrangement of tumor cells, separated from each other by a hyalinized stroma rich in blood vessels. Tumor cells are large oval to elongated in shape with round to oval mildly pleomorphic nuclei, pale granular chromatin, occasional small distinct nucleoli and abundant pink granular cytoplasm with indistinct cell borders (×400). (b) Occasional nuclei show intranuclear inclusions and grooves (circle mark) (×400)

on FNAC because of the similar nuclear features especially intranuclear cytoplasmic inclusions and grooves.[1,3,5-9,12,13] These represent a potential diagnostic pitfall. In our case, nuclear inclusions, grooves and overlapping are occasionally evident and not significant enough to consider them for PTC and even for HTT. Cytological features like trabecular pattern of cells, vague curved nuclear palisading, spindled or elongated cells, abundant cytoplasm with ill-defined border and hyaline material in our case prevent the over diagnosis as PTC. However, trabecular growth pattern is alone insufficient for the diagnosis of HTT as it is also seen in trabecular variant of PTC, but the distinct hyalinized stroma is not seen in trabecular variant of PTC.[5] HTT can also pose diagnostic difficulty with MTC especially hyalinizing trabecular adenoma-like or paraganglioma-like variant.[2,7,9] Great care should be taken to distinguish hyaline material from amyloid and colloid on cytology.[4] Cytological features of HTT and its comparison with PTC and MTC are given in Table 1.[1-15]

Histologically, HTT is an encapsulated (usually thin capsule) tumor or circumscribed solid nodule with classic trabecular pattern and intratrabecular hyalinization of matrix. Pseudofollicles, intranuclear cytoplasmic inclusions and grooves are also common.[1-16] On immunohistochemistry, HTT is positive for thyroglobulin and thyroid transcription factor (TTF)-1.[4,6,10] Calcitonin, HBME-1, synaptophysin, chromogranin, epithelial membrane antigen and vimentin are usually negative in HTT.[4,5,8-10] The proliferating cell nuclear antigen (PCNA) expression is high but its significance is uncertain.[3] Cytoplasmic and membranous expression of MIB-1 is useful in making the diagnosis of HTT even on cytology smears.[15] However, negative MIB-1 stain has no diagnostic value. Implementation of MIB-1 stain to all suspicious cytology smears is also not cost-effective.

Almost all cases of HTT fail to show unequivocal capsular, vascular, and stromal invasion and have not metastasized, suggesting a benign behavior.[1,2,4,5,8,16] Very rarely HTT can show vascular and capsular invasion, and pulmonary metastasis.[12] Misdiagnosis of HTT as malignant lesion on cytology is usually overtreated with total thyroidectomy and lymphnodes dissection.[1,6,8,12]

Table 1: Cytological features of HTT and its comparison with PTC and MTC

Cytology findings	Hyalinizing trabecular tumor	Papillary thyroid carcinoma	Medullary thyroid carcinoma
Cellularity Pattern of cell arrangement	Usually cellular smear Loose cohesive groups Large syncytial sheets Overcrowded clusters Less frequently single cells Trabecular arrangement of cells Vague curved nuclear palisading Radiating arrangement of cells around hyaline material	Cellular smear Papillary architecture with/without fibrovascular core Syncytial aggregates/flat sheets Significant nuclear crowding and overlapping Three-dimensional tissue fragments Focal anatomical edges Occasional follicular structures	Cellular smear Predominantly dispersed cells Few clusters and loose groups
Cell morphology	Mainly oval to polygonal, medium size cells Few spindle to elongated cells Low nuclear/cytoplasmic ratio Eccentrically located, slightly enlarged pleomorphic nucleus with pale chromatin Intranuclear cytoplasmic inclusions, nuclear grooves and nuclear overlapping are seen in some case Moderate to abundant fibrillary cytoplasm with cell processes Indistinct cell border Focal binucleated forms Intracytoplsmic yellow bodies	Enlarged ovoid pale nuclei Finely granular powdery chromatin Intranuclear cytoplasmic inclusions and grooves Dense cytoplasm with distinct cell border Rarely metaplastic cells	Polygonal cells with eccentric plasmacytoid nuclei or spindle cells or small cells Moderate anisonucleosis Binucleated and multinucleate forms Speckled/stippled nuclear chromatin On May Grunewald Giemsa stain, few cells display pink to red coarse cytoplasmic granularity
Background	Bloody background Small, irregular but well-defined and less solid acellular amorphous/fibrillar hyaline material, without streaked nuclear material On MGG stain: Purplish-red stromal material	Acellular thick colloid-chewing gum like viscous colloid	Amorphous/Fibrillar amyloid material On MGG stain: Blue to magenta colored amyloid On PAP stain: Pink to orange amyloid Amyloid may contain streaked nuclear material
Other features	Calcified and psammoma bodies are rare Congo red: Negative	Psammoma bodies are variable	Congo red: Apple-green birefringence under polarized light suggest amyloid material

HTT: Hyalinizing trabecular tumor, MTC: Medullary thyroid carcinoma, PTC: Papillary thyroid carcinoma, MGG: May grunewald giemsa

HTT without signs of metastases does not need aggressive treatment like total thyroidectomy or radioiodine ablation.[6] Hemithyroidectomy would have been a better option if cytology is suggestive or suspicious for HTT. Annual follow-up is required to exclude the very rare possibility of recurrence and metastasis.[6,16]

CONCLUSION

HTT is a benign neoplasm or at most, a neoplasm of extremely low malignant potential. HTT is a challenging entity on cytology due to overlapping features with malignant thyroid lesions. Differentiation of HTT from PTC and MTC on cytology is important due to different prognosis and therapeutic implication. Cytological diagnosis of HTT should be considered in presence of trabecular pattern of cells, vague curved nuclear palisading, radiating arrangement of cells around hyaline material, spindle to elongated cells, filamentous cytoplasmic processes with ill-defined cell border and yellow bodies. Nuclear overcrowding, grooves, and inclusions should be correlated with other features and evaluated with great care to differentiate HTT from PTC. Close attention is required to evaluate the hyaline material as it can mimic amyloid and colloid on cytology.

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