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Invited Commentary

The Impact of NIFTP on FNA Cytology: Can We Still Diagnose Papillary Thyroid Carcinoma?

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The term, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), was introduced by the Endocrine Pathology Society working group in 2015. Past nomenclature for this lesion included encapsulated follicular thyroid tumor with equivocal nuclear features, well-differentiated tumors of uncertain malignant potential (WDT-UMP), and noninvasive encapsulated follicular variant of papillary thyroid carcinoma (FVPTC). It is a highly indolent tumor and has demonstrated a risk of recurrence of less than 1% in more than 300 previously published cases with extended follow-up. Although associated with a high rate of *RAS* mutation, no *BRAF* mutations have been identified in these tumors. Compared with papillary thyroid carcinoma (PTC) or follicular carcinoma, more conservative management is recommended for patients with NIFTP. Such management may entail only hemithyroidectomy without radioactive iodine therapy (1). Histologic criteria for diagnosing NIFTP include a lack of capsular or vascular invasion, tumor encapsulation or a clear demarcation of tumor boundaries, and a pure follicular growth pattern with focal unequivocal or diffuse equivocal nuclear features of PTC.

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is widely used for reporting thyroid cytopathology. The system is composed of categories that are designed to risk-stratify thyroid lesions by their increasing probability of malignancy. Additionally, for each category, recommendations for clinical management are also outlined (2). Most NIFTP cases yield an indeterminate cytological diagnosis. As expected, reclassifying noninvasive encapsulated FVPTC as NIFTP has an impact on the rate of malignancy for each TBSRTC category. Faquin *et al*. published data showing that this reclassification had the most impact on the three indeterminate categories of TBSRTC (3). The atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) category demonstrated a decreased risk of malignancy from 13.6% to 5.2%. The follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) category also showed a decreased risk of malignancy from 15.1% to 9.9%. The suspicious for malignancy category showed a decreased risk of malignancy from 23.4% to 17.6%. Although the three indeterminate categories were the most affected by the reclassification, the malignant category was also influenced, as demonstrated by a decreased risk of malignancy from 3.3% to 2.5%. At some institutions within the United States, total thyroidectomy is performed for patients with a cytologic diagnosis that is malignant or suspicious for malignancy. Retrospectively, this may have led to overtreatment for 20-25% of patients with NIFTP who were preoperatively diagnosed as malignant or suspicious for malignancy by cytology (3).

A common question that has since had been raised by many pathologists and endocrinologists is "Can we ever diagnose PTC by fine-needle aspiration (FNA) again?" Our answer to this question is "Yes." At our institution, we use direct smears stained with the Diff-Quik and Papanicolaou stains to evaluate thyroid cytopathology, and we apply very strict criteria to definitively diagnose PTC. The following features are required before rendering a cytologic diagnosis of PTC: 1) the specimen must be cellular and contain diffusely atypical cells; 2) the atypical cells must contain oval, elongated nuclei with nuclear enlargement greater than two times the size of a red blood cell; 3) frequent nuclear membrane irregularities with prominent nuclear grooves must be observed; 4) the nuclei of the cells must demonstrate a fine chromatin pattern; and 5) the presence of nuclear pseudoinclusions must be noted. At our institution, a retrospective 5-year review of 2,531 cases showed no false positive diagnoses, and the risk of malignancy on surgical resection for a cytologic diagnosis of suspicious for malignancy was 93%. None of our NIFTP cases (n = 23) was diagnosed as malignant by preoperative FNA and only one case (4%) was diagnosed as suspicious for malignancy. The most frequent cytologic diagnosis for NIFTP was AUS/FLUS (n = 14, 61%), followed by FN (n = 4, 17%) and benign (n = 4, 17%). In contrast, for invasive FVPTC (n = 27), the most common cytologic diagnosis was suspicious for malignancy (n = 12, 44%) followed by PTC (n = 8, 30%) (4). In comparison with invasive FVPTC and classical PTC, the NIFTP cases displayed only subtle nuclear changes and overall were less cellular. A more thorough, high-power examination was required to spot the nuclear aberrations. The nuclear abnormalities often included delicate nuclear grooves or minor nuclear enlargement. Nuclear pseudoinclusions with defined, sharp borders were usually not present. The nuclei of the NIFTP tended to be more uniformly round and less irregular than invasive FVPTC and PTC. Similarly, Nishigami *et al*. also observed that when compared with invasive PTC, WDT-UMP (equivalent to NIFTP) showed less nuclear atypia (smaller size, more rounded nuclei with less maximum/minimum axis, and thin, subtle nuclear grooves) and did not contain definite nuclear pseudoinclusions (5). Krane *et al*. suggested that a definitive diagnosis of PTC should only be reserved for cases that, in addition to other characteristic features, demonstrate at least one of the following: a papillary architecture, psammoma bodies, or at

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least 3 nuclear pseudoinclusions (6). A microfollicular architecture and thick colloid are more frequently observed in cases of FVPTC and NIFTP than in classical PTC (7, 8). Among the cases that demonstrated a predominant follicular architecture on liquid-based cytology, Bizzarro *et al*. observed that the presence of prominent nuclear grooves and marked nuclear enlargement was suggestive of a malignant diagnosis, and the risk of malignancy was estimated to be 80% (9).

In summary, a definitive cytologic diagnosis of PTC can be achieved by applying strict morphological criteria. These criteria include high cellularity, nuclear enlargement with elongation of the nuclei, frequent dense grooves running across the long axis of the nuclei, and the presence of more than rare nuclear pseudoinclusions. In contrast, a cytologic specimen raises the differential diagnosis of NIFTP if it exhibits low to moderate cellularity, a microfollicular architecture, mild nuclear enlargement, and delicate nuclear grooves, but lacks papillae, psammoma bodies, or definite nuclear pseudoinclusions. The cytologic diagnosis of NIFTP usually falls within the indeterminate categories of the Bethesda system, most commonly in the categories of AUS/FLUS or FN/SFN. Patients with a diagnosis of AUS/FLUS or FN/SFN can be treated adequately with a conservative thyroid lobectomy and more aggressive intervention may be prevented. Although more studies are required to validate the morphological characteristics of NIFTP on cytologic specimens, we argue that a confident diagnosis of PTC can be achieved by FNA cytology using strict morphologic criteria.

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