



Challenges in Cytology Specimens With Hürthle Cells

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In fine-needle aspirations (FNA) of thyroid, Hürthle cells can be found in a broad spectrum of lesions, ranging from non-neoplastic conditions to aggressive malignant tumors. Recognize them morphologically, frequently represents a challenging for an adequately diagnosis and are associated with a significant interobserver variability. Although the limitations of the morphologic diagnosis still exist, the interpretation of the context where the cells appear and the recent advances in the molecular knowledge of Hürthle cells tumors are contributing for a more precise diagnosis. This review aims to describe the cytology aspects of all Hürthle cells neoplastic and non-neoplastic thyroid lesions, focusing on the differential diagnosis and reporting according to The Bethesda System for Reporting Thyroid Cytology (TBSRTC). New entities according to the latest World Health Organization (WHO) classification are included, as well as an update of the current molecular data.

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INTRODUCTION

The term “Oncocyte/Hürthle cell” indicates the particular morphological appearance of a thyrocyte which has a “swollen” cytoplasm due to the abundant increase in the amount of abnormally dysfunctional mitochondria. The cells are characterized by a large cytoplasm displaying a dense, granular, eosinophilic color with a distinct cell border and pink macronucleoli (1). What is defined by pathologists as “Oncocyte/Hürthle” and “oncocytoid/mitochondrion-rich” cells are a reflection of morphological alterations based on the number of cationic organelles in the cell by showing a spectrum from fully, dense, pink cytoplasm (oncocyte/Hürthle) to the less or incomplete oncocytic appearance (“oncocytoid/mitochondrion-rich” cells). However, neither at microscopy, nor at ultrastructural level, exists quantitative measurements for an exact distinction between “oncocytoid” cells from non-oncocytic counterpart (2).

Oncocytic cells are present in many benign and malignant lesions in all endocrine organs. They have been originally associated with senescence. They are encountered in chronic inflammatory lesions as a way of cell adaptation to stress. Oncocytic cell phenotype is considered a result of metaplasia. However, the oncocytic cell is not another distinct cell type. It rather represents a different phenotype of the same cell as an adaptation phenomenon related to changed mitochondrial homeostasis. Regarding the thyroid both follicular and C cells may show oncocytic profile. In addition, oncocytic cells express the same immunohistochemical markers with the cells of origin (3).

In thyroid, oncocytic cells are observed as focal areas in nodular goiter or forming hyperplastic adenomatoid nodules. They are also encountered in autoimmune disorders as chronic lymphocytic thyroiditis (CLT) and in nodules arising in its background, in long-standing Graves' disease, after head and neck irradiation therapy, and systematic chemotherapy (4).

In the 4th edition of the World Health Organization (WHO) Classification of Tumours of Endocrine Organs, Hürthle cell tumors (HCT) were accepted as a clinic-pathological entity that encompass benign and malignant neoplasms and not anymore variants of follicular adenoma and follicular carcinoma (5). Together with the new classification, one has kept the presence of oncocytic variants of papillary/medullary/poorly differentiated carcinoma (5). Recently, even cases of non-invasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP) showing oncocytic phenotype, have been described (6–8).

In thyroid cytology the discrimination between a true HCT and other thyroid tumours with oncocytic features is not always feasible in routine practice (9). During the past decade, molecular tests on fine needle aspiration (FNA) specimens have provided a deeper insight in the pathogenesis of Hürthle cells neoplasms (HCN), yet their accurate preoperative diagnosis is still a challenge (10).

Oncocytic lesions in thyroid cytology befall to almost all categories of the Bethesda system for reporting thyroid cytopathology (TBSRTC) (11). In routine practice, lesions with oncocytic cells are reported with higher frequency in the indeterminate categories, namely atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) and suspicious for follicular neoplasm/follicular neoplasm (SFN/FN), comparing to non-oncocytic lesions. They are also a source of increased interobserver variability (12, 13).

In this review comprehensive cytology of all Hürthle cells neoplastic and non-neoplastic thyroid lesions is described, focusing on the differential diagnosis and reporting according to TBSRTC. New entities according to the latest WHO classification are included, not reported in recent reviews and an update of the current molecular data is attempted.

NON-NEOPLASTIC CONDITIONS WITH HÜRTHLE CELL MORPHOLOGY

Chronic Lymphocytic Thyroiditis (CLT)

The most frequent lesion showing oncocytic cells in FNA smears is CLT. The cytology depends on the stage of the disease. In early stages, the samples are hypercellular composed of oncocytic follicular cells admixed with polymorphic lymphoid population. In later stages, fibrosis may be the reason for hypocellular samples. The typical cytology of Hashimoto thyroiditis shows oxyphilic cells arranged in usually small monolayered “honeycomb” groups, or isolated. They have abundant granular cytoplasm with well-defined borders and enlarged, hyperchromatic, often pleomorphic pyknotic nuclei, with conspicuous nucleoli. The lymphoid component consists of

small mature lymphocytes, plasma cells, and germinal center cells and lympho-histiocytic aggregates (4, 14).

It is well established that CLT is a major source of false-positive in thyroid FNAs (15–17). Occasionally, focal reparative atypia of Hürthle cells in CLT can be observed. It usually presents as enlarged nuclei, with delicate smudgy chromatin, anisonucleosis, conspicuous nuclear membranes, macronucleoli, nuclear grooves, and even rare nuclear pseudoinclusions and may pose difficulties in differentiating from papillary thyroid carcinoma (PTC) (18–20). If this cytological atypia is not predominant, not associated with other features of PTC, but focal in a background of CLT, it is more appropriate to classify the lesion as AUS/FLUS, instead of suspicious for malignancy (SFM) (11).

Dominant hyperplastic Hürthle cell nodules in CLT may be a diagnostic challenge in FNA. The specimen may consist exclusively of oxyphilic cells with few or absent lymphocytes. The smears can be cellular showing macrofollicular, microfollicular, trabecular, or solid arrangement of epithelial cells with different amounts of colloid present. In addition, if Hürthle cells have prominent nucleoli and intervening blood vessels are present, the risk of misinterpreting the lesion for a HCN is high (19, 20).

According to an earlier publication, the number of lymphocytes as a single feature is not enough to differentiate CLT from a thyroid neoplasm (21). However, the presence of lymphocytes, especially percolating the cell groups, strongly suggests a nonneoplastic Hürthle cell nodule (4). Furthermore, clinical parameters as ultrasound features and serological tests for antithyroglobulin and anti-thyroid peroxidase antibodies should be taken into consideration in such cases.

If the clinical setting is suggestive of Hashimoto thyroiditis it is prudent not to sign out the case as follicular neoplasm Hürthle cell type/suspicious for follicular neoplasm Hürthle cell type (FNHCT/SFNHCT), but rather as category AUS/FLUS, according to TBSRTC. An explanatory note should be provided that a sample consisting of Hürthle cells in a patient with Hashimoto thyroiditis, more likely represents a hyperplastic nodule; however, a Hürthle cell neoplasm cannot be entirely excluded (11).

Multinodular Goiter (MNG)

Nodules in MNG show diverse architectural histological patterns. Commonly, hyperplastic nodules consist of macrofollicles and/or microfollicles, occasionally showing oxyphilic changes to a variable extent. Atypia of the oncocytic cells similar to that seen in CLT such as anisonucleosis, prominent nucleoli, and multinucleation can also focally be found in MNG and Graves' disease (21).

These histological features are reflected in FNA specimens. In a setting of a benign hyperplastic nodule, oncocytic cells may be present in various numbers forming sheets or isolated and occasionally showing significant anisonucleosis and hyperchromasia. In addition, transitional cell forms from regular follicular cells to oncocytic cells may be noted (14). This admixture of cell types is consistent with a hyperplastic nodule and should be interpreted as benign, according to TBSRTC (11).

However, when a hyperplastic nodule in MNG is composed predominantly of oxyphilic cells, the issue of differentiating from a HCN emerges. Important parameters to consider are the presence of colloid, inflammatory cells, namely lymphocytes and histiocytes, and the percentage of oncocyctic cells, in order to avoid overcalling a hyperplastic nodule as neoplasm. Hypercellular samples with a monotonous Hürthle cell population of more than 90% of the specimen is a reliable criterion favoring neoplasia (4). Furthermore, a non-macrofollicular cell arrangement, presence of transgressing vessels and prominent macronucleoli are common features in neoplasms. Nevertheless, a false positive diagnosis cannot always be avoided (22–25).

In patients with multiple nodules, an FNA sample composed exclusively of Hürthle cells can be either classified as FNHCT/SFNHCT or as AUS/FLUS. In the latter case, an explanatory note defining that in the setting of MNG, it probably represents a hyperplastic nodule; nevertheless, a neoplastic process cannot be excluded. The AUS/FLUS category is meant to give the clinician the chance to decide towards a sonographic and clinical follow up rather than surgery (11).

Reparative changes are encountered in nodular goiter, particularly in nodules with cystic degeneration. Atypical cyst lining cells are elongated cells arranged in monolayers with well-defined cell borders, enlarged oblong nuclei and distinct nucleoli, occasionally resembling oncocyctic cells. They should not be confused with Hürthle cells, because their cytoplasm is not dense and granular as in oxyphilic cells but rather delicate basophilic. In addition, they may have grooves, and rarely scant intranuclear inclusions. These cells, often representing a small portion of the follicular cell population, are usually easily recognized (19, 26). When such changes are more widespread than focal in the specimen may raise a concern for papillary

carcinoma. If this is the case it should be classified as AUS/FLUS (11).

NEOPLASTIC CONDITIONS WITH HÜRTHLE CELL MORPHOLOGY

Hürthle Cell (ONCOCYTIC) Neoplasms (HCN)

Hürthle cell (oncocyctic) tumors are usually encapsulated neoplasms, consisting of follicular cells with oxyphilic morphology in at least 75% of their cell population (5). Two types of tumors are included in this category: adenoma (HCA) and carcinoma (HCC). Discrimination of these two entities is strictly defined by histology, based on capsular and/or vascular invasion. The criteria for diagnosing a HCN in FNA include cellular smears with monotonous, predominantly (>90%) oncocyctic cell population and absence of lymphocytes and plasmacytes (4, 23–25). Colloid is usually absent or scant (22, 23). However, cases of HCAs and HCCs showing abundant colloid have been reported (27). The cells are arranged in crowded microfollicular, syncytial, or trabecular aggregates or may be dyscohesive. They have enlarged central or eccentric round nucleus with macronucleoli and commonly show binucleation (22, 25). In addition, “small” or “large cell dysplasia” has been described as a characteristic of neoplastic Hürthle cells, initially identified in cases of HCC (28, 29). In “small cell dysplasia” the cell diameter is less than twice the nuclear diameter, which means cells smaller than the usual Hürthle cells with a higher nuclear cytoplasmic ratio. Whereas in “large cell dysplasia” the cell diameter is at least two-fold the nuclei diameter (**Figures 1A, B**). Transgressing blood vessels and intracytoplasmic vacuoles are also considered as features

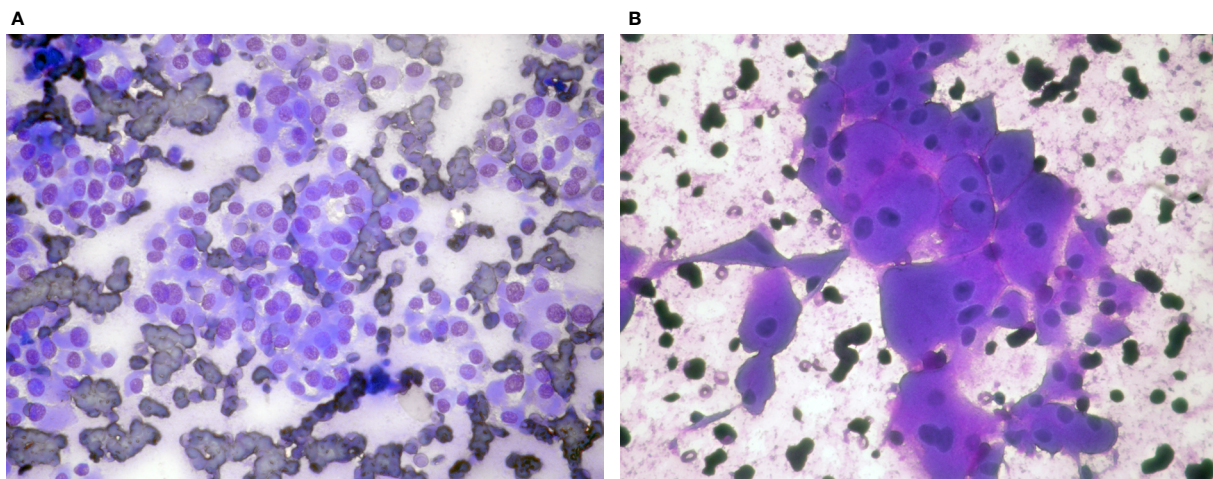


FIGURE 1 | Hürthle cell neoplasms: **(A)** (Giemsa stain ×40) Microfollicles and dyscohesive cells with small cell dysplasia, **(B)** (Giemsa stain ×40) Monolayer of cells with large cell dysplasia. Note binucleation and prominent nucleoli.

of diagnostic value for identifying HCN (22, 25, 28–31) (**Figures 2A B**). “Dysplasia”, in association with the above-mentioned criteria, is diagnostic of a neoplasm than a benign nodule with extensive oxyphilic change. According to TBSRTC these lesions should be classified in the category FNHCT/SFNHCT with no comments towards adenoma or carcinoma (11).

Tumors of Uncertain Malignant Potential (TUMPs)

Tumors of uncertain malignant potential are encapsulated neoplasms with follicular architecture and questionable capsular or vascular invasion. They are classified in two categories, based on the presence of nuclear characteristics of PTC. The follicular tumor of UMP (FT-UMP) is composed of follicular cells with no features of PTC, whereas the well differentiated tumor of UMP (WDT-UMP) shows well or partially defined nuclear features of PTC (5). FT-UMPs can also show Hürthle cell morphology (32). Considering that the diagnosis is based entirely on histological criteria, FT-UMPs consisting of Hürthle cells cannot be distinguished by cytology from HCN (HCA, HCC).

Tumors With Low-Grade Malignant Potential

Non-invasive follicular neoplasm with papillary-like nuclear features (NIFTP) is a circumscribed tumor with no capsular invasion, showing follicular architectural pattern and PTC nuclear features. It is associated with extremely low malignant potential (5). The diagnosis of NIFTP is histological, after detailed examination of tumor capsule and the adjacent thyroid parenchyma. Oncocytic morphology is not described among the diagnostic criteria of NIFTP, according to WHO classification. However, recent publications describe cases of NIFTP showing oncocytic features. These “oncocytic” NIFTPs share the same clinical outcome and RAS-related molecular

profile with the “classical” type. In addition, they bear mitochondrial DNA mutations, attributed to their oncocytic phenotype (6–8). In FNA samples they show typical Hürthle cell morphology, indistinguishable from HCN (HA, HCC) (8). NIFTP cytology befalls to the indeterminate categories AUS/FLUS, SFN, SFM (8, 11).

MALIGNANT TUMORS

Apart from HCC other malignant tumors can show oncocytic features, such as variants of papillary, poorly differentiated, and medullary carcinoma.

Papillary Thyroid Carcinoma (PTC)

The morphologic variants of PTC are well documented and described in the recent WHO classification (5). Recognizing PTC subtypes in cytology routine practice is occasionally challenging mainly due to unfamiliarity with rare variants. Identification of aggressive PTC subtypes preoperatively can change the design of the surgical approach and have a serious impact on the patient management and outcome (33).

Four PTC variants exhibit oncocytic cell morphology. The tall cell variant (TCV-PTC) and the hobnail variant (HV-PTC) are associated with aggressive behavior (34–37), whereas the oncocytic variant (OV-PTC) and the Warthin like variant (WL-PTC) have favorable prognosis similar to conventional PTC (38–40).

Tall Cell Variant PTC

In FNA, the TCV-PTC is easily recognized as PTC showing all the typical features, though true papillary structures are not frequent. The nuclei are enlarged hypochromatic with prominent centrally located nucleoli and frequent, often multiple nuclear pseudoinclusions occasionally giving “a soap

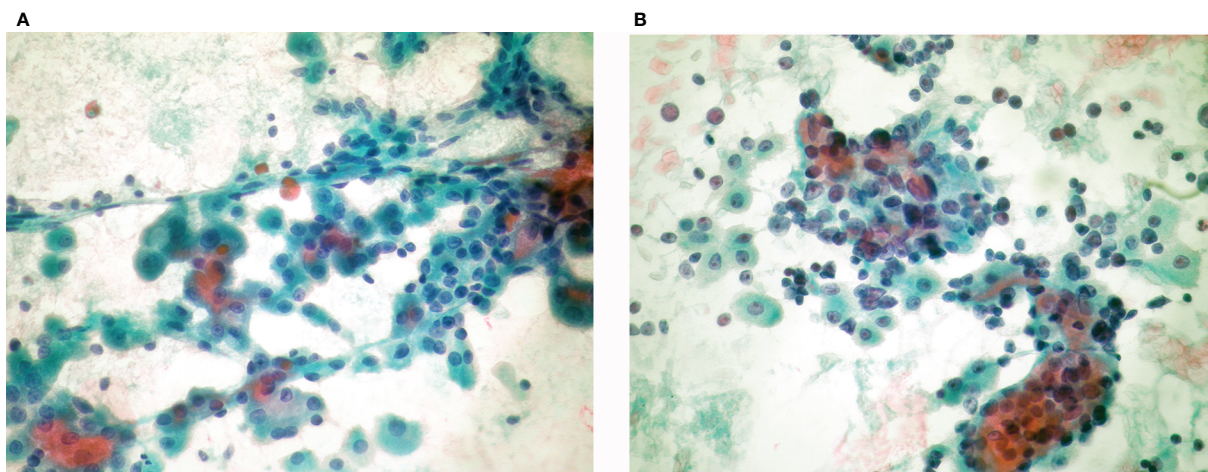


FIGURE 2 | Hürthle cell neoplasms: **(A)** (Pap stain $\times 40$) Hürthle cell adenoma: Monolayered groups and microfollicles with intervening blood vessels. **(B)** (Pap stain $\times 40$) Hürthle cell carcinoma: Syncytial, three dimensional crowded cell groups, dispersed cells, naked nuclei, marked anisonucleosis, hyperchromasia, and cherry red macronucleoli.

bubble” appearance. The cytoplasm is abundant, granular with well-defined borders and the cell shape vary from polygonal, elongated, or even cylindrical with eccentric nuclei (Figures 3A, B). The latter are usually described as “tail-like” cells. The background may have colloid and some lymphocytes (33, 41–43). If this “tall” morphology is appreciated in many cells of the sample a possibility TC-PTC may be raised. According to TBSRTC, is classified in the category malignant, PTC with a comment that tall cell variant is favored (11).

Hobnail Variant PTC

HV-PTC is a newly described type of PTC associated with poor prognosis (34, 37). In cytology specimens the cells are arranged in papillary-like and in micropapillary, tufting structures with prominent “hobnail” cells. There is a tendency towards loss of polarity and cohesion, therefore nuclear crowding and overlapping is not discernible. The hobnail cells have large eccentric nuclei bulging out of the dense oxyphilic cytoplasm. Also, single cells with eccentric nuclei and elongated cytoplasm described as “tear drop” cells are encountered. All PTC features are observed and “soap bubble” nuclei are also prominent (33, 36, 37). According to TBSRTC it is classified in the malignant PTC category.

TCV-PTC and HV-PTC have “aggressive looking” cells with all the PTC nuclear characteristics readily identified. Therefore, the differential diagnosis from Hürthle cell neoplasms is not problematic.

Oncocytic Variant PTC (OV-PTC)

The majority of cells (>75%) in aspiration samples of OV-PTC show granular oxyphilic cytoplasm with well-defined borders. The cells are in monolayers with honeycomb like cell arrangement, microfollicles, or lie dispersed, rather than true papillary structures. In addition, OV-PTC shows central macronucleoli, in contrast to the small eccentric nucleoli, observed in classical PTC. All PTC

nuclear characteristics namely enlargement, oval shape, pale chromatin, nuclear membrane irregularity, nuclear grooves, and nuclear pseudoinclusions are present (33) (Figure 4).

Earlier studies have shown that 12.8 to 26% of cases considered as HCN in cytology were eventually diagnosed as PTCs on the surgical specimen. This fact highlights the difficulty to interpret correctly atypia of neoplasms with oncocytic features on cytology (44–46). Furthermore, rare HCN show focal or extensive true papillary architecture (Figure 5). Histological, immunohistochemical, molecular, and clinical studies have proved that these encapsulated papillary oncocytic neoplasms (EPON) are mostly related to

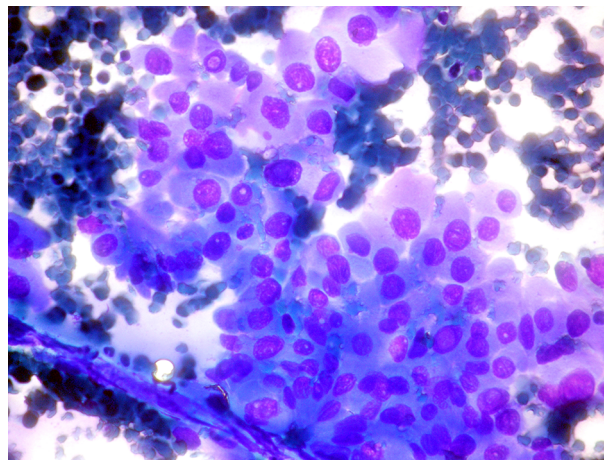


FIGURE 4 | Oncocytic variant papillary thyroid carcinoma: (Giemsa stain $\times 40$) Neoplastic cells with abundant dense cytoplasm in monolayer with minimal crowding. The cells show prominent nuclear atypia, with oval nuclei and intranuclear inclusions.

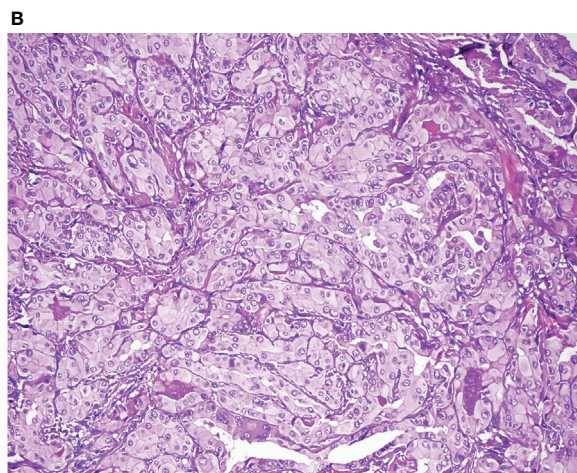
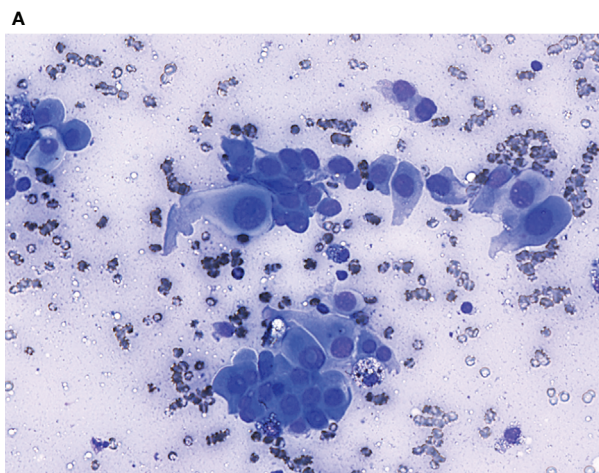


FIGURE 3 | Tall cell variant of papillary thyroid carcinoma: **(A)** (Giemsa stain $\times 40$) Neoplastic cells showing nuclear characteristics of PTC and elongated cytoplasm. **(B)** (HE stain $\times 20$) Histological section showing elongated follicles with parallel arrangement. See the nuclear features of PTC and the eosinophilic cytoplasm with distinct cell borders.

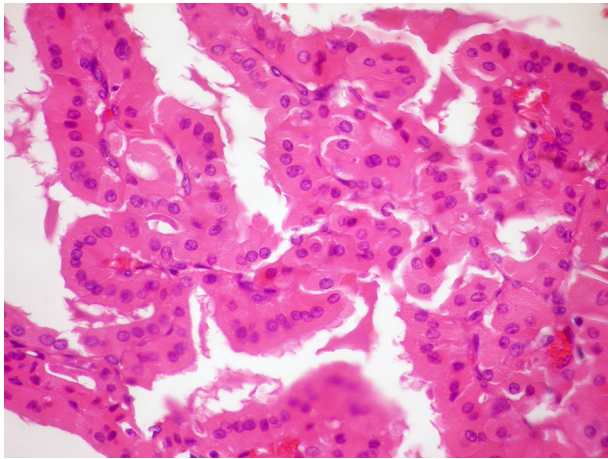


FIGURE 5 | (HE stain $\times 40$): Histology of Hürthle cell adenoma with papillary architecture.

follicular neoplasms and should be distinguished from papillary thyroid carcinoma (47, 48). Although FNA cytology of these tumors is intriguing, it can lead to the correct diagnosis (49). Papillary architecture should not be a synonym of malignancy. Searching for the presence or absence of all typical nuclear features of PTC is essential (1, 5, 33, 47–49). These cases can be classified either as category FNHCT/SFNHCT or as SFM with a note explaining the differential diagnosis (11).

Warthin-Like Variant PTC (WLV-PTC)

WLV-PTC is a circumscribed, though not encapsulated tumor, which shows a histologic pattern reminiscent of Warthin tumor of the parotid gland, often encountered in a background of Hashimoto thyroiditis (40, 50, 51).

In cytology specimens, large polygonal tumor cells with abundant dense granular oncocytic cytoplasm are observed in papillary formation or dispersed in a lymphoplasmacytic background. The tumor cells show all the nuclear features of PTC. Lymphocytes are seen infiltrating the epithelial groups and permeating the fibrovascular cores of the papillary structures. This latter feature is helpful in distinguishing WLV-PTC from the other oncocytic PTC variants, and from non-oncocytic PTC arising in a background of Hashimoto thyroiditis (19, 40). WLV-PTC, due to the exaggerated nuclear atypia, may raise suspicion of an aggressive type as TCV-PTC or HV-PTC (33). However, in WLV-PTC there are no elongated cells, the cells have larger amount of granular cytoplasm nucleoli are more prominent, and lymphocytes are abundant (33, 40).

Oncocytic Variant Poorly Differentiated Thyroid Carcinoma (OV-PDTC)

Poorly differentiated thyroid carcinoma (PDTC) is a rare thyroid carcinoma of follicular origin showing aggressive behavior with tendency of local recurrence, regional and distant metastases, and an overall 5-year survival of 60–70%. The oncocytic variant of PDTC (OV-PDTC) represents 30% of the cases in previous publications

and is associated with even worse survival rates (52–54). Cytological diagnosis of PDTC is challenging due to the rarity of these tumors and the overlapping characteristics with follicular tumors. In previous studies including large series of PDTC only 32.5% of the cases were classified correctly with FNA (55, 56).

Cytologic criteria of PDTC are cellular smears showing insular, solid, or trabecular cell arrangement with crowding, and disperse cells. The cells are small monomorphic with high N/C ratio and variable atypia. In addition, apoptosis, mitoses are frequent. Necrosis, with debris and leukocytes in the background, may occasionally be observed. As a rule, colloid is scant or absent. Endothelial cells forming transgressing vessel or wrapped around the neoplastic blasts are also encountered (11, 55).

There is only one report in the literature where OV-PDTC was suggested preoperatively on cytology. This case met the above-mentioned diagnostic criteria of PDTC, but the cells showed abundant granular oncocytic cytoplasm (57).

It is very important to differentiate OV-PDTC from HCNs, due to its aggressive behavior which requires a radical surgical approach. Small cell size, nuclear hyperchromasia and atypia, lack of macronucleoli, crowding, and necrosis are features uncommon for HCNs. Similarly, differentiating OV-PDTC from oncocytic variant of medullary thyroid carcinoma (OV-MTC) and metastatic tumors is not easy (46, 58). MTC shows salt and pepper chromatin and may also have amyloid in the background. An essential immunohistochemical panel including thyroglobulin, thyroid transcription factor 1 (TTF1) calcitonin, and carcinoembryonic antigen (CEA) is required to establish the correct diagnosis (57, 58).

According to TBSRTC if all cytologic criteria are identified it should be classified as malignant with a short description of the features suggestive of PDTC. However, if the findings are suspicious but not conclusive for malignancy it is preferable to be classified as SFN with a description of atypical cell features, signs of necrosis, and mitotic activity (11).

Oncocytic Variant of Medullary Thyroid Carcinoma (OV-MTC)

Medullary thyroid carcinoma (MTC) is recognized as the “great mimicker”, due to the great variety of morphological subtypes. The sensitivity of FNA in MTC diagnosis has been reported up to 89%, though a percentage of 56% has been estimated in a metanalysis study (59, 60).

OV-MTC is the only thyroid tumor with oncocytic morphology not originating from follicular cells. The diagnosis in FNA specimen is challenging even for experienced cytopathologists. The literature includes only one case of OV-MTC, diagnosed on FNA specimen, suspected by morphology and confirmed by immunohistochemistry (61). In another case molecular analysis of the aspiration material suggested the possibility of MTC in a neoplasm, otherwise diagnosed as a Hürthle cell adenoma by both cytology and histology (62).

Overlapping features with HCNs lead to diagnostic pitfalls (63–65). However, it is of utmost importance to differentiate preoperatively an OV-MTC from an HCN. HCNs occasionally show disperse cell pattern reminiscent of MTC,

which further complicates the differential diagnosis. One valuable clue is the quality of the cytoplasm. In HCNs it is dense and granular, whereas in OV-MTC it is loosely granular, with multivacuolization similar to histiocytes (**Figures 6A, B**). In addition, if cytoplasmic metachromatic granules in Romanowsky stain are discernible the diagnosis of MTC should be considered. Generally, MTCs show more prominent nuclear atypia and pleomorphism. The typical chromatin of neuroendocrine tumors can be appreciated in careful examination of OV-MTC cells, but the presence of prominent nucleoli can be misleading. Amyloid, if present, is a very helpful feature, though it can be mistaken for colloid. Sparse nuclear inclusions and microcalcifications may be observed and mislead to the erroneous diagnosis of PTC with oncocytic morphology. If MTC is included in the differential diagnosis, immunohistochemistry should be performed and measurement of calcitonin blood levels should be considered (61, 65).

According to TBSRTC the category malignant should be used only when the cytology is conclusive, and a sub-classification of the tumor is feasible. However, if the possibility of MTC is raised but the diagnosis is not definite due to scarce material or unusual cytological features, SFM, suspicious for MTC is more appropriate. A comment recommending correlation with calcitonin serum levels or repeat aspiration for immunohistochemistry or molecular study should be included (11).

MOLECULAR CYTOLOGY TESTING AND ITS USE IN EVALUATING HÜRTHLE CELL NEOPLASMS

There are mainly two types of challenges in evaluating aspirates with the predominance of Hürthle cell morphology. One is to decide if it is an HCN or not, the second is if it is Hürthle cell neoplasm, then is it an HCA or HCC? Obviously, answering the

second question is not compatible with real life since this challenge cannot be overcome by using cytology material without proving the presence of either vascular or capsular invasion in surgical pathology specimen (5, 11). The first challenge stems from the large spectrum of differential diagnosis of Hürthle cell neoplasms that was mentioned above in this article. There have been remarkable molecular advances in the understanding of the molecular genetics and epigenetics of HCNs in recent years (2). The characteristic alterations in oncocytic neoplasms are the increased mutations in mitochondrial DNA (mtDNA), that are distributed throughout the mitochondrial genome (tRNAs and rRNAs). This predominantly affecting genes encoding for complex I (CI) subunits of oxidative phosphorylation (OXPHOS) system, particularly *NADH-dehydrogenase 1* (ND1) and *NADH-dehydrogenase 5* (ND5) genes (2, 66). The 4977bp deletion in mtDNA which is known as “common deletion” is also frequent in HCNs of thyroid. Besides the somatic mtDNA mutations, variants of mtDNA variants also were described by Maximo et al. to be associated with HCC (2, 67). The most common gene mutations such as *rat sarcoma gene* (RAS), *v-Raf murine sarcoma viral oncogene homolog B* (BRAF), and *Telomerase reverse transcriptase promoter gene* (TERTp) mutations were described in HCC but always in lower frequency than in non-oncocytic neoplasms (2, 68–74). Similar results were found for *paired box 8/Peroxisome proliferator-activated receptor gamma gene* (PAX8/PPARG) and *rearranged during transfection gene* (RET/PTC) rearrangements (70, 75–79). Copy number variations were found more common in HCNs; Chromosomal gains were mostly seen in chromosomes 5, 7, and 12 and loss in chromosome 22 (2). Corver et al. documented “near-haploid” genotype and homozygosity in several chromosomes of the cases of HCC series, while chromosome 7 retained heterozygosity in the same group of cases, suggesting that it is important to favor the acquisition of oncocytic morphology (80, 81). Nikiforova et al. showed the overexpression of microRNAs: miR-183,

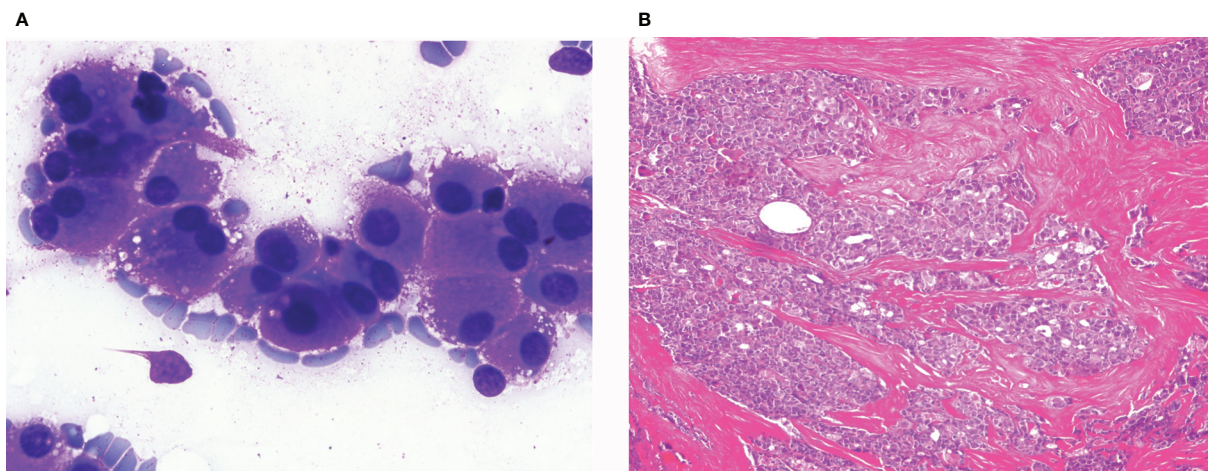


FIGURE 6 | Oncocytic variant of medullary thyroid carcinoma: **(A)** (Giemsa stain $\times 40$) Neoplastic isolated cells with abundant granular cytoplasm. **(B)** (HE $\times 20$) Histological sections showing infiltrating groups of neoplastic cells. These cells were positive for calcitonin.

miR-197, and miR-339 in HCCs and miR-31, miR-183, and miR-339 in HCAs in comparison with normal thyroid tissues together with the cluster analysis (82). These results endorsed the particular miRNA profile of HCNs and showing HCNs might be different class of tumor rather than a variant of non-oncocytic group. In 2013, Ganly et al. performed microarray analysis of gene expression in HCNs by using a clustering analysis, the authors observed that HA were more similar to MI-HCC (minimal invasive-HCC), whereas WI-HCC (widely invasive-HCC) were more distant from them with few exceptions (79). In 2018, the same group published a genomic report through RNA sequencing. The group showed MI-HCC and WI-HCC tend to cluster at some extent separately, based mostly in different enrichment in genes related to Eukaryotic Initiation Factor-2 and 4 (EIF2, EIF4) and mTOR pathways and related to mitochondrial activity (69).

Following the description of these molecular alterations, now, there are molecular tests such as the Afirma gene expression classifier (GEC) and ThyroSeq mutational panel applicable for the cytology material to stratify cytologically indeterminate thyroid nodules. Despite showing 92% sensitivity and 52% specificity for malignancy, the performance of the Afirma GEC was lower for Hürthle cell lesions (83–89). The most recent version of Afirma, the genomic sequencing classifier (GSC) uses a new algorithm incorporating RNAm expression, sequencing, and genomic copy number detection (10, 90). The most important improvements were in the categorization of Hürthle cell lesions. The sensitivity and specificity for HCN (HCA and HCC) were 89 and 59% respectively, compared with 89 and 12% in GEC (10, 90). The recent studies showed that the benign rate of Hürthle cell lesions detected in FNA is three times higher using GCS compared with GEC (91).

The latest version of ThyroSeq (ThyroSeq v3; multigene next-generation sequencing- based test) adding the copy number alterations have showed reliable performance in differentiating HCCs with the 93% sensitivity and 69% specificity (90). The study of Schatz-Siemers et al. focused a cohort of Hürthle cell lesions with indeterminate cytology by using ThyroSeq® (8). Negative results were found to be helpful for ruling out malignancy in the presurgical management of Hürthle cell lesions with indeterminate cytology (92). RAS mutations were the most prevalent and mostly they were associated with benign lesions and NIFTP (5). However, PAX8/PPARG rearrangement, *phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha* (PIK3CA), TP53, and TERT gene mutations were detected in malignant cases (2). Due to the limited data in the literature, differences in methodologies, and variability in the test version

used, until this moment is difficult to evaluate the performance of ThyroSeq versions in Hürthle cell lesions or compared with non-Hürthle cell lesions observed in FNA.

MANAGEMENT OF HCNs

The management of HCC is similar to follicular thyroid carcinoma. There are two characteristics about the clinical behavior of HCC. One is metastatic HCC seem to be less prone to concentrating I131, and the other is more frequent locoregional lymph nodes involvement (2, 93).

The description of HCC clinical management follows the most recent American Thyroid Association guidelines and National Comprehensive Cancer Network Thyroid Cancer management guidelines (92, 93). Total thyroidectomy is indicated in cases of invasive cancer and metastatic disease, and lobectomy is indicated in minimally invasive cancer without angioinvasion. If invasive cancer is identified with vascular invasion, completion of thyroidectomy should follow. Radioactive iodine therapy should be considered in cases of gross extrathyroidal extension, when the primary tumor is more than 4 cm, when there is extensive vascular invasion, or when post-operative unstimulated thyroglobulin levels are high (94, 95). As mentioned before, HCN cannot be defined as benign or malignant based only in cytology. So, tumors suspected of being Hürthle cell cancer are often treated like follicular neoplasms. A lobectomy is usually performed at first step. If cancer is confirmed, a completion thyroidectomy needs to be done. A bilateral thyroidectomy might be considered at the first step if there are signs that the cancer has spread or if the patient wants to avoid having a second surgery afterward (11, 94, 95).

AUTHOR CONTRIBUTIONS

ET: drafted the manuscript. SC: conceptualization and revision. FS: conceptualization and revision. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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