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Diagnosis of Non-invasive Follicular Tumor with Papillary-like Nuclear Features (NIFTP): A Practice Changer for Thyroid Fine-needle Aspiration Interpretation

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Abstract

Recently, a subset of follicular variant of papillary thyroid carcinoma that is encapsulated and non-invasive has been designated as "Non-invasive Follicular Tumor with Papillary-Like Nuclear Features" (NIFTP). This entity is considered as a "non-invasive neoplasia" rather than a carcinoma with clinical consequences for the management of the patients. This entity shares some morphological features of papillary thyroid carcinoma and creates a new challenge for the cytopathologist to recognize it in an attempt to avoid overtreatment. In this review, we discuss the morphological obstacles in diagnosing NIFTP on pre-operative fine needle aspirations, how to report these findings as well as the clinical utility of molecular algorithm that can help its diagnosis.

Keywords: Non-invasive follicular tumor with papillary-like nuclear features (NIFTP), follicular variant of papillary thyroid carcinoma (FVPTC), fine-needle aspirate, thyroid

Introduction

Historically, the differential diagnosis of a follicular-patterned lesion diagnosed on fine-needle aspiration cytology (FNAC) of thyroid includes: hyperplastic/adenomatoid nodule with a predominant follicular growth pattern, follicular adenoma (FA) and carcinoma (FTC), and follicular variant of papillary thyroid carcinoma (FVPTC). Recently, a subset of FVPTC that is encapsulated (EFVPTC) and non-invasive (NIFVPTC) has been designated as "non-invasive neoplasms", rather than carcinoma (1). It is advised this diagnosis to be entertained only in light of strict inclusion and exclusion criteria. The diagnostic term used for these tumors as it stands now, is "Non-invasive Follicular Tumor with Papillary-Like Nuclear Features" (NIFTP). Thus, it is a Neoplasm but "NOT CANCER" anymore! (1). This dramatic shift in paradigm has received much press from both clinical and public sources even though, this change in diagnostic paradigm of one of the most controversial entity in endocrine pathology may appear as "sudden", it is a mere reflection of what everyone was aware of: the indolent clinical behavior and molecular signature similar to benign follicular-patterned lesions such as FA (Figure 1) (2).

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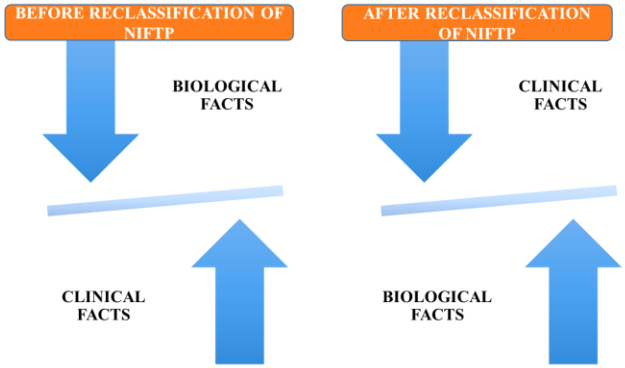

Fig. 1. The multidisciplinary aim of reclassification.

Furthermore, this reclassification is in accordance with the American Thyroid Association (ATA) guidelines, which promote the concept that treatment of thyroid tumors should be stratified based on a risk assessment, i.e., low- and high-risk to prevent overtreatment. Therefore, patients having low-risk disease can be treated with lobectomy, whereas those with high-risk disease may require total thyroidectomy combined with radioactive iodine therapy (RAI) (3).

Follicular-Patterned Lesions of Thyroid: The Battle of Architecture *vs*. Nuclear Cytology

The well-differentiated malignant tumors of follicular cell derivation are the commonly encountered malignancies in thyroid gland (2). By microscopy, they can present as encapsulated/well demarcated, or focally or diffusely infiltrative with sole or hybrid, papillary, follicular, and solid and trabecular growth patterns. Traditionally, the diagnostic criteria for diagnosing malignancy in thyroid include either invasive characteristics or nuclear cytology (4, 5). The latter is the hallmark criteria regardless of growth pattern for rendering the diagnosis of papillary thyroid carcinoma (PTC), which also landed itself as "the reliable" criterion and the most important morphologic feature for the cytopathologist to classify a FNAC specimen comprising of cells albeit architecture as "PTC" (6). However, the diagnosis of PTC in FNAC specimen is not always possible as some specimens from FVPTC may show complete lack of or paucity of diagnostic nuclear features (7). These are often classified as either atypical, follicular neoplasm, or

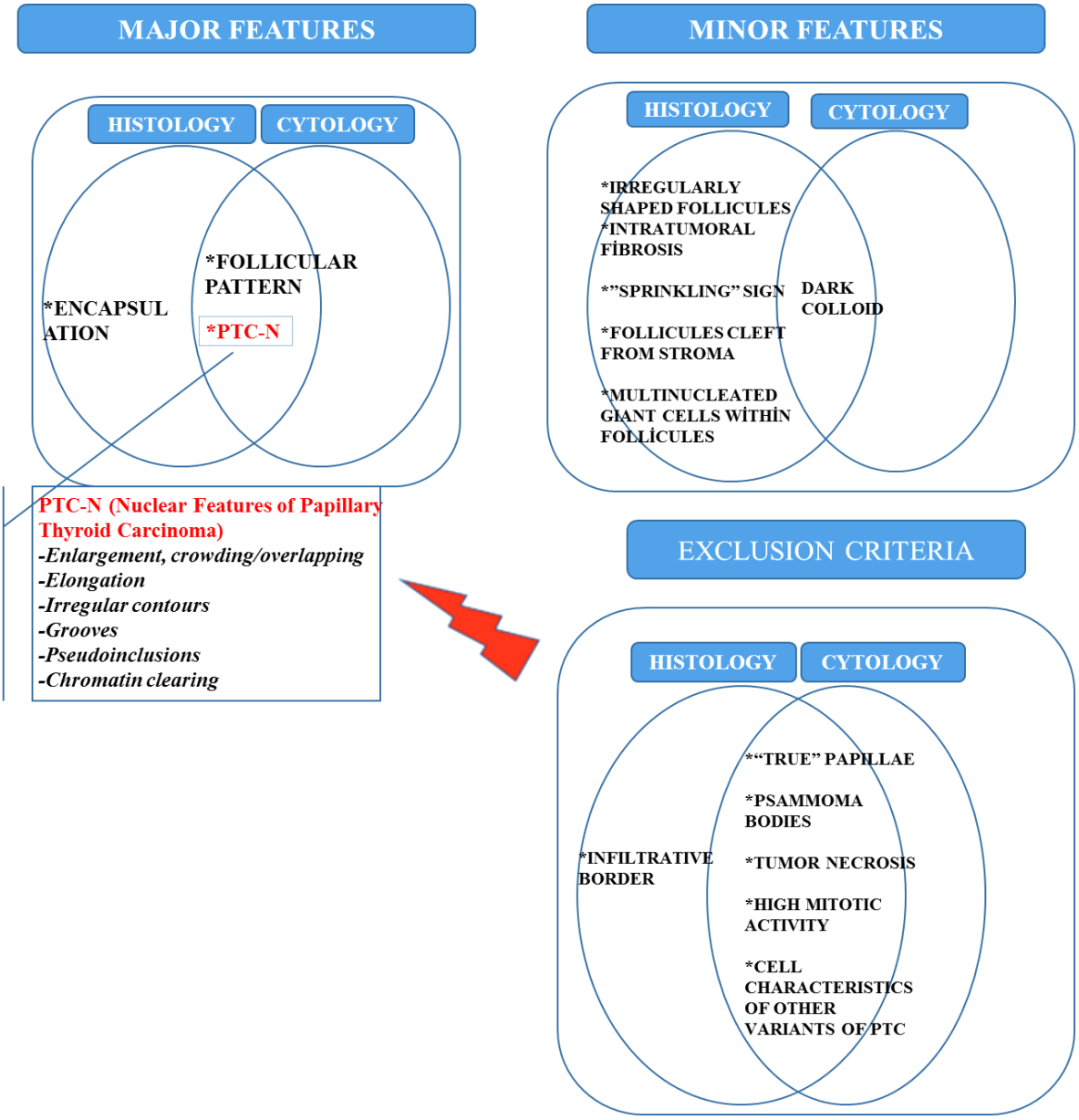

Fig. 2. Applicable cytomorphological findings of the diagnostic criteria of NIFTP.

suspicious for PTC. In the past twenty years or so, a good proportion of cytopathology literature on thyroid FNAC based on institutional experiences, has focused on highlighting the conundrums, most of which revolve around the follicular-patterned lesions with or without nuclear features suspicious for PTC (8-13). Despite these controversies, most pathologists agree that presence of microfollicles or a monotonous population of follicular cells lacking nuclear features of PTC should be classified as "follicular neoplasm/suspicious for follicular neoplasm" (FN/SFN), however, specimens lacking these features with ample background colloid regardless of cellularity be considered as benign follicular lesion/nodule (14). However, the same with an excess of microfollicles or foci of nuclear overlapping and crowding may be perceived by some as atypical, i.e., diagnosed as "atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)". Unfortunately, the specificity of AUS/FLUS and FN/SFN diagnosis for malignancy is poor (15).

Morphologic obstacles in diagnosing NIFTP on FNAC

The histologic diagnosis of NIFTP relies on strict inclusion and exclusion criteria (Figure 2). These include: presence of entirely follicular architecture with less than 1% of papillae formation; the nuclear features of PTC (finely dispersed chromatin leading to pale nuclei, and intranuclear grooves and pseudoinclusions); a clear demarcation between the tumor and the adjacent thyroid parenchyma (including encapsulated, partially-encapsulated, and well-circumscribed tumors), and the lack of infiltrative growth, i.e., capsular invasion or lymphovascular invasion (1). Tumors with solid growth pattern, tumor type

necrosis and psammoma bodies (reminiscent of papillary structures) cannot be classified as NIFTP (1).

On FNAC, the follicular architecture, presence of papillae and nuclear features are the criteria that can be readily assessed. However, the interpretation of follicular-patterned lesions is a challenge on FNAC with high false negative rates (29%) and low true predictive value (9-58%) (16). A predominant microfollicular pattern on FNAC leads to categorization of a given case as FN/SFN according to The Bethesda System for Reporting Thyroid Cytology (17). It has been reported that the aspirates of NIFTP predominantly consist of readily identifiable cohesive follicular groups (mostly microfollicles) with absence of papillae and psammoma bodies (1, 18). Based on published studies, these are reproducible findings (1, 18, 19). One of the challenges is the recognition of the nuclear features. Many authors accepted the presence of PTC-like nuclear features but pointed out the need to quantify these alterations. Strickland *et al*. proposed to divide the presence of pseudoinclusions in frequent (more or equal 3) or rare (1-2), being the former only associated with PTC (19). Other authors could not substantiate these findings, i.e., find pseudoinclusions in cases of NIFTP (20). The question is not exactly the presence or absence of PTC nuclear features, but the degree of the presence of these features making the nuclear scoring one important point for the standardization of the cytological diagnosis of NIFTP (Figure 2). There are a few studies that examined the reproducibility of "nuclear scoring" in cytology samples (18, 21). Maletta *et al*. evaluated the following nuclear features on a sliding scale: 1) nuclear enlargement (at least twice the size of a red blood cell); 2) nuclear membrane abnormalities (irregularities of contour, pseudoinclusions, and grooves); 3) optically clear, ground glass nuclei; and 4) nuclear molding (18). For the first three parameters, the extent to which each parameter was represented was recorded as a percentage. A score of "0" was assigned if a specific nuclear feature was absent or heterogeneously present in less than 50% of cells, and score 1 was assigned if a given nuclear feature was clearly evident in most cells of the lesion (≥50% of cells), thus yielding a final sum of the 3, scores ranging from 0 to 3. These authors reported that in some cases, the percentage of nuclear irregularities could not be reliably assessed because of low cellularity, fixation artifact, or poorly stained or partly obscured follicular cells (18). In these cases, the cytological score was assessed based on the presence/absence of a single parameter without considering the 50% cutoff. The conclusion of this study was that among the parameters analyzed nuclear enlargement; nuclear membrane irregularities, optically clear/ground glass nuclei, and nuclear molding were significantly associated with NIFTP diagnosis. A significantly different mean percentage of nuclear alterations was found between NIFTP cases and benign follicular lesions for each of the 3 parameters (63.8% *vs*. 33.5% for nuclear size with $P = 0.0004$, 69.6% *vs*. 10.3% for nuclear membrane irregularities with $P < 0.0001$, and 53.9% *vs*. 10% for chromatin clearing with $P < 0.0001$). However, these authors did not find significant difference on FNAC of NIFTPs and invasive EFVPTCs. Therefore, the presence of PTC nuclei in a follicular-patterned nodule observed in cytology should indicate the possibility of NIFTP, although PTC cannot be excluded. These results reinforce the need of further studies for the immediate standardization in diagnosing/suggesting NIFTP on both pathology and cytology. It is important to highlight the different criteria used by Western and Asian pathologists for this classification. Hirokawa *et al*. showed difference in the frequency of diagnosis of EFVPTC between American (25%) and Japanese (4%) pathologists (22). In 2015, Kakudo *et al*. proposed a new histologic term - low risk follicular cell tumors, to characterize precursor lesions and borderline lesions (23). Diagnostic categories for reporting thyroid FNAC cytology were also established in the same paper. This risk-stratification proposal was set up based on the two lineages of tumors as FA/FTC and PTC, and divides these two as low- and high-risk atypia based on the PTC nuclei alterations. However, this system still requires further validation and a solid support of molecular tests and clinical follow-up.

Reporting problems on FNA through the new terms came with NIFTP

FNAC is the most essential and reliable diagnostic method in the pre-operative evaluation of thyroid nodules as a part of triple test (FNAC, ultrasonography and hormone profile) (24). Deciding the necessity and type of surgery/RAI therapy in the management of NIFTP and non-NIFTP tumors is totally dependent upon evaluation on histopathologic evaluation (1). Therefore, identification or at least suggestion of NIFTP in FNAC reports is essential to prevent bilateral thyroidectomy with or without RAI therapy where lobectomy is simply enough (25). Although, the histologic criteria of this entity was clearly established, it is still not certain the reproducibility of NIFTP criteria on FNAC. Obviously some of these criteria cannot be given by cytomorphology such as encapsulation (25). Having a preoperative suspicion of NIFTP its confirmation by cytomorphology can prove to be beneficial for thyroid nodule management. Thus, nuclear scoring seems beneficial for cytology specimens; however chromatin clearing/glassy nuclei, one of the most debatable cytologic features, can differ between samples and is highly vulnerable to fixation or preparation artifacts (26, 27). Generally, cases of NIFTP have been placed in indeterminate and suspicious categories (AUS/FLUS, FN/SFN and suspicious for malignancy (SFM)) of TBSRTC (28). The first possible effect on risk of malignancy was highlighted in the first three reports, by Strickland *et al*. and Canberk *et al*. as the two single-institute studies and the multi-institutional study of Faquin *et al*. (28-30). Strickland *et al*. noted the most dramatic decrease in the SFM category, whereas Faquin *et al*. and Canberk *et al*. found it in the SFN/FN category (28-30). The studies of those three authors already indicated reduced requirements for surgical resections as the latest ATA suggested (3). So far very few studies have been published about the reproducibility of major, minor and exclusion criteria of NIFTP on FNAC (19, 21). The question arises, is it time for cytology to have its own major, minor and exclusion criteria to make a suggestion diagnosis of NIFT-P (Figure 2). The recent study of Strickland *et al*. was aimed to differentiate NIFTP from classical PTC on FNAC (19). It is the first prospective analysis established to test cytomorphological features from 56 nodules of 52 patients. The results were supported that the lack of papillae, intranuclear cytoplasmic pseudoinclusion and psammomatous calcification in the presence of microfollicular predominance might suggest NIFTP. Interestingly, these first two cytomorphological findings were the most reliable ones in the diagnosis of PTC, especially in face of its mimickers, such as chronic lymphocytic thyroiditis, cystic or hyaline degeneration (14). In another words, the rest of PTC nuclear features except intranuclear cytoplasmic pseudoinclusion(s) and papillary formations are not so reliable and suffer from poor reproducibility (14). Based on the results, Strickland *et al*. set up a proposal: NIFTP is more likely placed in SFM category instead of malignant category, however, SFM category most often leads to total thyroidectomy (19). Strickland *et al*. suggested lobectomy for SFM category of TBSRTC due to that majority of NIFTP cases has been placed in this category based on

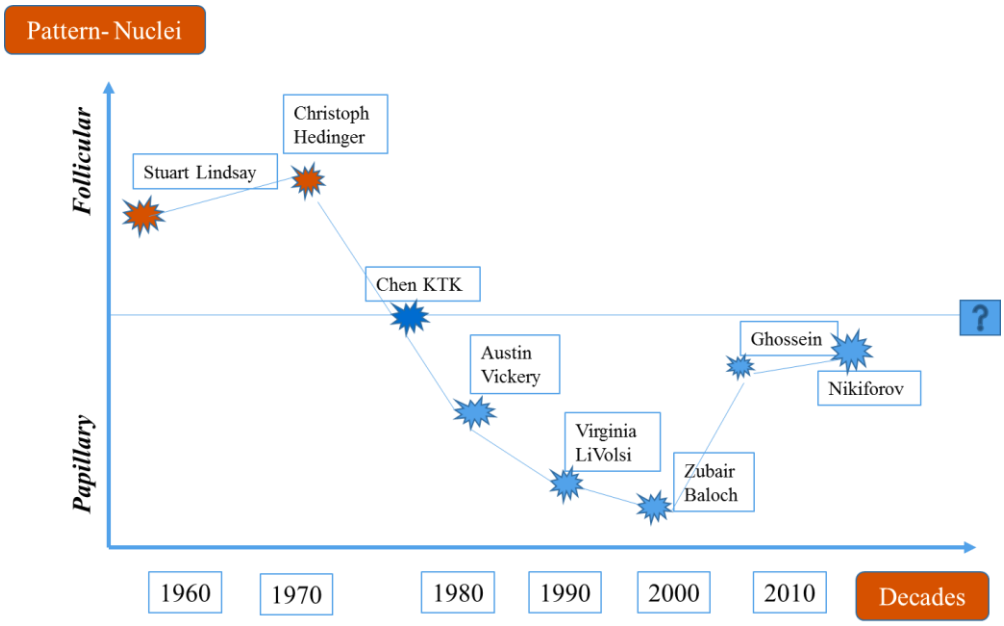

Fig. 3. Time diagram of NIFTP.

their data. Also they suggested to report SFM category with a note saying that the histologic follow-up may include NIFTP. These retrospective studies of Strickland, Faquin and Canberk *et al*. clearly represents the need of placing of NIFTP cases as one of the histopathologic outcome for cases classified as AUS/FLUS, FN/SFN, and SFM categories to stay the "surgeon's hand" (28-30). However, one must also be cognizant of the fact that the thyroid nodule management is also dependent on many factors; presence of multiple nodules, functional state of the thyroid gland and presence of other tumors in the thyroid gland with a metastatic potential (31).

Molecular algorithm in diagnosing and clinical management of NIFTP

As commented before, the identification or at least suggestion of NIFTP in FNAC reports is essential for an appropriate management of the patients with thyroid nodules. Although, the histologic criteria of this entity are established, there are few studies about the reproducibility of this diagnosis on cytology (18-21). Most of the cases included in these studies so far have been classified as indeterminate or suspicious for malignancy (AUS/FLUS, SFN/FN, and SM). Although the role of molecular studies in the setting of NIFTP is not completely established, the analysis of the molecular profile of the NIFTP is very important to rightly place this tumor in the classification of thyroid tumors (32).

In 2014, The Cancer Genome Atlas Research Network studied tumor samples and matched germline DNA from 496 non-irradiated patients with primary PTCs, classified as classical type (69.4%), follicular-variant (21.2%), tall cell variant (7.5%), and others uncommon or not histologically characterized variants (33). One of the most striking findings of this study was that PTC is a MAPK-driven cancer that has two mutually exclusive drivers with distinct signaling consequences: $BRAF^{V600E}$ and mutated *RAS*. This differential signaling results in clear phenotypic differences. For example, the expression of genes responsible for iodine uptake and metabolism are reduced in $BRAF^{V600E}$ tumors, in contrast to the "*RAS*" tumors in which expression of these genes is largely preserved. From the morphological point of view, the $BRAF^{V600E}$ tumors have predominant papillary architecture (classical variant), while the *RAS*-mutation tumors are associated with follicular-pattern architecture, corresponding to the FVPTC, invasive and non-invasive (NIFTP) (33). These molecular findings reinforce the commentaries by many experts - regarding "the backward time travel" of this entity - because they justified the reclassification of follicular-patterned thyroid lesions (Figure 3) (4, 34). There was a time when follicular-patterned PTCs (i.e., *RAS*-PTCs) were classified as follicular carcinomas (4). Now is the time to revise the classification of thyroid cancer to join the follicular variant of PTC with follicular carcinomas.

The question arises, how these molecular findings can be helpful for the clinical management of patients with NIFTP? The current but limited evidence suggests that on FNAC, NIFTPs generally fall into indeterminate categories, which most agree can be managed with adjunct molecular testing (35). However, the field of thyroid molecular diagnostics of FNAC samples is still evolving, especially regarding the molecular characterization of NIFTP. The results observed in the literature clearly demonstrate that this group of tumors are associated with presence of *RAS* mutations (*N*-, *H*- and *K-RAS*), lack of $BRAF^{V600E}$ mutations and in some instances the presence of *PAX8-PPARγ* rearrangements, similar to FAs and FTCs (4, 36). In a recent paper, Paulson *et al*. demonstrated that NIFTPs accounted for over half of RAS-mutated thyroid tumors (37). In a retrospective study, Jiang *et al*. characterized eight cases of histologically proven NIFTP, diagnosed cytologically as indeterminate diagnostic categories of TBSRTC (35). These cases were submitted to the two most common commercial molecular platforms used in the USA on thyroid FNAC: Gene Expression Profiling (GEC) - Afirma and ThyroSeq V2. All cases were "suspicious" based on GEC-Afirma

analysis and were positive for *RAS* mutations (*N-RAS, K-RAS*) in ThyroSeq, confirming previous results. Intriguing was the presence of *TERT* promoter mutation in one case. This result must be interpreted with extreme caution, since the association between *RAS* and *TERT* mutations in differentiated thyroid cancer is associated with worse prognosis (38).

The ability to differentiate NIFTP from classical PTC on cytology would facilitate the conservative surgical management of these patients (lobectomy instead of total thyroidectomy). There are still few papers exploring cytomorphological features that can favor the diagnosis of NIFTP over classical PTC on FNAC (19, 21, 23). Although further studies in larger series are still lacking, it is predictable that in some cases, the association of the morphological findings with molecular results (*RAS*-positive and *BRAF*-negative) can be used to distinguish the majority of NIFTP and other follicular-patterned lesions from classical PTC, with important clinical impact and cost-benefits for the patients (39).

In conclusion, rendering a diagnosis of NIFTP is in accordance with the clinical classification of low risk thyroid tumors as endorsed by endocrine societies and the molecular profiling of thyroid tumors. Even though this new diagnostic paradigm can and is going to pose "challenges" for the thyroid cytopathology, we believe it is a step in the right direction as we will be relying and utilizing data from ultrasound and molecular diagnostics in conjunction with morphology to manage patients with thyroid nodules.

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