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Cytomorphologic Features of Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP): A Comparison with Infiltrative Follicular Variant of Papillary Thyroid Carcinoma

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Abstract

The change in nomenclature from noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has been proposed to more accurately reflect the indolent behavior of this neoplasm and has implications for diagnosis and treatment. However, the ability to recognize NIFTP and reliably distinguish it from infiltrative follicular variant of papillary thyroid carcinoma (IFVPTC) presents a significant challenge for cytopathologists. To identify cytologic features useful in this distinction, all cases of NIFTP and IFVPTC with a preceding diagnostic FNA were reviewed. Twenty-two cases of NIFTP and twenty cases of IFVPTC were identified. The cytomorphologic features of NIFTP and IFVPTC were compared. The majority of NIFTP cases were diagnosed as either follicular neoplasm/lesion (FN/L) (11/22) or atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) (10/22). None were diagnosed as suspicious for malignancy (SUS) and only 1 of 22 was diagnosed as PTC on cytology. In contrast, the majority of the IFVPTC cases were diagnosed as PTC on FNA (12/22) (P = 0.0004). Among the IFVPTCs, 5/20 were classified as FN/L, 2/20 as SUS, and only 1/20 was diagnosed as AUS/FLUS. No particular cytomorphologic features could reliably distinguish NIFTP from IFVPTC; however, the presence of microfollicular architecture (P = 0.03) and absence of pseudoinclusions (P = 0.008) were significantly associated with NIFTP. Nuclear crowding and overlapping (P = 0.03) as well as grooves and irregular nuclear contours (P = 0.0004) were significantly associated with IFVPTC. Eight IFVPTC cases were positive for *BRAFV600E* mutation, while all tested NIFTP cases were negative. Additional studies are required to further explore cytomorphologic features and molecular signatures that may assist in the preoperative diagnosis of NIFTP.

Keywords: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), infiltrative follicular variant of papillary thyroid carcinoma (IFVPTC), cytology, histopathology, *BRAF* gene mutation

Introduction

Follicular variant of papillary thyroid carcinoma (FVPTC) is the second most common subtype of papillary thyroid carcinoma (PTC), and comprises 22-34% of all PTCs (1). Two major subvariants of FVPTC have been described: encapsulated/well-circumscribed (EFVPTC) and infiltrative (IFVPTC). EFVPTC is further divided as noninvasive and invasive based on absence or presence of capsular and/or vascular invasion. Recent studies have suggested that in contrast to other forms of PTC, noninvasive EFVPTC is a distinct entity with indolent behavior, low rates of lymph node metastasis and extremely low rate of recurrence, if any (1-6). As a result, an international group of expert endocrine pathologists and clinicians recently proposed that noninvasive EFVPTC be reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), to reflect the indolent nature of these tumors and reduce the incidence of overtreatment (7). The histomorphologic criteria of NIFTP requires encapsulation or clear demarcation, an entirely follicular pattern of growth with <1% papillae, and nuclear features of PTC including enlargement, elongation, overlapping, grooves, pseudoinclusions, and chromatin characteristics such as nuclear clearing and margination (Figure 1). The presence of infiltrative growth, capsular and/or lymphovascular invasion, psammoma bodies, necrosis, high mitotic index (>3 per 10 high power fields), and predominance of tubular, insular, or solid growth (>30%) excludes the diagnosis of NIFTP (7). Studies with long-term follow up demonstrate that NIFTP may be treated with lobectomy alone, and that completion thyroidectomy and/or radioiodine therapy may not be indicated (1, 7-9).

The introduction of NIFTP poses a significant challenge for cytopathologists and is expected to decrease the estimated risk of malignancy as currently defined for each category in The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) (10). Furthermore, this histologic reclassification has a significant impact on patient management. Several studies, most of which use liquid-based cytology, suggest that the majority of NIFTPs are diagnosed as TBSRTC categories III (atypia of undetermined significance or follicular lesion or undetermined significance), IV (follicular neoplasm or suspicious for a follicular neoplasm), or V (suspicious for malignancy) (11-16). However, the cytologic

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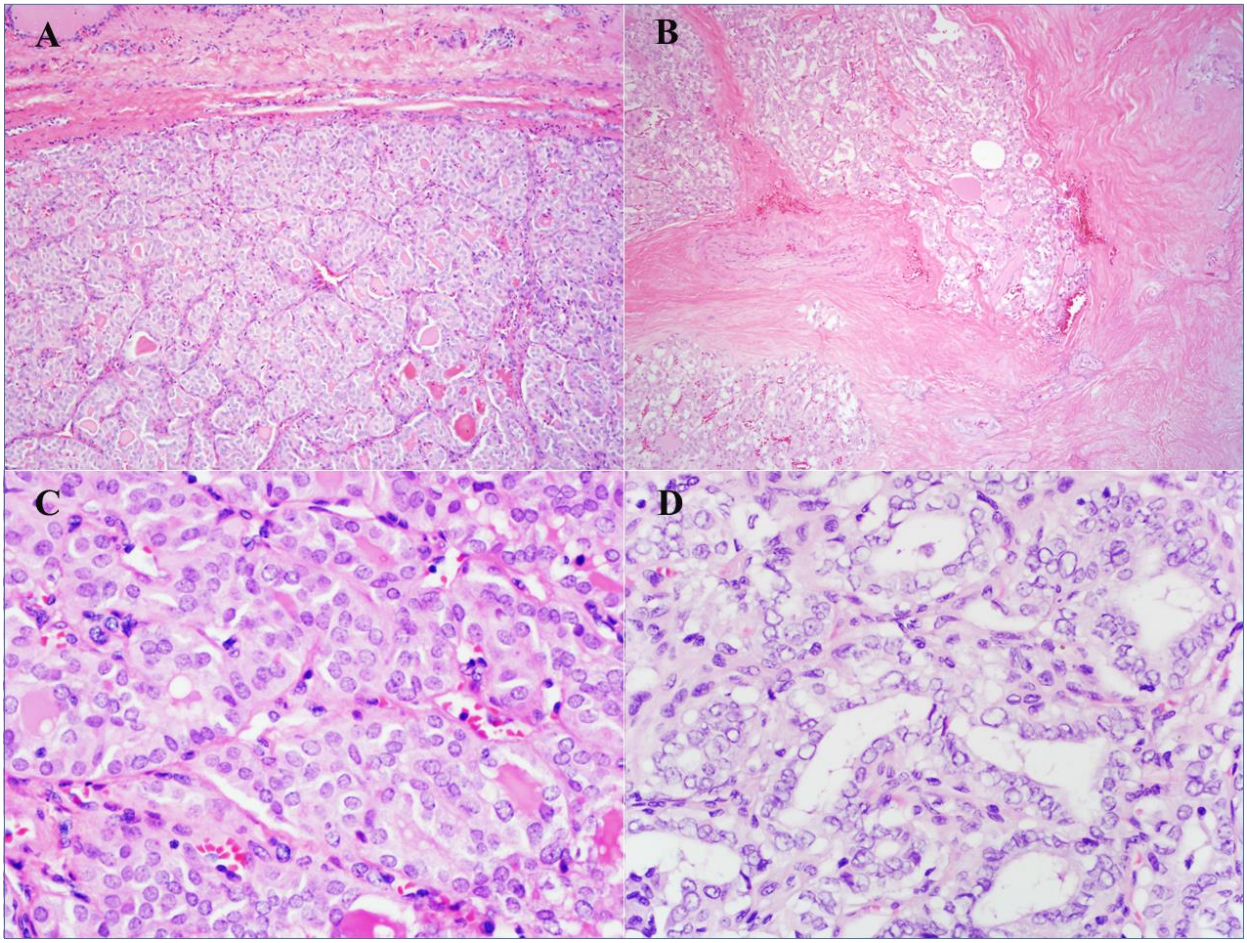

Fig. 1. Well-demarcated periphery of NIFTP (A), in contrast with infiltrative border of IFVPTC (B) (H&E, 100x). Mild nuclear enlargement, occasional grooves, and nuclear clearing in NIFTP (C) (H&E, 400x). Enlarged overlapping irregular nuclei with glassy chromatin and multiple intranuclear pseudoinclusions in IFVPTC (D) (H&E, 400x).

diagnosis of NIFTP as TBSTC category V can be problematic since this result is typically followed by total thyroidectomy, when lobectomy alone may have been sufficient. Therefore, the ability to differentiate NIFTP from PTC on fine needle aspiration (FNA) is critical for optimal patient care. The aim of this study is to determine whether NIFTP and IFVPTC can be reliably distinguished by FNA biopsy.

Materials and Methods

A search of the University of California, San Francisco (UCSF) pathology database was performed for all thyroid nodule aspirates performed from 2005-2016 with diagnoses of PTC, follicular neoplasm/lesion (FN/L), suspicious for malignancy (SUS), indeterminate, non-specific pattern, and atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). Cases with subsequent surgical resection were identified and all cases with available slides (505 surgical specimens) were reviewed by three pathologists (DN, EK, ZVM/NTC).

Resection specimens were carefully evaluated for nuclear features, tumor infiltration, and capsular and/or lymphovascular invasion. Twenty cases met criteria for a diagnosis of NIFTP, with two probable cases of NIFTP in which the capsule was mostly, but not entirely, submitted for histologic evaluation. Twenty cases met criteria for IFVPTC. The preceding FNA diagnoses for each of these nodules were identified. Data on the size of tumor, original surgical diagnosis, FNA diagnosis, and presence of lymph node or distant metastases was extracted from the pathology report and electronic medical record.

At UCSF, FNAs were performed with a 25 or 23-gauge needle under ultrasound guidance by either radiologists, pathologists or endocrinologists, and if amenable, under palpation guidance by pathologists or endocrinologists. Direct smears were prepared in all cases, while a sample was collected in Cytolyt for a Papanicolaou-stained thin layer preparation (ThinPrep, Hologic, Marlborough, MA) in only a subset of patients. Prior to the TBSRTC, our institution used diagnostic categories that were equivalent to the 6 TBSRTC categories with the addition of "indeterminate" and "non-specific pattern", which were considered equivalent to AUS/FLUS for purposes of this study. In cases where more than one FNA was performed on the same nodule, the cytologic diagnosis associated with the highest risk of malignancy was included. FNA specimens were re-reviewed in order to evaluate cytomorphologic features; the pathologists were blinded to the FNA diagnosis at the time of review.

Table 1. Summary of clinical and histopathologic findings (n = 42)

Characteristic	NIFTP (n = 22)	IFVPTC (n = 20)	P-value
Age at diagnosis, median	47	49	
Sex			
Male	4	6	
Female	18	14	
Tumor size (cm)*, mean	2.3	2.2	
Multicentric	1	9	
Lymph node metastases	0	4	
Distant metastases	0	0	
Follow-up time (months), mean	0-132,23.7	0.5-56,13.9	
BRAF			
Negative	5	11	
V600E	0	8	
K601E	2	0	
FNA diagnosis			
AUS/FLUS	10	1	0.009
FN/L	11	5	0.17
SUS	0	2	0.43
PTC	1	12	0.0004
Diagnosis prior to review			
Follicular adenoma	14	0	
Non-invasive EFVPTC	7	0	
Classic PTC	0	6	
IFVPTC	0	13	
Follicular carcinoma	0	1	
Follicular neoplasm with atypia	1	0	

*Based on size of largest nodule

Table 2. Cytologic findings of NIFTP *vs*. IFVPTC (n = 36)

	NIFTP (n = 18)	IFVPTC (n = 18)	P-value
Cellularity			
Abundant	9 (50%)	11 (61.1%)	0.74
Moderate	4 (22.2%)	4 (22.2%)	1
Scant	5 (27.8%)	3 (16.7%)	0.69
Architectural pattern			
Microfollicular	16 (88.9%)	9 (50%)	0.03
Sheets	0 (0%)	0 (0%)	1
Papillary	0 (0%)	1 (5.6%)	1
Mixed (microfollicular and sheets)	2 (11.1%)	6 (44.4%)	0.23
	0 (0%)	1 (5.6%)	1
Mixed (papillary and sheets)	0 (0%)	1 (5.6%)	1
Mixed (microfollicular, sheets and papillary)			
Colloid			
Abundant	0 (0%)	3 (16.7%)	0.23
Moderate	2 (11.1%)	2 (11.1%)	1
Scant	16 (88.9%)	13 (72.2%)	0.4
Bubble gum colloid	0 (0%)	3 (16.7%)	0.23
Multinucleated giant cells	2 (11.1%)	6 (33.3%)	0.23
Hemosiderin-laden macrophages	5 (27.8%)	6 (33.3%)	1
Psammoma bodies	0 (0%)	0 (0%)	1
Nuclear features			
Enlargement	13 (72.2%)	15 (83.3%)	0.69
Crowding/overlapping	12 (66.7%)	18 (100%)	0.03
Elongation	6 (33.3%)	10 (55.6%)	0.31
Grooves/irregular nuclear contours	8 (44.4%)	17 (94.4%)	0.004
Open chromatin	16 (88.9%)	14 (77.8%)	0.65
Pseudoinclusions			
Absent	13 (72.2%)	4 (22.2%)	0.008
Rare	1 (5.6%)	4 (22.2%)	0.34
Frequent (≥3)	4 (22.2%)	10 (55.6%)	0.09
Cytoplasm			
Normal	14 (77.8%)	11 (61.1%)	0.47
Vacuolated	1 (5.6%)	1 (5.6%)	1
Dense	3 (16.7%)	5 (27.8%)	0.69
Mixed (dense and vacuolated)	0 (0%)	1 (5.6%)	1

BRAF testing

All specimens were formalin-fixed and paraffin-embedded. Tumor mapping in at least 50% cellular areas was performed on hematoxylin-eosin-stained slides by a pathologist. These areas were scraped from corresponding unstained slides for DNA extraction using either the QIAamp DNA Mini Kit or EZ1 automated extraction system (both, Qiagen, Valencia, CA).

Prior to 2015, the *BRAF* Mutation Testing assay was performed as follows: A portion of *BRAF* exon 15 encompassing codon 600 was amplified by polymerase chain reaction (PCR) with specific primers, and codon 600 was analyzed with fluorescence-labeled hybridization probes in a real-time LightCycler 480 PCR (Roche Applied Science, Indianapolis, IN) melting curve assay following the protocol of Rowe *et al*. (17). A melting temperature of approximately 65°C corresponds with the wild-type sequence, while melting at approximately 60°C indicates the T to A transversion at nucleotide 1799 that results in the V600E mutation. This assay was validated to have sensitivity for V600E mutation detection down to a minimum of at least 25% tumor cells in the specimen. Equivocal results would be followed with Sanger sequencing (see below) for confirmation.

From 2015 to present, the *BRAF* Mutation Testing assay utilizes PCR amplification and dye termination sequencing of exon 15 of the *BRAF* gene using specific PCR primers. DNA was extracted from tumor areas and exon 15 of the *BRAF* gene was amplified in a PCR reaction. PCR products were purified using the Exo/SAP method. Sequencing reactions were performed using Big Dye v3.1 (Applied Biosystems, Foster City, CA) using M13 forward and reverse primers. The sequencing products were separated by capillary electrophoresis on an Applied Biosystems 3500XL Genetic Analyzer. Sequence traces were analyzed using Mutation Surveyor (Softgenetics, State College, PA). Mutations were reported based on NCBI Reference Sequence: NM_004333.4. The limit of detection for Sanger sequencing has been reported to be approximately 20% mutant allele.

Statistical analysis

Fisher's exact test was used to evaluate the statistical significance of categorical correlations. P values less than 0.05 were considered significant. Association between the diagnosis levels and the cytomorphological characteristics (i.e., cellularity, architecture, presence of colloid, type of colloid, multinucleated giant cells, hemosiderin-laden macrophages, psammoma bodies, and nuclear and cytological features) was examined using cross-tabulations and Fisher's exact test. Comparison of frequencies in the observed characteristics between the diagnostic groups was based on 2-sample test for equality of proportions. Analyses were performed using R language for statistical computing (18).

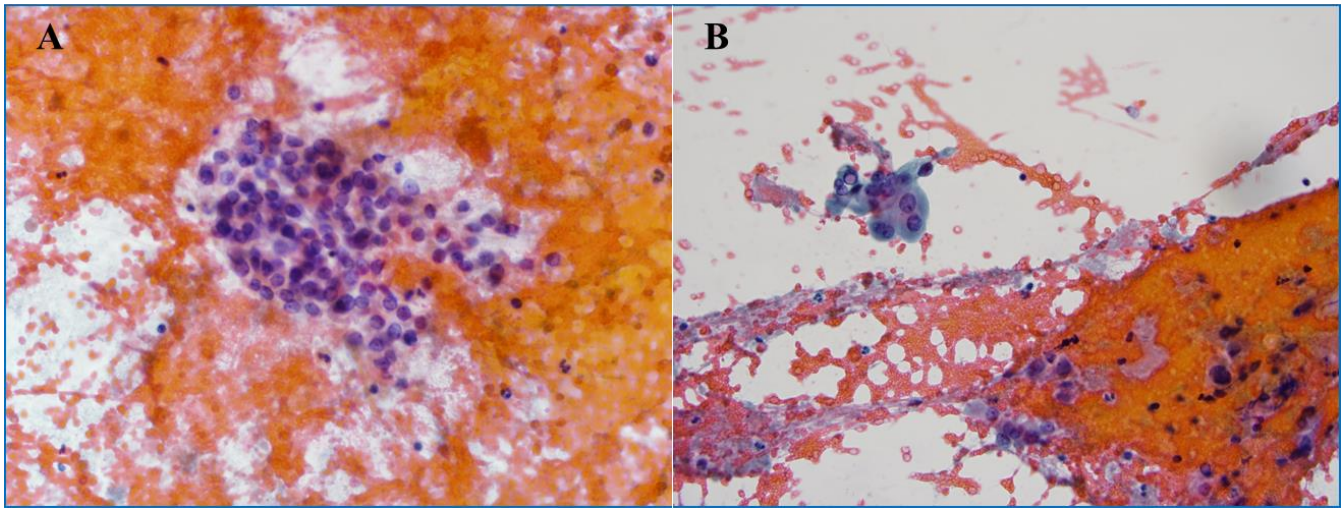

Fig. 2. Cytomorphological features of NIFTP with microfollicular pattern, slight nuclear irregularities, and no intranuclear pseudoinclusion (A) in comparison with IFVPTC with dense cytoplasm, enlarged overlapping nuclei, and numerous intranuclear pseudoinclusions (B) (Pap stain, 400x).

Results

The clinical and histopathologic findings of this study are summarized in Table 1. Twenty-two cases were histologically classified as NIFTP on review with size range 0.4-3.9 cm (mean 2.3 cm). Patients (4 men, 18 women) had an age range of 21-79 years (median 47 years). One case was multicentric. On preceding FNA, 11 cases were diagnosed as FN/L, 10 as AUS/FLUS, and 1 as PTC. None were classified as SUS. The original histologic diagnosis for 14 cases was follicular adenoma, 7 were classified non-invasive EFVPTC, and 1 as "follicular neoplasm with atypia." None of these patients had a prior diagnosis of PTC. The entire capsule was submitted for 20 of the NIFTP cases. Five cases had lymph nodes submitted; no lymph node metastases were seen. No distant metastases were reported in any of the cases (mean follow-up time, 23.7 months). The seven cases originally diagnosed as EFVPTC were tested for *BRAF*; 2 cases demonstrated a *BRAFK601E* mutation, while the other cases were negative for a *BRAF* mutation.

Twenty cases were histologically classified as IFVPTC with size range 0.4-4.7 cm (mean 2.2 cm). Patients (6 men, 14 women) had an age range of 26-89 years (median 49 years). Nine cases were multicentric. On preceding FNA, 12 cases were diagnosed as PTC, 5 as FN/L, 2 as SUS, and 1 as AUS/FLUS. The original histologic diagnosis for 13 cases was IFVPTC, 6 were classified as classic PTC, and 1 as follicular carcinoma with angioinvasion. Lymph nodes were evaluated in 12 cases; 4 cases were positive for lymph node metastasis. No distant metastases were reported in any of the cases (mean follow-up time, 13.9 months). *BRAF* PCR results were available in 19 IFVPTC cases; 8 (42%) were positive for *BRAFV600E* mutation.

The cytologic findings of this study are summarized in Table 2. Cytologic material was available for review for 18 NIFTP cases (Figure 2A). Cellularity was abundant in 9 cases, moderate in 4 cases, and scant in 5 cases. Two cases had both sheets and microfollicles, while the remainder of cases had solely a microfollicular pattern. None of the cases had abundant colloid, 2 cases had moderate colloid, and 16 cases had scant colloid. None of the cases had bubble gum colloid. Two cases had multinucleated giant cells, 5 cases had hemosiderin-laden macrophages, and none of the cases had psammoma bodies. Fourteen cases had normal cytoplasm, 1 case had vacuolated cytoplasm, and 3 cases had dense cytoplasm. In terms of nuclear features, 13 cases had nuclear enlargement, 12 cases had crowding and/or overlapping, 6 cases had elongation, 8 cases had grooves and/or irregular nuclear contours, and 16 cases had open chromatin. Four cases had frequent (≥3) pseudoinclusions, 1 case had rare pseudoinclusions, and 13 cases lacked pseudoinclusions.

Cytology slides were available for 18 IFVPTC cases (Figure 2B). Cellularity was abundant in 11 cases, moderate in 4 cases, and scant in 3 cases. One case had a microfollicular pattern in addition to sheets and focal papillary architecture, while 6 cases had both sheets and microfollicles. One case demonstrated sheets with focal papillary caps. Nine cases had a solely microfollicular pattern, and one had only papillary architecture. Three cases had abundant colloid, 2 moderate colloid, and 13 scant colloid. Three cases had bubble gum colloid, 6 cases had multinucleated giant cells, and 6 cases had hemosiderin laden macrophages. None of the cases had psammoma bodies. The cytoplasm was normal in 11 cases, vacuolated in 1 case, dense in 5 cases, and both dense and vacuolated in 1 case. Fifteen cases had nuclear enlargement, 18 had crowding and/or overlapping, 10 had elongation, 17 had grooves and/or irregular nuclear contours, and 14 had open chromatin. Four cases had rare, 10 cases had frequent (≥3), and 4 cases lacked pseudoinclusions.

While IFVPTC was significantly associated with the preceding diagnosis of PTC on FNA (P = 0.0004), NIFTP was associated with the preceding diagnosis of AUS/FLUS (P = 0.009). NIFTP was significantly associated with microfollicular architecture on cytology (P = 0.03). Absence of pseudoinclusion was also significantly associated with NIFTP (P = 0.008). Nuclear crowding and overlapping (P = 0.03) as well as grooves and irregular nuclear contours (P = 0.004) were significantly associated with IFVPTC. Frequent pseudoinclusions were seen more often in IFVPTC, but this finding did not reach statistical significance (P = 0.09).

Discussion

The NIFTP diagnostic category has been instituted in order to diminish overtreatment of clinically indolent tumors. It has significant impact on both treatment algorithms and prognosis. This diagnostic category changes the risk of malignancy as described in the current TBSRTC and impacts best diagnostic practices for cytopathologists. Because of the importance of FNA diagnosis in evaluation of thyroid lesions, cytopathologists should ideally differentiate NIFTP from classical and other PTC variants so that patients with NIFTP can be appropriately triaged for conservative surgical management. Several studies have shown that NIFTP, formerly non-invasive EFVPTC, can be adequately treated with lobectomy without adjunctive radioactive iodine whereas most cases of PTC and its variants greater than 1-2 cm are treated with total thyroidectomy.

Molecular analyses have revealed that NIFTPs tend to have *RAS* and *BRAFK601E* mutations or *PAX8/PPARγ* or *THADA* gene fusions, genetic changes also found in follicular neoplasms such as follicular adenomas and follicular carcinomas. Two of our NIFTP cases contained a *BRAFK601E* mutation. This is in contrast to classical PTC, which tends to harbor *BRAFV600E* mutations without molecular alterations in *RAS* and *PAX8/PPARγ* (19-21). Similar to other follicular neoplasms, definitive diagnosis of NIFTP cannot be made by cytology alone and requires histologic evaluation to assess for architecture and the presence or absence of capsular/lymphovascular invasion for appropriate classification.

In the current literature, the majority of NIFTP cases are diagnosed as AUS/FLUS, FN/L or SUS (11-16), while most tumors classified as "malignant" have a high rate of concordance with classical PTC (11, 12, 16). In prior studies using liquid-based cytology preparations (predominantly ThinPrep), the rate of NIFTPs classified as SUS ranged from up to 14.4% to 48.9%. The presence of a predominantly microfollicular pattern along with the absence of papillary architecture, psammoma bodies, and nuclear pseudoinclusions was noted to be helpful in distinguishing cases of NIFTP from classical PTC (11, 13, 16). However, in this study most cases of NIFTP had cytologic diagnoses of FN/L or AUS/FLUS; only 1 case was categorized as PTC. On cytology, this case was moderately cellular and showed clusters of follicular cells in a microfollicular pattern with hemosiderin-laden macrophages in the background. Nuclear grooves, crowding, open chromatin, and frequent pseudoinclusions were observed; however, the nuclei were round and not enlarged. This case represents a true false positive as the capsule was entirely submitted for histologic examination and the nodule was negative for *BRAF* mutation. In our experience, aspirates of NIFTP are significantly associated with microfollicular pattern and absence of nuclear crowding/overlapping. These findings are concordant with the published literature. The presence of frequent pseudoinclusions has been previously described as being rare in NIFTP. However, 4 (22%) cases of NIFTP that we examined had frequent pseudoinclusions, which have previously been defined as ≥3 pseudoinclusions (22). Therefore, the finding of frequent pseudoinclusions does not exclude a diagnosis of NIFTP. Moreover, as expected psammoma bodies are absent in all cases reviewed and did not assist in our ability to distinguish NIFTP from IFVPTC. In our study, cases of IFVPTC were significantly associated with nuclear crowding and overlapping as well as grooves and irregular nuclear contours on FNA, but not nuclear enlargement. Hemosiderin-laden macrophages and multinucleated giant cells were seen in both NIFTP and IFVPTC and were not features that can distinguish between NIFTP and IFVPTC.

While the introduction of the diagnostic category of NIFTP was intended to reduce the incidence of overtreatment and rename a tumor previously categorized as malignant to one that has indolent behavior, our review demonstrates the majority (63%) of NIFTP cases were originally diagnosed on histology as follicular adenoma and only 8 (36%) were classified as FVPTC at our institution. Because of the broad spectrum of inter-observer variability and diagnostic practices, this finding raises the question of whether the NIFTP diagnostic classification results in more strict criteria being applied to follicular neoplasms, potentially increasing the rate of diagnosis of neoplasia with low malignant potential and malignancy at some institutions.

There are a few limitations in our study, including the fact that these results represented a retrospective analysis of a limited number of cases from a single academic center. Thyroid nodules with a preceding benign FNA were not included in this study. There were, potentially, cases of NIFTP which were "benign" on FNA, but were then excised because the nodule had clinically concerning features. We did not evaluate these cases or attempt to calculate the false negative rate for a benign FNA. This particular issue has not been addressed by other studies. Many of the other studies describing the cytomorphologic features of NIFTP used LBC preparations, while our practice depends primarily on direct smears, with only a minority of cases using ThinPrep only as an adjunct preparation. Our findings may not be applicable to LBC preparations and may explain the marked difference in the number of NIFTP cases categorized as SUS. Additional studies, which include ultrasound findings and molecular studies, may help refine our ability to distinguish between NIFTP and PTC preoperatively.

From our experience using direct smears, cytopathologists can reliably triage NIFTP for conservative management based on cytologic evaluation and accurately diagnose classic PTC (and often IFVPTC) as suspicious for malignancy or malignant, while the majority of NIFTP cases can be appropriately classified as AUS/FLUS or FN/L. As NIFTP comes into wider practice and cytopathologists begin to identify and refine the cytologic and molecular criteria of NIFTP, the ability to accurately diagnose and appropriately triage this tumor will most likely improve. Additional and larger studies are needed to further explore and validate our findings.

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