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Hyalinizing trabecular tumor of the thyroid: fine-needle aspiration cytological diagnosis and correlation with histology.

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ABSTRACT

Hyalinizing trabecular tumor (HTT) is a rare thyroid neoplasm of follicular cell origin characterized by a trabecular growth pattern and prominent intratrabecular and intertrabecular hyalinization. These peculiar histological features allow the prompt recognition of this neoplasm in surgical specimens. However, cytological diagnosis of HTT remains elusive and misleading because of overlapping characteristics with other thyroid tumors, particularly papillary thyroid carcinoma (PTC), medullary thyroid carcinoma (MTC) and the newly described noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Nevertheless, the proper recognition of this neoplasm on preoperative cytological preparations is important to avoid unnecessary overtreatment of this indolent lesion.

A thorough review of the literature has revealed that the correct diagnosis of HTT in cytological smears is achieved in only 8% of cases. In a further 6% of cases, diagnostic doubt has been indicated. 60% of published cases of HTT have been misdiagnosed as suggestive, suspicious or positive for PTC. These findings underline the difficulties of a cytological-based diagnosis of such entity.

In this article we review the cytomorphological features of HTT and their correlation to histological features, to provide the reader with the tools to improve diagnostic performance in the identification of HTT on pre-operative cytology.

INTRODUCTION

Hyalinizing trabecular tumor (HTT) is a distinct but rare thyroid neoplasm of follicular cell origin characterized by a trabecular growth pattern and prominent intratrabecular and intertrabecular hyalinization. It usually occurs between the fourth and seventh decade of life and shows a marked predilection for females.[1] By and large, the clinical behavior of HTT is benign and should therefore be treated conservatively, although it is worth noting that rare cases of invasive hyalinizing trabecular carcinomas have been reported in earlier literature.[2-4]

Although the peculiar histological features of this neoplasm allow prompt recognition in surgical specimens, cytological diagnosis of HTT remains elusive and misleading because of overlapping characteristics with other malignant thyroid tumors, including papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma (MTC). For this reason, HTT recognition in fine-needle aspiration (FNA) preparations is important to avoid unnecessarily aggressive treatment of such a benign neoplasm.[5] Furthermore, it is difficult to distinguish between HTT and the recently described “noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)” in cytological preparations, mainly due to the fact that the cytological diagnostic criteria for both entities have not been well established yet.[6 7]

The purpose of our review is to highlight the cytological and immunocytochemical features of HTT to help the practitioner cytopathologist with the difficult diagnosis of HTT, which represents the starting point for a correct therapeutic approach.

HISTORICAL PERSPECTIVE

The first two reports of HTT were described by Zipkin (1905) and Masson (1922), who reported cases of HTT that they interpreted as carcinomas.[8 9] Later, in 1982, Ward and colleagues described a similar case under the moniker "hyaline cell tumor of the thyroid with massive accumulation of cytoplasmic microfilaments".[10] However, the concept of HTT as a benign lesion originates from Carney and coworkers who, in 1987, reported 11 cases of noninvasive and non-metastasizing encapsulated thyroid tumors showing peculiar histological features, such as polygonal and elongated cells with a trabecular pattern of growth, associated with hyaline amyloid-like substance. They defined such lesions as hyalinizing trabecular adenomas (HTAs).[11]

Following Carney's description, most authors used the term HTA to define this neoplasm, and it was also adopted by the second edition of the WHO handbook on classification of thyroid tumors, where it was included in the chapter "Other adenomas", together with salivary gland-type adenomas and adenolipomas.[12] Subsequently, since some authors described a few cases showing malignant behavior (including metastases, vascular invasion or invasive growth into thyroid parenchyma) and *RET/PTC* rearrangements, the term HTT was considered a better moniker than HTA, and the lesion was classified as such in the third edition of the WHO classification.[1]

ULTRASONOGRAPHIC FEATURES

In two out of three small published series investigating US features of HTT, authors found that none of the patients showed any findings indicative of malignancy;[13 14] in the third one, only 29% of patients showed malignant US findings.[15] Overall, authors described the vast majority of HTT as being solid tumors, hypoechogenic or markedly hypoechogenic.[13-15]

CYTOPATHOLOGIC FEATURES

Goellner and Carney first reported the cytological characteristics of HTT, acknowledging that this lesion showed features suggestive of both PTC and MTC.[16] Cytological smears generally show cells that may be isolated, arranged in cohesive (Figures 1A, B) or loosely cohesive groups (Figure 1C) or syncytial tissue fragments with a trabecular pattern (Figure 1D). At times, neoplastic cells appear to radiate from central cores of acellular hyaline material or form follicle-like structures around it. Neoplastic cells are polygonal to spindle-shaped, containing a pale to dense cytoplasm that is often difficult to visualize, and oval to elliptic nuclei containing evenly distributed chromatin and micronucleoli. Intranuclear pseudoinclusions and nuclear grooving (Figure 1B, D) are frequently observed. The yellow cytoplasmic bodies observed by histology may also be seen in cytological samples.[17] The presence of nuclear grooving, intranuclear pseudoinclusions and psammoma bodies may easily result in the diagnosis of PTC; indeed, the vast majority of published FNA cases were diagnosed on preoperative cytology as suggestive, suspicious or positive for PTC.[16 18-21]

The hyaline material may be misinterpreted as amyloid, therefore suggesting a diagnosis of MTC, or even overlooked as colloid and not taken into account at all for diagnostic purposes. However, MTC aspirates show loosely cohesive groups with a dispersed pattern without any specific architectural configuration or isolated cells, whose nuclei are eccentric, pleomorphic, containing “salt and pepper” chromatin and no nucleoli. Nuclear grooving and psammoma bodies are not observed in MTC. The strange combination of features of both PTC and MTC, as well as the fact that these features do not completely fit the criteria for either entity, is the most useful clue for recognizing HTT by cytology.[16] Immunocytochemical staining can help in distinguishing these entities.

The difficulty of a cytological diagnosis of HTT is underlined by the fact that 60% of published cases of HTT in which a cytological diagnosis was included were misdiagnosed as suggestive, suspicious or positive for PTC (Table 1): among them, 41% were diagnosed as positive for PTC; 48% as suspicious for PTC; 6% as suggestive of PTC; 2% as consistent with PTC; 2% was diagnosed as follicular variant (FV)-PTC and 1% as a “trabecular epithelial tumor in keeping with PTC”. Of the remaining 40%

of cases, 6% were reported as PTC versus HTT; 10% as follicular neoplasms (FN); 1% as MTC; 10% as atypia of undetermined significance (AUS); and, finally, only 8% of cases were correctly identified as HTT by FNA (Figure 2).[16-33]

Although architectural features are diminished in cytologic samples, they are not absent, and must be taken into account and correctly interpreted when making a diagnosis. When considering the cytomorphologic features of HTT, the absence of papillary structures and denuded fibrovascular stalks and the presence of elongated epithelial cells associated with acellular hyaline stroma, are all significant clues. Moreover, cell blocks from residual material or needle rinse fluid can provide additional information and material for ancillary studies, i.e. immunocytochemistry.

Futhermore, in challenging cases, cytomorphologic findings can be integrated with US features to better refine the cytologic diagnosis: in cases with discordant cytologic-ultrasonographic findings, a note can be added to the diagnosis suggesting that when benign US features are present, HTT must be considered in the differential diagnosis of samples suspicious for malignancy (PTC).

HISTOPATHOLOGIC FEATURES

Grossly, HTT is usually a single, solid, well-circumscribed or encapsulated lesion that presents a homogeneous and delicately lobulated yellow-tan cut surface, measuring 2.5 cm or less in diameter (Figure 3A).[1]

Microscopically, the main distinctive features are a diffuse trabecular-alveolar growth pattern and a prominent hyalinized intratrabecular stroma that closely resembles amyloid although it is negative for amyloid stain (Figure 3B). Neoplastic cells are medium to large sized, polygonal or fusiform, with a finely granular amphophilic, acidophilic or clear cytoplasm and nuclei showing prominent grooves and intranuclear pseudoinclusions (Figure 3C). They are arranged in trabeculae supported by a delicate fibrovascular stroma.[1] In some cases, the spindle cell component may be so important as to suggest MTC (Figure 3B, inset); however, immunostaining for calcitonin, CEA, and thyroglobulin helps in the differential diagnosis. The so-called “yellow bodies”, round paranuclear

cytoplasmic pseudoinclusions with a light yellow tinge, slightly refractile and surrounded by a clear halo, are a peculiar feature of this neoplasm.[34] Colloid is scant or absent and calcifications/psammoma bodies may be observed.[1] In places, cells may be arranged in compact clusters closely resembling the "Zellballen" of paraganglioma, hence the alternative name of *paraganglioma-like* adenoma sometimes encountered in the literature.[35] The hyaline material is closely associated with the trabeculae of HTT, is PAS positive and appears to be directly produced by neoplastic cells. It must be distinguished from the perivascular stromal hyalinization that is characteristic of other thyroid tumors and which results from degenerative changes within the lesion.[1 35]

Ultrastructurally, the main features of HTT are the accumulation of intermediate filaments in the cytoplasm of the tumor cells and the abundance of extracellular basal membrane material that suggest a deregulation of secretory patterns.[36-38] The yellow cytoplasmic inclusion bodies observed on hematoxylin and eosin-stained sections using electron microscopy are giant secondary lysosomes of multivesicular body subtypes.[34]

IMMUNOCYTOCHEMISTRY AND IMMUNOHISTOCHEMISTRY

HTT shows a distinctive cell membrane and cytoplasmic positivity for Ki-67 (using clone MIB-1) when the reaction is performed at room temperature. The cross-reactivity of the monoclonal MIB-1 antibody with an epitope expressed at the cell membrane level seems to represent the putative mechanism of such findings.[39] Positive immunoreactivity with MIB-1 in cytoplasmic and membranous patterns has been described in cytological specimens as well, and it has been suggested as a useful test when applied to aspirates in which HTT is suspected, but whose cytological features do not permit a definitive diagnosis.[40 41] Therefore, immunocytochemistry can support the cytopathologist in diagnosing HTT in suspicious cases (Figure 3D, E). Although most authors propose immunohistochemical staining for MIB-1 as a useful diagnostic tool, others have recommended that the results of this test need to be carefully interpreted, as its specificity is not proven.[39 42-44] It is

worth noting that such a staining pattern is obtained only with the MIB-1 clone and not with other Ki-67 clones, and only when the procedure is carried out at room temperature.[39] If this peculiarity is not taken into account and staining with the MIB-1 clone is carried out at 37 °C, a low-grade nuclear positivity will ensue and will lead to the wrong diagnosis.

In keeping with their presumed follicular cell origin, most tumor cells are positive for thyroglobulin, thyroid transcription factor (TTF)-1 and negative for calcitonin (Table 2).[1] Studies have shown discrepant results of cytokeratin (CK) profiling, with variable degrees of positivity for CK 7, 8, 18 and 19.[45-47]

The staining for galectin-3, a β-galactosidase-binding lecithin used to differentiate benign and malignant follicular tumors, has been reported to be strong in 40% and weak or negative in 60% of HTTs.[48]

Neuroendocrine differentiation, demonstrated by positivity for neuroendocrine markers such as chromogranin A and neuron-specific enolase, has been reported and proposed to account for the resemblance of an HTT growth pattern to paraganglioma and MTC.[36 49 50]

MOLECULAR BIOLOGY

Original detection of *RET/PTC1* rearrangements in a percentage of cases similar to that described in PTC seemed to support the relationship between HTT and PTC that had also been suggested by some authors on the basis of morphological and cytological features.[51-53]

In the study by Papotti et al., 4 of the 14 (28.6%) HTT investigated, using reverse transcription-polymerase chain reaction (RT-PCR) and Southern blot analysis, harbored *RET/PTC1* rearrangements;[51] with the same method, Cheung and colleagues detected such rearrangements in 5 out of 8 (62.5%) HTTs.[52] Salvatore et al. found *RET/PTC1* rearrangements in 13 out of 28 (46.4%) cases, but did not show evidence for any *RAS* or *BRAF* mutations.[53] Because of such findings, the authors proposed that HTT might represent the “hyalinizing trabecular” variant of PTC and the moniker “tumor” is preferred to the benign connotation of the term “adenoma”. More recent

evidence provided by comparisons of microRNA expression in the two tumors did not support the hypothesis that HTT represents a variant of PTC: the expression of five microRNAs known to be upregulated in PTC was retrospectively analyzed in HTT and found to be different.[54]

To date, no Next-Generation Sequencing study is available for HTT, nor have molecular analyses been applied to cytological material yet.

DIFFERENTIAL DIAGNOSIS

A review of the literature shows that the correct preoperative cytological diagnosis of HTT has been achieved in only 8% of cases, and in another 6% a diagnostic doubt has been indicated, while in the majority of cases the cytological diagnosis of malignancy was not confirmed on the resected surgical specimens (Table 1). Although it is generally believed that HTT can be frequently misdiagnosed as either PTC or MTC (because of the prominent PTC-like nuclear features and the presence of amyloid-like hyaline material, respectively), only 1% of HTT has been diagnosed as MTC by preoperative cytology, compared to 60% which were diagnosed as PTC.

Another entity that may appear in the differential diagnosis of HTT is NIFTP: confusion may arise because both entities present overlapping nuclear features of PTC in FNA material and because criteria for unequivocally identifying these entities by cytology have not yet been defined.

Primary thyroid paraganglioma, although extremely rare, may enter into the differential diagnosis, as HTT may present compact clusters that can be misinterpreted as “Zellballen” typically observed in paraganglioma.

MANAGEMENT

FNA is an essential procedure in the preoperative evaluation of thyroid nodules. Its main role is the triage of patients who actually require surgery, thus reducing the number of unnecessary thyroidectomies and possible complications thereof.[55]

Although radiologic and US features are often not provided to cytopathologists, they must be searched for and taken into account to plan appropriate patient management in a multidisciplinary tumor board. Recent literature suggests that HTT should be included in the differential diagnosis of solid tumors with benign US features but cytology suggestive of PTC.[13-15]

As a cytological diagnosis of PTC entails an aggressive surgical treatment including complete thyroidectomy associated or not with central neck dissection, the correct distinction between HTT and PTC by FNA is important to guide proper management of patients and to avoid overtreatment because HTT can be treated by a simple lobectomy.

It is important to note that an accurate diagnosis of HTT (and of any other neoplastic lesion) by FNA crucially depends on the sample being representative and adequate in cellularity and appropriately processed and stained, in order to provide high-quality preparations for assessment. When these conditions are not met, repeat sampling with or without on-site assessment should be considered prior to surgical management. Intraoperative consultation after a suboptimal cytologic assessment is not the method of choice in patient management.

However, frozen section evaluation may have a role in guiding the correct surgical decision intraoperatively when it is prompted by a result of FNA cytology suspicious for malignancy on a sample that is representative of the lesion and well processed: providing a trabecular pattern is identified, an initial lobectomy may be performed and total thyroidectomy may be deferred, thus preventing patients who are diagnosed with HTT by a definitive histopathological report from undergoing unnecessary total thyroidectomy.[56]

In conclusion, if a clinically indolent tumor is suspected on the basis of radiological and cytological findings, judicious use of an indeterminate category (e.g. “Follicular Neoplasm/Suspicious

for a Follicular Neoplasm"), that in The Bethesda System for Reporting Thyroid Cytopathology entails a diagnostic lobectomy, may be the most appropriate course of action.

CONCLUSION

The history of the rare hyalinizing trabecular tumor is interesting and is marked by significant controversies; to date, uncertainty still remains concerning its malignant potential and, therefore, the most appropriate moniker for it.

Although the identification of HTT on resection specimens is more straightforward, its recognition by FNA is misleading. However, careful attention and a high index of suspicion may help cytopathologists in providing a correct diagnosis and thus appropriately guide the surgeon and clinician, as HTT is virtually always benign and should be treated by a simple lobectomy.

TAKE HOME MESSAGES

- Cytologic samples of HTT show elongated cells that may be isolated, arranged in cohesive/loosely cohesive groups, or syncytial tissue fragments with a trabecular pattern; hyaline material may form central cores surrounded by neoplastic cells or may be observed in the background of the smear.
- Although intranuclear pseudoinclusions and nuclear grooving are frequently observed, the absence of papillary structures and fibrovascular stalks associated with the presence of a hyaline substance is an important clue to HTT diagnosis.
- HTT should be included in the differential diagnosis of thyroid neoplasms with discordant US–cytology readings, with FNA suspicious for PTC after a US without findings suggestive of malignancy.
- When HTT is suspected on cytologic samples, judicious use of an indeterminate category leading to diagnostic lobectomy may be the most appropriate course of action on the part of the cytopathologist.

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Competing interest

None declared.

FIGURE LEGENDS

Figure 1 Cytomorphological features of HTT. Cytology findings show a cellular smear with cells forming follicle-like structures (A, PAP x40) or cohesive aggregates (B, PAP x200) with large fragments of eosinophilic, hyaline, amorphous matrix (C, PAP x100). Neoplastic cells demonstrate well-formed intranuclear pseudoinclusions (arrow) and cells organized in trabecular structures (D, PAP x200).

Figure 2 Cytological diagnoses of HTT in published literature. Only 8% of cases reported in the literature have been correctly diagnosed as HTT by cytology. The great majority have been reported as suspicious for PTC and PTC. The PTC category comprises cases diagnosed as: PTC, consistent with PTC, suggestive of PTC.

Figure 3 Histological features of HTT. Low-power magnification shows an encapsulated lesion (A, H&E scanned slide) with the typical trabecular architecture and intratrabecular hyalinization (B, H&E x100). Rare spindle cell variants of HTT exist, and may create diagnostic confusion with the spindle cell variant of MTC. (B, inset, H&E x200). High-power magnification demonstrates intranuclear pseudoinclusions (arrow) and nuclear grooving (arrowhead) (C, H&E x400). Immunohistochemical staining with Ki-67 antibody (Mib-1 clone) at room temperature results in the characteristic peripheral cytoplasmic and membranous staining (D, x200); when the reaction is performed at 37 °C, no membrane localization is observed (E, x200).

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Table 1. **Summary of all reported cases of hyalinizing trabecular adenoma for which cytological diagnosis is available in the literature.**

Author	No. of cases	Sex		Age		Diameter		Site			Cytological diagnosis												Thyroidectomy		
		M	F	Mean	Range	Mean	Range	Right lobe	Left lobe	Other	HTT	HTT vs PTC	AUS/ FLUS	FN/ SFN	Suspicious/ suggestive of PTC	PTC	ND	N/A	MTC	FV-PTC	Suspicious for malignancy	Other	Hemi	Sub-total	Total
Jang, 2016[13]	12	1	11	55	44-70	1.3	0.5-4.1	N/A	NA		1	2	1	1	3	3	-	1	-	-	-	-	6	2	4
Bakuła-Zalewska, 2015[17]	2	1	1	64	63-65	3.0	1.0-5.0	1	-	1	-	-	-	1	1	-	-	-	-	-	-	-	1	-	1
Choi, 2015[15]	19	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-	-	6	-	9	2	1	-	1	-	-	-	N/A	N/A	N/A
Howard, 2013[19]	1	-	1	57	-	6.0	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	-	1	-	-
Smith, 2012[30]	1	1	-	57	-	1.8	-	1	-	-	-	-	-	-	-	-	-	-	-	1	-	-	N/A	N/A	N/A
Kim, 2011[29]	7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-	2	-	-	3	2	-	-	-	-	-	-	2	-	5
You, 2012[20]	1	-	1	76	-	0.4	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1
Arena, 2011[31]	1	-	1	43	-	1.0	-	-	1	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1
Lee, 2011[14]	10	9	1	48	26-81						-	2	-	-	2	6	-	-	-	-	-	-	3	-	7
Agarwal, 2010[28]	1	1	-	25	-	2.0	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	N/A	N/A	N/A
Gupta, 2010[27]	1	1	-	28	-	3.1	-	-	1	-	-	1	-	-	-	-	-	-	-	-	-	-	1	-	-
Evenson, 2007[21]	7	2	5	60	48-71	1.4	1.0-2.5				-	-	-	-	6	1	-	-	-	-	-	-	1	-	6
Casey, 2004[40]	29										-	-	2	-	12	11	-	4	-	-	-	-			
Kuma, 2003[26]	16	2	14	48	19-85	4.1	2.7-7.2	10	6	-												-	N/A	N/A	N/A
Boccato, 2000[25]	2	-	2	38.5	34-43	N/A	N/A	1	1	-	1	-	-	-	1	-	-	-	-	-	-	-	N/A	N/A	N/A
Jayaram, 1999[24]	1	1	-	47	-	4.5	-	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	N/A	N/A	N/A

Akin, 1999 [32]	3	1	2	39.3	34-45	2.5	2.0-3.0	2	1	-	2	-	-	-	1	-	-	-	-	-	-	-	N/A	N/A	N/A
Kaleem, 1997 [22]	2	-	2	42.5	28-57	2.4	0.5-6.0	1	1	-	-	-	-	1	-	1	-	-	-	-	-	-	1	-	1
Strong, 1990 [33]	1	-	1	53	-	2.0	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	1 (thyroiditis)	1	-	1
Goellner, 1989 [16]	5	1	4	44	29-69	N/A	N/A	N/A	N/A	N/A	-	-	-	1	3	1	-	-	-	-	-	-	N/A	N/A	N/A

M, male; F, female; HTT, hyalinizing trabecular tumor; PTC, papillary thyroid carcinoma; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm, suspicious for follicular neoplasm; ND, non diagnostic; MTC, medullary thyroid carcinoma; FV-PTC, follicular variant of papillary thyroid carcinoma; N/A, not available.

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448 Table 2. **Immunocytochemical staining in the differential diagnosis of hyalinizing trabecular tumor**
449 **on FNA.**

	HTT	**PTC**	**MTC**
Thyroglobulin	+	+	-
TTF-1	+	+	+
Calcitonin	-	-	+
CEA	-	-	+
Chromogranin	-	-	+
Synaptophysin	-	-	+
Ki-67 (clone MIB-1)	+ (membranous) 100% expression at room temperature incubation; + (nuclear) low expression at 37 °C incubation.	+ (nuclear), usually low expression	+ (nuclear), variable expression
HTT, hyalinizing trabecular tumor; PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma.			

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Figure 1

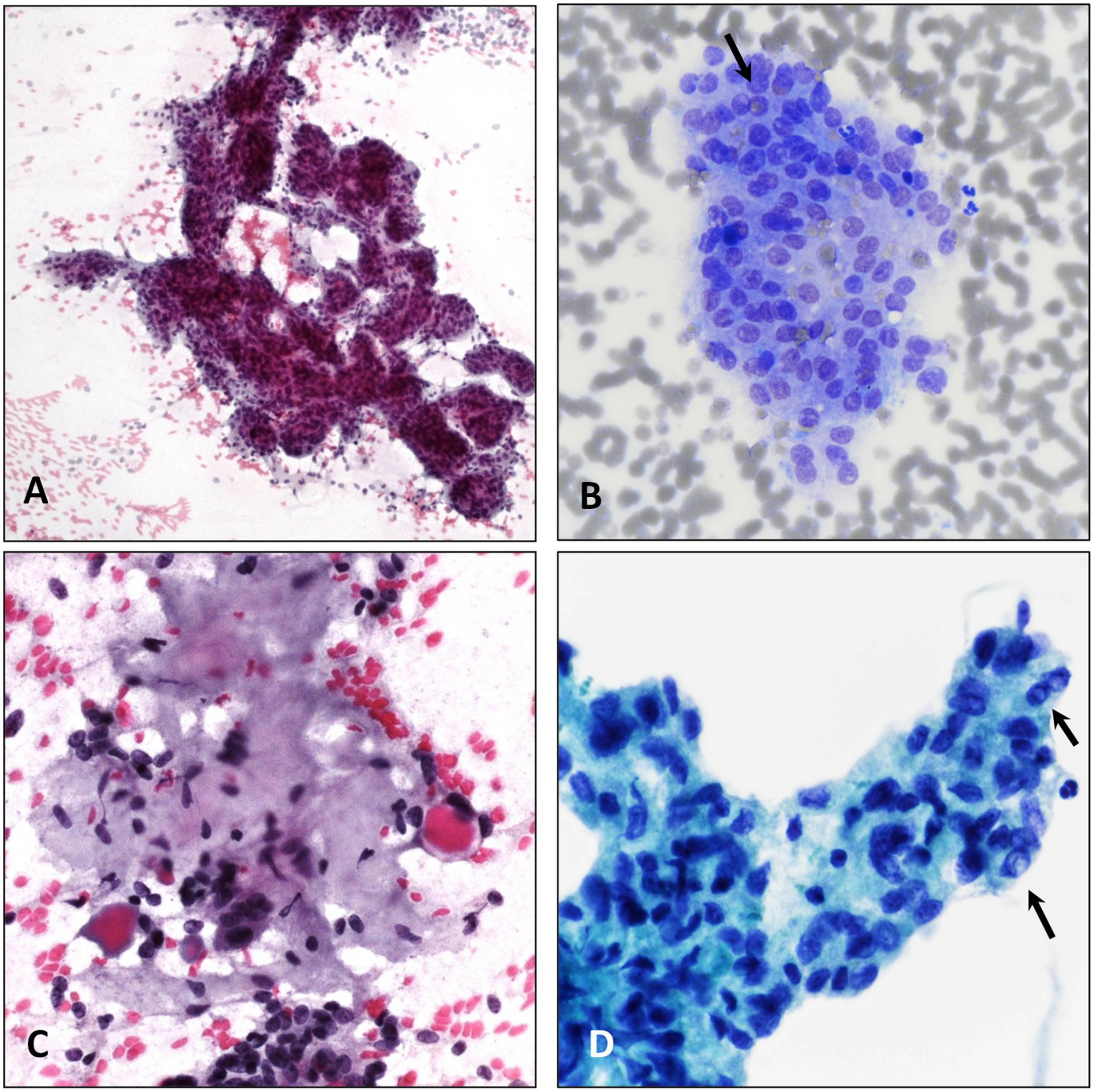
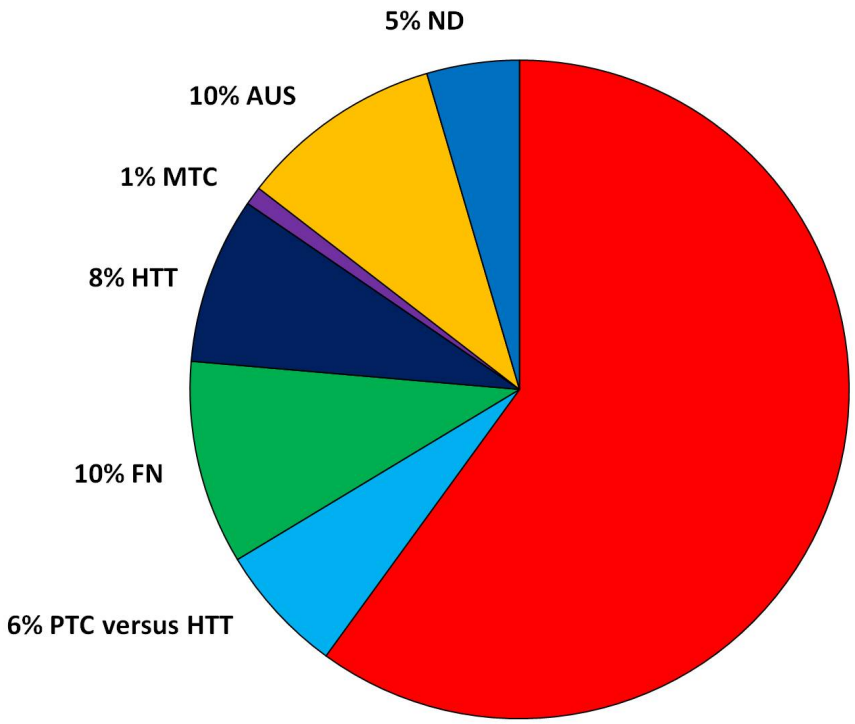


Figure 2

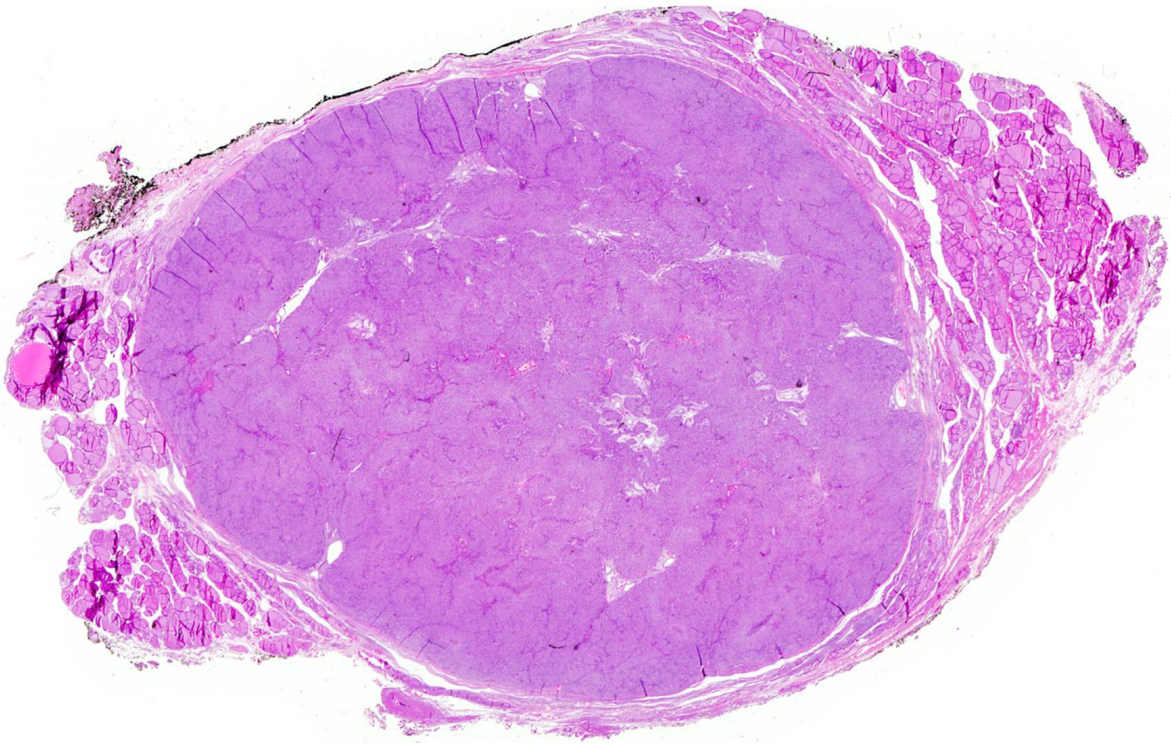


60% Suspicious for PTC / PTC

Subdivided as follows:

- **48% Suspect for PTC**
- **41% Positive for PTC**
- **6% Suggestive of PTC**
- **2% Follicular variant of PTC**
- **2% Consistent with PTC**
- **1% Trabecular epithelial tumor in keeping with PTC**

Figure 3



A

Figure 3