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ORIGINAL ARTICLE

Distinguishing non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) from classic and invasive follicular-variant papillary thyroid carcinomas based on cytologic features

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Introduction An international panel recently recommended reclassification of non-invasive follicular variant of papillary thyroid carcinoma (PTC) to non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). NIFTPs have little or no risk of recurrence and can be treated with lobectomy alone. Preoperative distinction of NIFTP from PTC will help avoid overtreatment.

Materials and Methods All thyroid tumors with a histologic diagnosis of PTC and preceding diagnostic cytology (n = 299) over a 5-year period were identified. Cases meeting criteria for NIFTP were reclassified as such. All NIFTP cases with available cytology (n = 6) and a similar number of randomly selected invasive follicular variant of papillary thyroid carcinoma (IFVPTC; n = 9) and classic PTC (cPTC, n = 11) were evaluated for 18 cytologic features.

Results A total of 35 (12%) lesions were reclassified as NIFTP, 194 (65%) were cPTC, and 70 (23%) were IFVPTC. The NIFTPs had a preceding cytologic interpretation of benign (31%), atypia of undetermined significance (34%), follicular neoplasm (9%), suspicious for malignancy (12%), or malignant (14%). Cytologically, NIFTP was distinguished from cPTC by absence of any architectural features in all 6 cases, and by absence of pseudoinclusions ($P < 0.001$) and multinucleated giant cells ($P = 0.027$) in nearly all. Nuclear pseudoinclusions ($P = 0.001$), marginal micronucleoli ($P = 0.018$), irregular branching sheets ($P = 0.025$), and linear arrangement ($P = 0.025$) favored IFVPTC over NIFTP.

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Conclusions NIFTPs were originally assigned to a variety of cytologic categories. There are several cytologic differences between NIFTP and cPTC or IFVPTC. Our findings support restricting the definitive diagnosis of PTC to cases with architectural features of PTC and/or intranuclear pseudoinclusions.

Introduction

Papillary thyroid carcinoma (PTC) is the most common form of thyroid malignancy, representing about 80% of all thyroid cancers. Only half are classic PTCs (cPTC) and the majority of the remaining cases are follicular variant of PTC (FVPTC).[1] There has been an increase in the incidence of PTC in the United States and some other countries over the last few decades, due in large part to increased surveillance, but also to increased sensitivity among pathologists to FVPTC.[2-4] A significant proportion of FVPTC are the non-invasive, encapsulated follicular variants of PTC (NIFVPTC).[2] These lesions generally follow an indolent course with no local recurrence or distant metastasis.[5] They are also biologically distinct from cPTCs, harboring a distinct set of mutations, involving most commonly *RAS*, *PPARG*, and *THADA* gene fusions, and (less commonly) *BRAF K601E* mutations rather than mutations commonly seen in cPTC, particularly *BRAF V600E* mutations.[6,7] Hence, an international multidisciplinary panel of experts recently recommended reclassifying NIFVPTC to non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[7] This group further recommended that NIFTPs can be treated with lobectomy rather than total thyroidectomy, and no radioactive iodide treatment is necessary. This reclassification aims to avoid overdiagnosis and subsequent overtreatment of an otherwise indolent lesion. Presently, the diagnosis of NIFTP is made on surgical pathology material based on a set of histologic criteria. Distinguishing these lesions preoperatively from PTC, however, can aid in choosing appropriate therapeutic options.

Fine-needle aspiration cytology (FNAC) represents the key presurgical diagnostic test in the evaluation of thyroid lesions. FNAC helps guide initial treatment in primary tumors and aids in the follow up of recurrent lesions. PTC is thought to have distinct cytologic features, allowing a definitive diagnosis on cytology in most cases, although the creation of an entity explicitly having nuclear features of PTC but no longer diagnosed as malignant raises concerns about the predictive value of thyroid FNAC. The cytologic features of this novel lesion have not been thoroughly studied to date. The aim of this study was to evaluate the effectiveness of a range of cytologic features for distinguishing NIFTP from invasive follicular variant of papillary carcinoma (IFVPTC) carcinoma and cPTC.

Material and methods

A search was performed of the pathology laboratory information system of the University of Maryland Medical Center (UMMC). All cases with a histologic diagnosis of PTC over a 5-year period, from January 2011 to January 2016, with preceding cytopathology at UMMC were identified. For all cases diagnosed as encapsulated follicular variant of papillary thyroid carcinoma, the surgical pathology report and slides were reviewed, and cases meeting the histologic criteria used by Nikiforov et al for NIFTP were reclassified as such. In brief, those criteria are: 1) encapsulation or clear demarcation; 2) follicular growth pattern (with <1% papillae, no psammoma bodies, <30% solid/trabecular/insular growth pattern); 3) nuclear score 2-3 (defined as presence of at least 2 of: nuclear size and shape abnormalities; nuclear membrane irregularities; and chromatin abnormalities); 4) no vascular or capsular invasion; 5) no tumor necrosis; and 6) no high mitotic activity. The prior cytologic interpretation for each case was recorded, in accordance with The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).

Thyroid cytology classification[8]

Prior cytology slides for all cases reclassified as NIFTP for which cytology slides were available, and a comparable number of randomly selected cPTC and IFVPC, were reviewed for the presence or absence of 18 preselected cytologic features. Direct smear slides stained with modified Giemsa and Papanicolaou stains and liquid-based preparations (SurePath™, BD, Franklin Lakes, NJ) were reviewed independently by 2 pathologists (1 practicing pathologist and 1 trainee) who were blinded to the surgical pathology and cytology diagnoses. Discrepancies were resolved by a third blinded practicing pathologist. In cases with multiple nodules, we included only cases in which we were able to confirm that the sampled nodule was identical to the nodule diagnosed as PTC on surgical resection by comparing the reported cytology location with the surgical pathology location.

The cytoarchitectural features assessed were: 1) nuclear enlargement; 2) oval/elongate nuclei; 3) nuclear grooves; 4) nuclear pseudoinclusions; 5) other nuclear contour irregularities; 6) pale, powdery chromatin; 7) marginal micronucleoli; 8) nuclear overlap; 9) nuclear molding; 10) true papillae (with fibrovascular cores); 11) papillary caps; 12) irregular branching sheets; 13) swirling sheets; 14) linear arrangement of cell groups on the slide (described further in discussion); 15) absence of follicular architecture, 16) psammoma bodies; 17) bubble gum colloid; and 18) multinucleated giant cells.

Table 1 Initial cytology diagnosis for cases of NIFTP, IFVPC, and classic PTCs.

Cytology diagnosis	NIFTP (n = 35) n (%)	IFVPTC (n = 70) n (%)	cPTC (N = 194) (n, %)
Benign	11 (31.4)	2 (2.8)	-
AUS/FLUS	12 (34.3)	13 (18.6)	4 (2)
FN/SFN	3 (8.5)	13 (18.6)	3 (1.5)
SFM (PTC)	3 (8.5)	16 (22.8)	38 (19.6)
SFM (NOS)	1 (2.8)	5 (7.1)	21 (10.8)
PTC	5 (14.3)	21 (30)	128 (66)

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm; IFVPTC, invasive follicular variant of papillary carcinoma; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; NOS, not otherwise specified; PTC, papillary thyroid carcinoma; SFM, suspicious for malignancy.

All features were graded simply as present or absent, with even a single instance of the feature considered "present." For instance, a single pseudoinclusion counted as present, whereas a single follicle counted as absence of "absence of follicular architecture. Although the meaning of each criterion was discussed together as a group before slide review to ensure all participants understood them, no specific guidance was given to participants beforehand as to the degree of changes required for continuous variables such as nuclear enlargement, elongation, overlap, or pale powdery chromatin, other than that they should be to a degree that would raise concern for PTC.

The results were compared among different groups: NIFTP versus cPTC and NIFTP versus IFVPC by the χ^2 test, using Stata 12.1 (StataCorp LLC, College Station, TX) statistical software, and a significance level of 0.05 was considered to be statistically significant.

Results

Cytodiagnostic categorization of NIFTP

A total of 299 lesions with a histologic diagnosis of PTC had a prior cytology diagnosis. Of these, 194 (64.8%) were cPTC and 70 (23.4%) were IFVPC. A total of 35 (11.7%) were reclassified as NIFTP.

Most of the NIFTPs were originally diagnosed as benign (31.4%) or atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS; 34.3%), fewer were assigned to the follicular neoplasm/suspicious for follicular neoplasm (FN/SFN; 8.5%) or suspicious for malignancy (SFM; 11.3%) categories. Five cases (14.3%) were diagnosed as positive for malignancy, PTC (Table 1). In comparison, 30% of IFVPTC and 66% of cPTC were interpreted as malignant.

Cytologic features of NIFTP

As UMMC is a referral center for thyroid surgeries, most of the cytologic diagnoses were made on referred cytologic materials that had been returned and were unavailable for review; slides were available for only 6 NIFTPs. Cytology slides from 9 IFVPTCs and 11 cPTC were selected at random for comparison. The initial cytologic interpretations of the cases selected for cytologic evaluation are listed in Table 2.

Among the cytomorphologic features evaluated, none of the NIFTP cases demonstrated any of the architectural features of PTC: true papillae, papillary caps, irregular branching sheets, swirling sheets, linear arrangement of cells, or absence of follicular architecture. These features were all statistically significantly different from cPTC. In addition, pseudoinclusions ($P < 0.001$) and multinucleated giant cells ($P = 0.027$) were significantly less common in NIFTP lesions when compared with cPTC cases (Table 3).

Table 2 Initial cytology diagnosis for reviewed cases of NIFTP, IFVPC, and classic PTCs.

Cytology diagnosis	NIFTP (n = 6) n (%)	IFVPTC (n = 9) n (%)	cPTC (n = 11) n (%)
Benign	2 (33)	-	-
AUS/FLUS	2 (33)	2 (22)	-
FN/SFN	-	1 (11)	-
SFM (PTC)	-	2 (22)	-
SFM (NOS)	1 (17)	-	-
PTC	1 (17)	4 (45)	11 (100)

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; cPTC, classic papillary thyroid carcinoma; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm; IFVPTC, invasive follicular variant of papillary carcinoma; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; NOS, not otherwise specified; PTC, papillary thyroid carcinoma; SFM, suspicious for malignancy.

Table 3 Frequency of different cytomorphologic features in NIFTP, classic PTC, and IFVPTC.

Variables	NIFTP (n = 6) n (%)	cPTC (n = 11) n (%)	*P*-value[a]	IFVPTC (n = 9) n (%)	*P*-value[b]	*P*-value[c]
Nuclear enlargement	4 (67)	11 (100)	0.041	8 (89)	0.29	0.057
Oval nuclei	3 (50)	9 (82)	0.17	7 (78)	0.26	0.057
Nuclear grooves	4 (67)	11 (100)	0.041	8 (89)	0.29	0.057
Pseudoinclusions	1 (17)	11 (100)	<0.001	9 (100)	0.001	<0.001
Contour irregularity	4 (67)	9 (82)	0.48	7 (78)	0.63	0.5
Pale powdery chromatin	4 (67)	11 (100)	0.041	9 (100)	0.063	0.007
Marginal micronucleoli	3 (50)	9 (82)	0.17	9 (100)	0.018	0.023
Nuclear overlap	4 (67)	11 (100)	0.041	9 (100)	0.063	0.007
Nuclear molding	4 (67)	10 (91)	0.21	8 (89)	0.29	0.17
True papillae	0 (0)	9 (82)	0.001	4 (44)	0.057	0.005
Caps	0 (0)	9 (82)	0.001	4 (44)	0.057	0.005
Irregular branching sheets	0 (0)	10 (91)	<0.001	5 (56)	0.025	0.001
Swirling sheets	0 (0)	6 (54)	0.025	2 (22)	0.22	0.063
Linear arrangement	0 (0)	5 (45)	0.049	5 (56)	0.025	0.027
Absence of follicular architecture	0 (0)	10 (91)	<0.001	1 (11)	0.4	0.017
Psammoma bodies	0 (0)	1 (9)	0.45	0 (0)	-	0.58
Bubble gum colloid	1 (17)	6 (54)	0.13	6 (67)	0.057	0.063
Multi nucleated giant cells	1 (17)	8 (73)	0.027	0 (0)	0.2	0.29

Abbreviations: AUSIFVPTC, invasive follicular variant of papillary carcinoma; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma.
[a]*P*-value comparing NIFTP versus classic PTC.
[b]*P*-value comparing NIFTP versus IFVPTC.
[c]*P*-value comparing NIFTP versus combined IFVPTC and classic PTC.

In comparison with IFVPTC, pseudoinclusions ($P = 0.001$), marginal micronucleoli ($P = 0.018$), and linear arrangement ($P = 0.025$) were significantly less common in NIFTP. Interestingly, IFVPTC cases fairly commonly showed at least some architectural features of PTC despite the definitional predominance of follicular architecture (Table 3).

Discussion

The new proposed reclassification of NIFTP is based on histologic criteria and is presently considered a surgical diagnosis.[7] Implementation of this terminology will necessarily impact the practice of thyroid cytology, however, given the essential role of cytology in the initial evaluation of thyroid lesions. An accurate cytologic diagnosis of NIFTP, especially the distinction of NIFTP from PTC, would significantly impact the subsequent management of these lesions because they can adequately be treated with lobectomy rather than total thyroidectomy and/or radioiodine therapy.

Cytomorphologic evaluation of NIFTP is the subject of only limited research to date.

We concluded that 11.7% of all thyroid lesions diagnosed as PTC in our institution could be reclassified as NIFTP. This is in agreement with most prior studies, which show that encapsulated follicular variant of papillary thyroid carcinoma represents 10% to 20% of all thyroid cancers.[2,9] This represents a substantial number of patients who can be spared a diagnosis of cancer, avoiding harmful overtreatment and generating substantial cost savings.

Those lesions reclassified as NIFTP had initial cytologic diagnoses that included all of the categories of TBSRTC. Most fell into indefinite categories, particularly AUS/FLUS, but a substantial number of cases (31%) were called benign, and several cases (14%) were diagnosed as malignant. These findings are comparable to other reports.[10] As most NIFTPs are found in the indeterminate categories, the risk of malignancy of these categories is particularly likely to decline. In the largest study to date, Faquin et al found a decrease in the risk of malignancy for AUS/FLUS from 31% to 18%, SFN/FN from 33% to 18%, and SFM from 83% to 59%.[11] Others have found similar effects.[12-16] These shifts may lead to changes in management recommendations for the indeterminate categories. In particular, the option of total thyroidectomy for SFM may no longer be appropriate given the reduced risk of malignancy for this category. At the same time, changes in cytology practice following widespread adoption of the NIFTP terminology may shift the categorization of these neoplasms compared to that seen in pre-adoption studies, and further prospective multinstitutional studies of risk of malignancy are essential.

The high number of NIFTP cases cytologically interpreted as benign in this series and other studies means that many NIFTPs do not go on to surgical resection presently, presumably without later developing PTC, further supporting the likely indolent nature of these lesions. Conversely,

although only a small proportion of malignant cytology interpretations were NIFTPs, these cases are clinically important, as they are potentially subject to an unnecessary total thyroidectomy and subsequent permanent hormone therapy replacement. Identifying cytomorphologic features that allow these lesions to be reclassified to a lesser diagnostic category is the most important goal of cytologic study of NIFTP.

The low percentage of malignant cytologic interpretations in NIFTPs suggest that their cytomorphologic features fall short of the cytologic criteria typically associated with PTC. We evaluated a large number of cytologic features in a series of NIFTPs, as compared to IFVPTCs and classic PTCs. These features can be broadly classified into cytoarchitectural (true papillae with fibrovascular cores, papillary caps, irregular branching sheets, swirling sheets, linear arrangement of cell groups, absence of follicular architecture, and psammoma bodies), nuclear (enlargement, oval nuclei, grooves, pseudoinclusions, other contour irregularities, pale powdery chromatin, marginal micronucleoli, nuclear molding, and nuclear overlap), and other (multinucleated giant cells, bubble gum colloid).

We found that all cytoarchitectural features evaluated showed significant distinction between NIFTP and classic PTC. In fact, none of these features were present in any NIFTPs, although some of them were present in some IFVPTCs. This finding is not unexpected, given that NIFTPs, by definition, should have no more than 1% papillary architecture. Although most of the architectural features we evaluated are textbook features of cPTC requiring no additional explanation, linear arrangement of cell groups merits further discussion. This is an architectural feature we have observed anecdotally in cPTCs but have not noted in the literature. It is a pattern in which the cell groups are deposited in lines running parallel to the direction of slide smearing (Fig. 1). The residual fibrovascular core can often be noted at one end of the line. We hypothesize that this pattern is formed when an intact papilla rolls along the slide during smearing, depositing its cells along the way, a pattern we have analogized to a tumbleweed depositing its seeds as it rolls along, and which we sometimes refer to as the "tumbleweed pattern. As with the more established architectural features, this feature was seen in both cPTCs and IFVPTCs, but no NIFTPs. Larger studies are necessary to determine the reliability of this pattern.

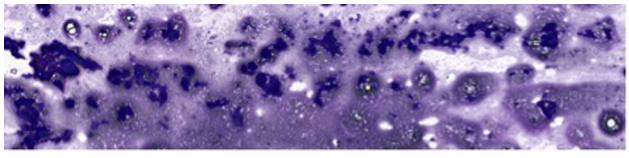

Figure 1 A representative case of cPTC showing linear or "tumbleweed" arrangement in which cell groups are deposited in lines parallel to the direction of slide smearing (Diff-Quik stain, low power).

Architectural features typical of papillae were seen in a significant number of IFVPTCs. One explanation for these findings is that FVPTC is traditionally defined as having exclusively or almost exclusively follicular architecture, which implies that the presence of a limited amount of classic papillary growth pattern is allowed. In some studies up to 20% of FVPTC contain these papillary areas, which can be represented in cytology samples.[17] However, more than 1% papillary growth excludes a diagnosis of NIFTP, so the proportion of the remaining IFVPTC with papillary areas could be even higher. Previous reports have likewise found that some of the architectural features of PTC, including swirling sheets and papillary fragments, are present in a significant number of FVPTCs.[17-20]

Psammoma bodies are probably also best categorized as an architectural feature, as they are a common finding in most lesions with papillary architecture. However, they can rarely be found in benign lesions such as multinodular goiter.[21] Only one of our cPTCs showed psammoma bodies and none of the NIFTPs and IFVPTCs showed any.

Among the nuclear features, the presence of nuclear pseudoinclusions was the most useful discriminator of cPTC and IFVPTC from NIFTPs, as they were seen in only a single case of NIFTP but in all cPTCs and IFVPTCs. Nuclear pseudoinclusions are herniations of cytoplasm into the nucleus and are present in more than 90% of PTCs. The pseudoinclusions in PTC are large and occupy more than 50% of the nuclear area and are more optically clear than the surrounding nuclear chromatin. Other studies have mirrored our finding that the vast majority of NIFTPs lack pseudoinclusions, and when they are present they are few in number. Krane et al have proposed requiring frequent pseudoinclusions (>3), rather than merely the presence of any pseudoinclusion, for the diagnosis of PTC to improve the performance of that diagnosis.[22]

NIFTPs were also less likely to have every other nuclear feature we evaluated than cPTC or IFVPTC. Several of these features achieved statistical significance compared to cPTC, despite our relatively small sample size, including nuclear enlargement, nuclear grooves, pale powdery chromatin, and nuclear overlap. However, each of the nuclear features other than pseudoinclusions was present in several cases of NIFTP, so the actual practical utility of any of these features in isolation is limited. On the other hand, it is safe to say that in general the nuclear features of NIFTP are not identical to those of cPTC, but are in fact only somewhat "papillary-like."

The rates of most of the nuclear features of IFVPTC appear to be in between those of NIFTP and cPTC, so cytologic distinction of IFVPTC from NIFTP is more challenging. Nevertheless, our results show that IFVPTC was diagnosed on cytology as malignant twice as often as NIFTP, suggesting that there are some cytologic differences between these two lesions. Similar results were documented in other studies: Bizzarro et al documented a 10.8% versus 33.3% rate of malignant diagnosis between NIFTP and

IFVPTC.[23] Maletta et al reported that increased nuclear size, nuclear membrane irregularities, and chromatin clearing were able to distinguish NIFTP from benign follicular lesions but not from encapsulated follicular carcinoma with invasion (IFVPTC).[24] In our study, pseudoinclusions appeared to be the best discriminator between these lesions. The only other nuclear feature that statistically discriminated NIFTP from IFVPTC was marginal micronucleoli.

Bubble gum colloid was very rare in NIFTP but was present in the majority of cPTCs and IFVPTCs. The difference was statistically significant. Multinucleated giant cells were likewise seen in only 1 NIFTP. They were absent in IFVPTCs but present in most cPTCs. The presence of either of these features may be supportive evidence of a malignant diagnosis in the presence of other features of malignancy.

This study has important limitations. The number of cases of NIFTP that could be evaluated cytologically is relatively small. It also represents the experience of a single institution. Given the lack of standardization of histologic diagnostic criteria for FVPTC, and the known limitations of interobserver reproducibility for this diagnosis, there is likely to be variation between institutions in the classification of these tumors. In general, however, our findings are similar to those reported in other limited literature to date on this topic. Further multi-institutional studies with larger sample sizes would be helpful to determine the reproducibility of our findings and further refine diagnostic criteria for NIFTPs.

Conclusion

NIFTP was categorized across the entire spectrum of TBSRTC categories, but was only rarely called malignant outright. In contrast, 30% of IFVPTCs and most cPTCs were classified as malignant on cytology. NIFTP was cytologically distinct from cPTC across a large number of cytomorphologic criteria. All cytoarchitectural features of cPTC were absent in NIFTP. Nuclear pseudoinclusions were present in nearly all PTC and were only found (in small numbers) in a single NIFTP. Most other nuclear features of cPTC could be present in NIFTP, but were all seen less commonly than in cPTC. Bubble gum colloid and multinucleated giant cells were also seen in only 1 NIFTP each. We found fewer criteria that were helpful in the distinction of NIFTP from IFVPTC: nuclear pseudoinclusions, marginal micronucleoli, bubble gum colloid, and the presence of architectural features of PTC favored IFVPTC. Using a combination of cytologic features rather than relying on single or few features would likely help in the distinction of NIFTP from both IFVPTC and cPTC. Our data support the approach advocated by others of limiting the diagnosis of PTC to cases with clear papillary cytoarchitectural features and/or multiple well-developed intranuclear pseudoinclusions.[22,25] For cases that do not meet this bar, placement in an indeterminate TBSRTC category, allowing diagnostic hemithyroidectomy rather than a total thyroidectomy, seems to be a prudent approach.

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