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Follicular Growth Pattern Disease on Thyroid Fine-needle Aspiration Biopsy

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Thyroid nodules are a common worldwide health problem and a diagnostic challenge for clinicians and cytopathologists. Follicular growth pattern constitutes the majority of thyroid lesions. Thyroid nodules can be neoplastic or non-neoplastic, and neoplastic nodules can be classified as benign, malignant, or gray zone. Gray zone lesions include different benign and malignant entities that might be resulted in unnecessary thyroidectomies with risk of morbidity and higher health care costs. Depending on the cellularity, most cases might fall into the follicular neoplasia (FN)/ suspicious for FN (SFN) category or follicular lesion of undetermined significance (FLUS) in The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Pathologists must be aware of the relationship between this diagnostic category and follow-up patient management and avoid over-diagnosing by mastering the diagnostic criteria.

Thyroid lesions are global health problem, taking into account both non-neoplastic and neoplastic nodules, whereby a correct diagnosis represents an importance for patient management and follow up. Over diagnosis might lead to unnecessary surgeries, causing both morbidity and high health expenditure. On the other hand, underdiagnosis may cause to the exclusion of malignant lesion from follow-up or delayed intervention.[1-3]

Fine-needle aspiration biopsy (FNAB) is a noninvasive and primary diagnostic method used in the management of thyroid nodules. Numerous studies have reported that more than 70% of all thyroid nodules are reported as benign, 5-10% are malignant, and the remaining 20% represent the so-called gray zone.[4,5] Most gray zone lesions are follicular-patterned thyroid lesions which malignancy cannot be definitively detected via cytology due to the requirement of evaluating the capsular and vascular status of the pathology specimen. Thus, the FN/SFN category remains a limited technique in screening lesions. Gray zone lesions are segregated in the FN/SFN category of TBSRTC. Identification of nonneoplastic lesions, which can be managed conservatively, and neoplastic lesions, which will be treated with surgical resection, is possible with the use of FNAB.[6,7]

HISTORY OF VARIOUS CLASSIFICATION SYSTEMS OF FOLLICULAR PROLIFERATIONS

Several classification systems for reporting thyroid cytopathology have been introduced in recent decades, such as the UK, Japanese, Australian, Danish, and Italian classifications[8-19]. TBSRTC, which is a widely accepted reporting system, was proposed in 2007. It aimed to bring uniformity in the categorization of the wide spectrum of lesions, particularly gray zone lesions.[20] Over the years, the need for the regulation of TBSRTC arose, and the renewed system guidelines were published in 2017.[7,21,22] A notable flaw of this system was an implied risk of malignancy for each diagnostic category combined with the lack of correct recommendations concerning the management of patients.

TBSRTC proposed three categories for indeterminate cytology: atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), FN/SFN, and suspicious

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for malignancy (SM)[23-26]. The literature revealed the difficulties in AUS/FLUS and FN/SFN diagnoses that might lead to overdiagnosis and overtreatment, such as lobectomy or bilateral total thyroidectomy.[27-33] These diagnostic problems in TBSRTC led to new pursuits and the application of ancillary techniques, such as immunocytochemistry (ICC) and molecular analysis, on cytology samples. Currently, these techniques can be performed in all cytology preparations. However, the use of liquid-based cytology (LBC) techniques might facilitate their application in exceeding the difficulties faced with conventional cytology.[34-40] The cytopathologic features, as well as the differential diagnoses of the follicular lesions, will be discussed in this article using TBSRTC.

FOLLICULAR PATTERN LESIONS IN THE BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY

Follicular neoplasms: follicular adenoma (FA) and follicular carcinoma (FC) are generally classified into the FN/SFN category of TBSRTC. In addition, the FN/SFN category includes a few cases of follicular variants of papillary carcinoma and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), which cannot be diagnosed as malignant cytologically because they do not definitively show the nuclear features of papillary thyroid cancer (PTC). In the differential diagnosis of this category, the follicular pattern of medullary carcinoma, dyshormonogenetic goiter, parathyroid lesions, and poorly differentiated carcinoma should be considered [41,42] (Table 1).

CYTOMORPHOLOGIC FEATURES OF THYROID FOLLICULAR LESIONS AND DIFFERENTIAL DIAGNOSIS

Thyroid aspiration slides should be evaluated with all elements together on the microscopic area. When the slides are predominantly composed of micro follicles, the background of the slides and the accompanying components should be carefully analyzed. In the presence of the thyroid follicular epithelial cell sheets in a honeycomb arrangement, the presence of abundant colloid, numerous histocytes, lymphocytes, stromal fragments, and cystic changes mostly indicate benign entities, whereas the uniform proliferation of micro follicles with scant colloid suggests neoplastic lesions.[41-46]

TABLE 1. Differential Diagnosis of Follicular Pattern Thyroid Lesions in Fine Needle Aspiration Biopsy

Follicular pattern thyroid lesions in fine-needle aspiration biopsy
■ Adenomatous/hyperplastic nodules
■ Follicular adenoma
■ Follicular carcinoma
■ Follicular variant of papillary thyroid carcinoma
■ Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
■ Follicular pattern of medullary carcinoma
■ Dyshormonogenetic goiter
■ Parathyroid lesions
■ Poorly differentiated carcinoma

Cytological evaluation of the FN/SFN category is usually accompanied by thyroid follicular lesions. Although the diagnostic criteria of follicular lesions on FNA are not clearly defined, cellular aspirates with scanty amount of colloid, which are composed of follicular epithelial cell groups with microfollicular patterns >50-70%, are diagnosed as FN/SFN.[1] This category likewise has two alternative names. FN and SFN are synonymous terms and should not be used like two different diagnostic terms. Generally, SFN is preferred by most laboratories because histopathologic studies supported that a significant number of cases (up to 35%) prove not to be neoplasms but rather hyperplastic proliferative lesions, which are most commonly nodular goiter.[43-46]

Notably, the accurate definition of the microfollicular/macrofollicular terms is important. Microfollicles are composed of less than 15 overlapping thyroid follicular epithelial cells, which form a circle that is at least two-thirds complete. Macrofollicles are composed of small or large flat groups/sheets or even rows of follicular epithelial cells. Cell circles and overlapping are not characteristic findings for macrofollicles.[47] An important diagnostic clue is not to call the crowded small groups, which create a pseudo microfollicular appearance in a clot, such as microfollicles in bloody smears. In these slides, observing microfollicles out of the clot may be helpful for diagnosis. Sometimes, sampling from the microfollicular/cellular areas of benign nodules can lead to a cytological misdiagnosis of FN/SFN. Reactive/degenerative nuclear features that are not distinguishable but arouse suspicion may also lead to the overdiagnosis of PTC. The 2017 TBSRTC supported a modification to the definition and diagnostic criteria for the FN/SFN category in light of NIFTP. The new description reads as follows: "Follicular-patterned cases with mild nuclear changes (increased nuclear size, nuclear contour irregularity, and/or chromatin clearing) can be classified as FN/SFN so long as true papillae and intranuclear pseudoinclusions are absent, a note that some nuclear features raise-the possibility of an FVPTC or NIFTP, can be included".[7,48]

In the following parts of this article, the cytological features and differential diagnoses of the major follicular growth pattern disease of the thyroid will be discussed.

Adenomatous, Hyperplastic Nodules

These lesions show single-layer groups, honeycomb-pattern follicles, and/or single thyroid follicular epithelial cells. The presence of abundant watery colloids is an important feature of smears. Follicular epithelial cells have small, round nuclei and scanty, abundant, mildly vacuolated, or oncocytic cytoplasm (Figure 1). Although they are simple diagnostic criteria, diagnostic difficulties are sometimes experienced in the FNA of hyperplastic nodules. In relation to this, sampling from the microfollicular/cellular areas of benign nodules can be a challenging condition for a cytopathologist, and such cases can be misdiagnosed as FN/SFN.[43,49-53] It should also be noted that the nuclei of follicular lesions/neoplasms are expected to be round and with coarsely granular chromatin (rather hyperchromatic), which might be slightly larger than regular thyroid follicular epithelial cells.

The presence of abundant loose/watery colloids can help to the cytopathologist for away from over-diagnosis[48-53].

Follicular Adenomas/Follicular Carcinomas

FAs/FCs are the most important and classical categories of follicular pattern lesions. Cytomorphological features do not allow the differentiation of FAs from FCs. The main differential diagnosis criteria of these lesions are based on capsular and vascular invasion, which can be diagnosed only with a thorough histologic evaluation of the nodule. With this knowledge, we are faced with the fact that FN is a screening test rather than a diagnostic test in this situation [41,43,54].

These lesions exhibit the main findings of the FN/FNS category. The cytological definition of FA/FC is "cellularity-rich aspirates consisting of follicular cells with crowding or microfollicle formation on colloid poor background." The nuclei of follicular epithelial cells are round, slightly larger than normal thyroid follicular epithelial cells, and hyperchromatic with coarsely granular chromatin (Figure 2). Due to the inability to distinguish FAs from FCs with these findings, many studies have been explored clinicopathologic findings, as well as patient demographics, to increase diagnostic accuracy. Most of these studies have suggested that nodules larger than 3-4 cm predict malignancy. These findings

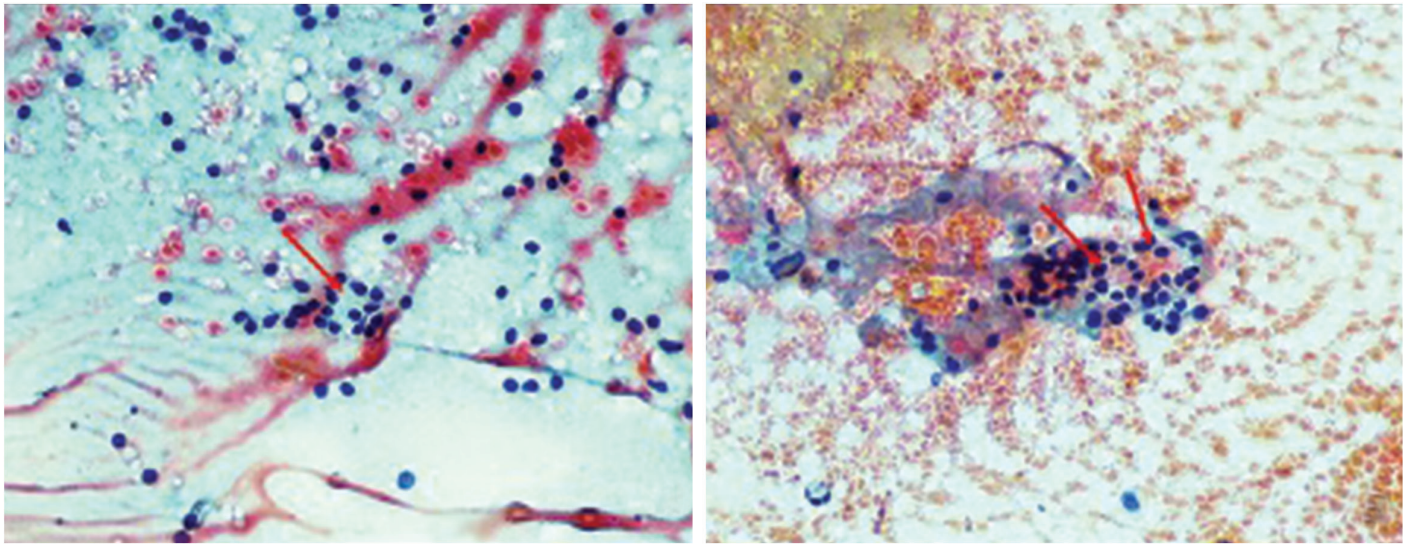

FIG. 1. Hyperplastic nodule on fine-needle aspiration biopsy. Benign follicle epithelial cells with few follicular structures (arrows) near colloidal material (PAP x200)

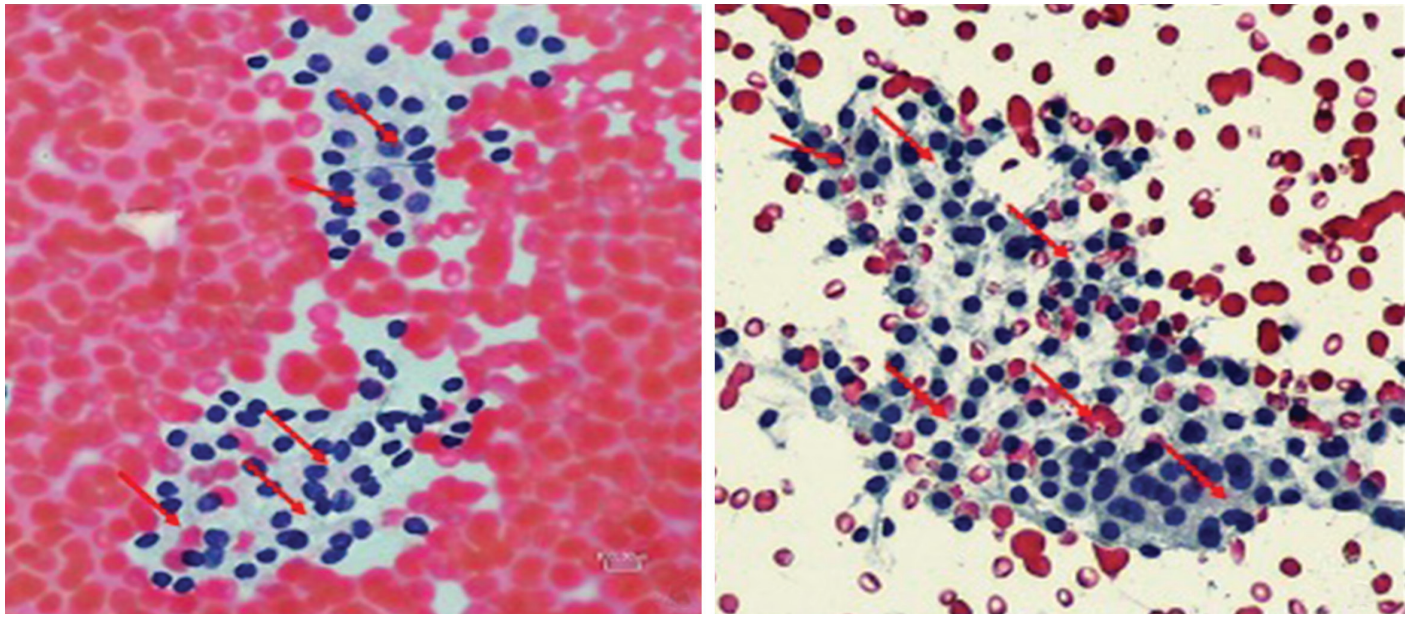

FIG. 2. Follicular neoplasms (FN)/suspicious for FN (SFN) with numerous microfollicules (arrows) on fine-needle aspiration biopsy (PAP x400)

prove once again the importance of evaluating cases with clinical findings in the pathology routine.[7,51-54]

Although the definition of follicular lesions in FN remains unclear, cellular aspirates consisting of >50-70% microfollicles and insufficient colloid amount are considered FN/SFN.[55] Microfollicles show a uniform appearance; other features of these lesions include trabeculae, crowded cell groups, and isolated single cells in the background.[56,57] Cases with scanty colloids with a macro/microfollicular pattern are not covered by this term even if the smear is hypercellular. These lesions should be considered benign nodules or AUS/FLUS depending on the amount of colloid, microfollicle ratio, and cellularity.[7,43]

Follicular Variant of Papillary Thyroid Carcinoma/NIFTP

The exclusion of FVPTC is the most important clue for the differential diagnosis of the FN/SFN category. In smears, these cases can have an abundance of microfollicles or monolayer fragments mimicking a follicular neoplasm. Undoubtedly, the most important criteria are the evaluation of specific nuclear features of PTC, such as nuclear enlargement, membrane irregularities, crowding, elongation, chromatin clearing, pseudoinclusions, and grooves (Figure 3). However, unfortunately FVPTCs do not show always the characteristic nuclear features of PTC and present with subtle nuclear findings. In case of determination of nuclear features suspicious for PTC, should be reported as SM regardless of their prominent microfollicular pattern.[13,24,45] But, the presence of subtle nuclear changes and microfollicles together can be misleading for cytological examination, and ignoring of this nuclear changes can result in an FN/ SFN diagnosis. Thus, approximately 15-20% of cases diagnosed as FN/SFN later turn out to be FVPTC.[51,55] The relationship between FVPTC and NIFT-P can be compared to FC and FA. Encapsulation as a differential diagnostic feature of these entities cannot be given by cytomorphology. In case of cytologic features suggestive of FVPTC/NIFTP, optional notes in cytological diagnosis may be used to acknowledge NIFTP: "Although the architectural features suggest a follicular neoplasm, some nuclear features raise the possibility of an invasive FVPTC or its recently described indolent counterpart, NIFTP; definitive distinction among these entities is not possible on cytological material".[56]

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) is an aggressive neoplasm of the thyroid, which is typically characterized by many single cells and loose fragments; follicular formation is an unexpected finding. However, MTC may reveal nested/trabecular/loose microfollicular patterns and could be misdiagnosed as follicular neoplasm. Some tumors may show oncocytic cytoplasm mimicking oncocytic follicular neoplasm (Figure 4). For differential diagnosis, a predominantly dispersed cell pattern, presence of both plasmacytoid and spindle type cells, nuclear neuroendocrine type chromatin, binucleation, and eccentric nuclei can help identify MTC. If it can be identified, the presence of amyloid is a supportive diagnostic finding. ICC studies (calcitonin, CEA, TTF-1 etc.) may help provide the final diagnosis. Clinically requesting serum calcitonin analysis is important clue.[1,56,57]

Dyshormonogenetic Goiter

These lesions are characterized by a microfollicular pattern and a lack of colloid. Therefore, they should be considered in the differential diagnosis of FN/FNS. The presence of congenital hypothyroidism is supported by dyshormonogenetic goiter and clinical history. Empty follicles (microfollicules without intrafollicular colloid) and anisokaryosis with bizarre cells are typical cytopathologic findings for dyshormonegenetic goiter.[58]

Intrathyroidal Parathyroid Adenoma

Parathyroid adenomas (PAs) may show sheets/clusters or microfollicules and many bare nuclei. Due to these findings, patients are misdiagnosed as FN/FNS. Occasionally colloid-like parathyroid secretions can be seen in PA smears. Parathyroid cells typically reveal a neuroendocrine-type nuclear chromatin

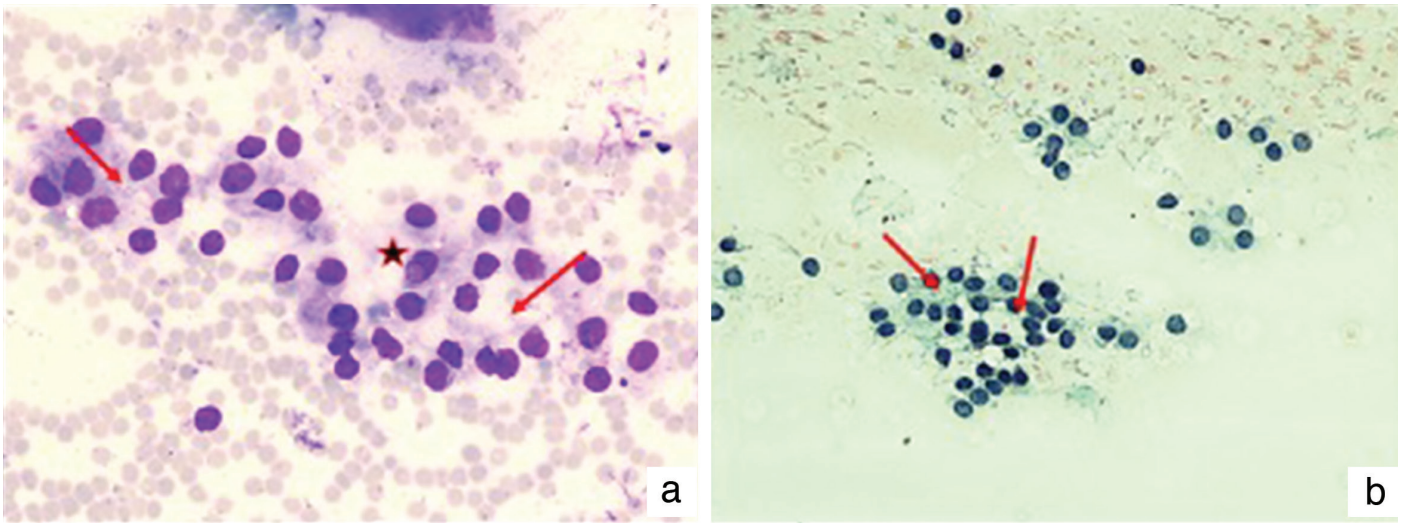

FIG. 3. Follicular variant papillary thyroid carcinoma with few follicular structures on fine-needle aspiration biopsy (arrows: microfollicles, asterisk: intranuclear pseudo inclusion), (a. Giemsa x400, b. PAP x200)

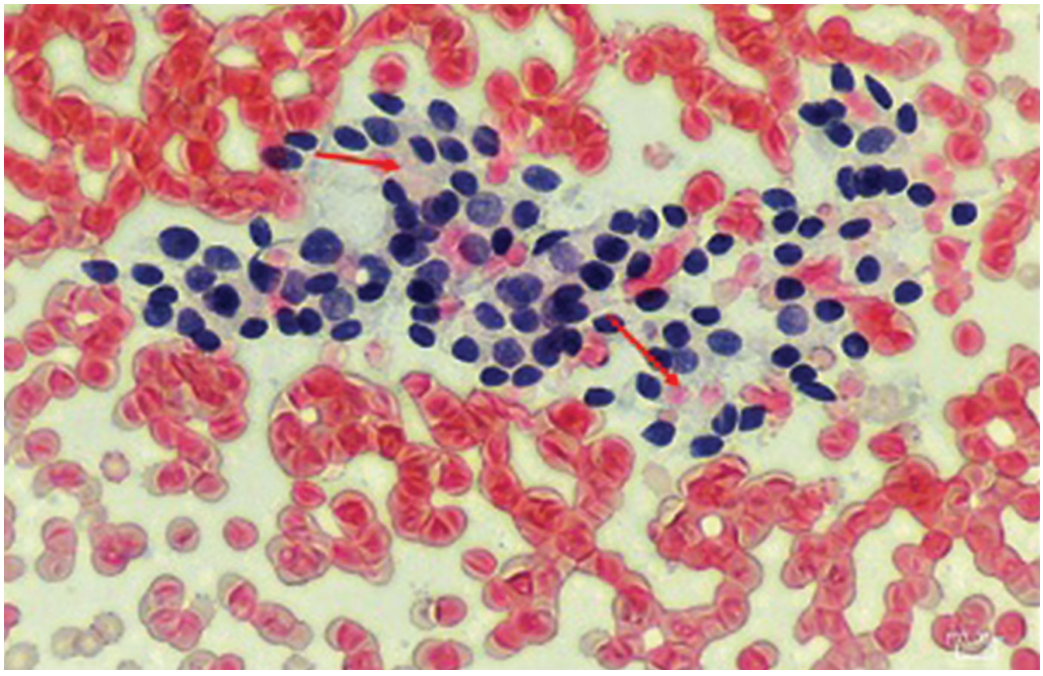

FIG. 4. Medullary carcinoma with few follicular structures (arrows) on fine-needle aspiration biopsy (PAP x400)

and prominent vascular network. Performing synchronous PTH assays on FNA and immunohistochemical studies on cell blocks are important diagnostic assistive techniques for PAs.[59]

Poorly Differentiated Thyroid Carcinoma

Poorly differentiated thyroid carcinomas (PDTCs) are aggressive tumors derived from thyroid follicular epithelium. These thyroid malignancies commonly represent naked nuclei and solid/trabecular/insular patterns; however, microfollicles may sometimes be seen. If the microfollicular pattern is dominant, it frequently causes a misdiagnosis of FN/SFN, which can lead to inadequate patient management. Careful microscopic evaluation of nuclear details is important for differential diagnosis. The cells of PDTC are characterized by small, convoluted nuclei, speckled chromatin, and scant cytoplasm on smears. Nuclear pleomorphism, coarser chromatin, and anisokaryosis can be detected clearly in PDTCs at a high magnification.[60,61]

ANCILLARY TECHNIQUES USED FOR DIFFERENTIAL DIAGNOSIS OF FOLLICULAR LESIONS

Immunocytochemistry

Diagnosing FNs by FNA is the main problem because one cannot evaluate the capsule and vascular status; thus, follicular-patterned dominant FNAs are the candidates for ancillary tests.[62-67] The current version of guidelines for patients with thyroid nodules and differentiated thyroid cancer published by the American Thyroid Association suggests using these tests, and this approach has become popular among cytopathologists.[10,68] However, the recommendation of TBSRTC or many other reports does not include any information about thyroid ICC and other molecular tests in the group of FN/FNS. The low specificity of ICC and possible false-positive and false-negative results of ICC have been claimed as an important reason.[69,70] It should be noted that LBC methods eliminate this problem to a great extent.[71,72] There are many studies stating that ICC can be used in the differentiation of benign/malignant lesions as well as in the differentiation of lesions derived from thyroid follicle epithelial cells and C cells.[73-77] Various studies that evaluated different antibodies supported the finding that HBME-1 and galectin-3 have the highest specificity and sensitivity, which is highly suggestive of thyroid malignancies. However, none of these antibodies presented enough sensitivity and specificity to be used in routine practice.[78-83] In recent years, a specific monoclonal antibody (Ve1) against the mutated V600E BRAF protein began to be used for differential diagnosis and patient management. Few reports on the cytological application-assisted application of BRAF Ve1 antibody suggest that immunohistochemistry can be performed more reliably in cell block preparations, and false-positive results in direct smears may limit the benefit; thus, caution should be exercised in interpretation. VE1 expression may be an alternative method for detecting BRAF (V600E) when molecular detection is unavailable. Some studies suggest that the VE1 antibody can be used as a first-line approach for the evaluation of the BRAF mutation and case selection for molecular analysis; however, others do not support this approach.[84-90]

Molecular Tests

The application of molecular tests on cytology samples can contribute to the diagnosis and prediction of prognosis, and these findings may represent a new era for new targeted therapies aimed at individual molecular targets.[10,62,63,68,84-93]

The application of molecular testing to indeterminate thyroid FNAs for detecting specific somatic mutations, gene rearrangements, or microRNA (miRNA) expression profiles is a new era for thyroid cytology since the last 20 years. These methods have a high predictive value for benign and malignant thyroid lesions.[10,62,94]

Recent data from various studies have shown that molecular alterations of specific pathways play a pivotal role in thyroid carcinogenesis; thus, they may be used as markers of malignancy. The main mechanism for thyroid carcinogenesis works through the MAPK pathway, which is associated with cell proliferation, differentiation, and apoptosis. The BRAF gene results in the constitutive activation of MAPK and PI3K/AKT pathways and plays a major role in carcinogenesis. In particular, papillary carcinoma, the most common thyroid malignancy, may carry BRAF, RET/PTC, or NRAS mutations in 70% of cases.[95-100]

The presence of the V600E BRAF mutation is associated with higher aggressiveness and less favorable prognosis.[101-104] In our institutional experience, histopathologic features, presence of tumor capsular invasion, extrathyroidal extension, absence of pathologically detected lymphocytic thyroiditis, and radioiodine I-131 treatment were significantly higher in patients with the BRAF V600E point mutation (+) detected with DNA sequencing molecular tests.[105] Ancillary molecular tests can be done in-house using the commonly altered genes (BRAF, RAS, RET/PTC, and PPARc/PAX8), but there are three commercially available and established testing panels (Afirma gene expression classifier (GEC), ThyroSeq v.2, and ThyGenX/ThyraMIR). The Afirma GEC can be used to rule out malignancy for the AUS/FLUS and SFN/FN categories and has a high negative predictive value. In contrast, ThyroSeq v.2 and multipanel testing with ThyGenX/ThyraMIR can be used to rule in as well as rule out malignancy with high positive and negative predictive values.[106,107]

In recent years, molecular-based studies have been focused on the effects of epigenetic changes on gene transcription and their relationship with oncogenic pathway activation in thyroid carcinomas. Data supported that TCs are strongly influenced by epigenetic alterations at the differentiation and proliferation mechanisms. The PTEN promoter gene, which presents with hypermethylation in ~50% of PTCs and nearly 100% of FTCs and FAs, is an important example. In contrast, activating mutations of BRAF in PTCs were linked to altered methylation of other genes (TIMP3, SLC5A8, DAPK, and RARb2) associated with aggressive behavior. The promoter methylation involving the RAS association family 1A (RASSF1A) tumor-suppressor gene was seen in approximately 30% of benign and malignant thyroid tumors, including anaplastic thyroid carcinoma; this finding has a role in regulating several key cell processes, suggesting that this change may occur early in tumorogenesis.[108-118]

The FN/SFN category is the gray zone of thyroid cytology, and intra/interobserver variability is a diagnostic challenge.

When microfollicles dominate FNA, the background of aspiration should be evaluated carefully for the presence of sheets/macrofollicles, colloids, lymphocytes, and blood.

The presence of PTC nuclear features and other atypical nuclei should be considered and avoided while downgrading nuclear atypia.

Although FNA is a powerful diagnostic method in thyroid cytology, limitations in this diagnostic group should be considered.

Ancillary techniques, especially molecular tests, can be used in differential diagnosis and guiding treatment.

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