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Invited Commentary

NIFTP Diagnosis: Roses and Thorns for Cytopathologists and Histopathologists

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Several authors have been debating the controversial nature of the follicular variant of papillary thyroid carcinoma (FVPC) mostly because it represents a heterogeneous group of carcinomas including both encapsulated/non-invasive (NI-FVPCs) and invasive FVPCs (I-FVPCs), which are not prognostically and molecularly alike (1-15). Whilst I-FVPCs show a more aggressive behavior characterized by lymph nodes metastases, recurrences and prevalence of *BRAF* mutations, NI-FVPCs (50%-70% of the entire subset of FVPCs) show a less aggressive outcome (10). Taking all these into account, the endocrine pathology society meeting, held at the 2015 USCAP in Boston, suggested the revision of the diagnosis of carcinoma for these NI-FVPCs, and renamed those NI-FVPCs as "non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). This entity is defined by a set of morphological features including nuclear membrane irregularities, ground glass appearance of the nuclei, and larger nuclear size in a contest of encapsulated follicular tumor (10). Not only has the new diagnostic category impacted on histology but also it implied to evaluate how this new terminology might significantly affect both the cytological diagnosis of thyroid lesions and the categories of different cytological classification systems (11-18). Given that, in the last months, several authors aim at the evaluation of the allocation of NIFTPs in the different cytological categories, and of the impact on the risk of malignancy (ROM) in different diagnostic categories. A recent analysis by Faquin *et al*. has confirmed that the decrease in the ROM for each diagnostic category is directly related to the rate by which NIFTPs are diagnosed on the histological samples (14). Specifically, the highest decrease in ROM impacts the reclassification of NIFTPs in the indeterminate categories, showing that it dwindled from 23.5% to 13.6% mostly in the (atypia of undetermined significance/ follicular lesions of undetermined significance (AUS/FLUS) in which, several series, probably due to NIFTP inclusion, reported a ROM slightly higher than that expected from the Bethesda system for reporting thyroid cytology (TBSRTC) (14).

In this issue of the Journal of Basic and Clinical Medicine, Pusztaszeri *et al*. evaluated their institutional experience with NIFTPs (19). They proposed a revision of their retrospective series of all PTCs, from 2005 to 2015, which could be re-classified as NIFTPs. According to other recent papers, these authors found that 71.4% of NIFTPs had a cytological diagnosis of indeterminate categories with the majority of them diagnosed as either suspicious for malignancy (SM; 47%) or follicular neoplasm (FN; 21%). This is in agreement with the data from Maletta *et al*. and Bizzarro *et al*., who conclude that the majority of these NIFTPs are diagnosed as indeterminate lesions (13, 17). Furthermore these latter authors, separately, focused on the different morphological features that could be useful for a morphological suggestion of NIFTPs. These parameters included microfollicular structures, nuclear features of PTC, and additional peculiar nuclear findings.

Pusztaszeri *et al*. also discussed the impact of NIFTP on the ROM of TBSRTC (19). In fact, different authors emphasize that the majority of NIFTPs are frequently diagnosed in the categories of AUS/FLUS (at ~31.2%), FN/SFN (at ~26.6%), and SM (at ~24.3%), indicating the inter-observer variability of these entities and also the most significant decreasing in the ROM for the SM and FN categories. Hence, Howitt *et al*. in a series of 72 NIFTPs found that the highest ROM resulted in 48.6% of SM category, which reflects the data by Ustun with 38% of their FVPCs diagnosed as either SM or positive for malignancy (PM) (12, 18). Pusztaszeri *et al*. confirmed that only 6.3% of their PMs resulted in a NIFTPs, which was in perfect alignment with the data provided by Maletta *et al*. who found that 2% of their NIFTPs belonged to the PMs whilst there were only four of 37 NIFTPs in the series from Bizzarro *et al*. (13, 17, 19). However, in the recent series from Zhao *et al*., 18% of their NIFTPs (n = 50) were diagnosed as PMs (20).

For the time being, there is a growing literature investigating the relevance of ancillary techniques (including immunocytochemistry but also the DNA and RNA platforms) to achieve a conclusive discrimination between I-FVPC and NIFTP. For instance, the perusal of literature states that the low prevalence (20-25%) of *BRAF* mutations harbored in FVPCs may not be helpful in the differential diagnosis with PTCs on cytology (1-10). Nonetheless, some authors emphasize that NIFTP has a very high association with other follicular-patterned neoplasms and in fact, Nikiforov *et al.*, have demonstrated that their NIFTPs, mostly harboring *RAS*, *PAX8/PPAγ* or other mutations, can be defined as "neoplasms" rather than "hyperplastic proliferations" due to the fact that they are driven by clonal genetic alterations, which are therefore different from those commonly expected in PTCs (10). However, further studies are required to assess the possible correlation of the NIFTPs with specific genetic alterations.

Nonetheless, the cytological identification of NIFTPs ought to be addressed not only for a uniform algorithm approach on thyroid lesions but also for the patient management (lobectomy *vs*. total thyroidectomy). In this perspective, Pusztaszeri *et al*. suggested that, in their daily practice, explanatory notes should be added to the cytological diagnoses about the possibility of either a FVPC or

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NIFTP on histology (19). This is of relevance because the correct cytological detection of NIFTPs is mandatory for a conservative approach that is the best recommended therapy in cases of suspected NIFTPs.

In conclusion, the new terminology of NIFTP will have significant impact even though further studies including large series are necessary in order to define the clinical management and the long term follow-up.

Conflict of Interest

The author has no conflict of interests.

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