ORIGINAL RESEARCH PAPER

Pathology

NONINVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES (NIFTP): APPLICATION OF DIAGNOSTIC CRITERIA

KEY WORDS: NIFTP, EFVPTC

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ABSTRACT

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is an encapsulated or clearly delimited, noninvasive neoplasm with a follicular growth pattern and nuclear features of papillary thyroid carcinoma (PTC). In 2015, an international thyroid working group re-evaluated NI-EFVPC and its diagnostic criteria. The new terminology of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) was accordingly introduced to replace NI-EFVPC. It is considered a 'premalignant' lesion of the RAS-like group. Ultrasonography (US), cytology and molecular tests are useful to suspect thyroid nodules that correspond to NIFTP but there is wide overlap of the results with the encapsulated follicular variant of PTC (E-FVPTC). In these nodules that possibly or likely correspond to NIFTP, if surgery is indicated, lobectomy is favored over total thyroidectomy. The diagnosis of NIFTP is made after complete resection of the lesion by observing well-defined criteria. While the definition of NIFTP is based on specific morphological parameters, recent studies have questioned whether the criterion allowing less than 1% of true papillae should be revised to a total absence of papillae. Since NIFTP is not 'malignant', tumor staging is not necessary and patients are not submitted to thyroid cancer protocols or guidelines. Recent revisions in the morphological criteria for NIFTP emphasize the need to adhere to very stringent histomorphologic criteria when making a diagnosis of NIFTP.

INTRODUCTION

Noninvasive follicular thyroid neoplasm with papillarylike nuclear features (NIFTP) is an encapsulated, noninvasive neoplasm with a follicular growth pattern and nuclear features of papillary thyroid carcinoma (PTC), but without well-formed papillae or psammoma bodies and without typical findings of the aggressive subtypes of PTC or poorly differentiated carcinoma. The WHO classification of tumors of the endocrine organs in 2017 abolished the old diagnostic category of non-invasive encapsulated follicular variant Papillary Thyroid Carcinomas (EFVPTC), and replaced by the new terminology Noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP). The diagnosis of NIFTP is performed only on surgical specimens with strict histopathological criteria.[1]

The change from the noninvasive encapsulated follicular variant of PTC (E-FVPTC) to NIFTP

Nikiforov et al. in 2016 proposed the term NIFTP when it was already known as encapsulated tumors of FVPTC without vascular/capsular invasion and had an excellent prognosis after complete resection, even when treated only with lobectomy. Compared to data that include it as 'malignant' tumor, with NIFPT no longer being considered 'cancer', a reduction in the risk of 'malignancy' is observed in thyroid nodules. This fact has possible implications for the predictive value for 'malignancy' of ultrasonography (US), cytology,, molecular tests and fluorodeoxyglucose positron emission tomography (FDG-PET). Tumors that nowadays correspond to NIFTP were included in the group of low-risk PTC that is, tumors restricted to the thyroid without vascular invasion or typical components of aggressive subtypes, in the absence of the BRAFV600E mutation.[2]

Diagnostic Considerations

Clinical Features

Clinically, NIFTP presents similarly to most thyroid neoplasms by detection of a nodule on routine examination or incidentally during unrelated diagnostic imaging. If NIFTP grows large enough, it can also potentially present by mass effect on surrounding structures, leading to dysphonia or airway compromise[3]

Histopathology

The classification criteria proposed by Nikiforov *et al.*[1] introduced in the WHO classification of tumours of the endocrine organs of 2017 is as follows:

- Presence of capsule, thin or thick, or clear demarcation of the lesion with respect to the surrounding parenchyma and absence of vascular or capsular invasion
- Follicular growth pattern, with absence of papillae, absence of psammomatous bodies, solid/trabecular/insular growth pattern <30%, absence of necrosis and low mitotic index (less than 3 mitoses per 10 high power fields)
- PTC-like nuclear characteristics, with nuclear score (NS) of 2 or 3. The nuclear score included the evaluation of the size, shape and clarification of the tumour nuclei
- Negative immunohistochemical BRAF ve staining with confirmation of the wild type BRAF status by reverse hybrid allele specific oligonucleotide hybridization

Impact on Cytopathology

The introduction of the NIFTP nomenclature has posed a potential problem for cytopathologists. Often, the first specimens obtained from thyroid nodules for review by a pathologist are fine needle aspirates (FNA), on which evaluation of capsular invasion is not possible, and differentiating nuclear features of NIFTP and papillary thyroid carcinoma can be challenging. Many worry that making the diagnosis of PTC on cytopathology now carries the risk of a false-positive result in NIFTP. The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) assigns a risk of malignancy to each of the possible diagnostic categories into which biopsies are placed by the pathologist. The creation of NIFTP has introduced a shift to the currently described risk of malignancy for each of these categories. Early studies seem to indicate that the risk of false-positive for a Bethesda VI diagnosis is low, with most NIFTPs being classified on preoperative FNA into indeterminate categories.NIFTP was most often classified into the indeterminate categories of the BSRTC (including atypia of undetermined significance/

follicular lesion of undetermined significance, follicular neoplasm, and suspicious for malignancy) and thus correspondingly significantly lowered the risk of malignancy associated with each of these indeterminate categories. Most significantly, the risk of malignancy in the suspicious for malignancy category decreased by 41.5% . These findings elucidate the need to revisit guidelines for surgical management since they are currently based on the risk of malignancy associated with BSRTC diagnostic categories that do not take NIFTP into account. On FNA specimens with nuclear features of PTC and/or follicular architecture, NIFTP is now on the differential diagnosis, just as was EFVPTC. [4,5]

Molecular findings

The genetic analysis responsible for NIFTP include RAS oncogene alterations, similar to those driving follicular adenoma and follicular carcinoma tumors, in contrast to the BRAF oncogenes mutated in the classic papillary thyroid cancer pathway. In the literature on encapsulated follicular variant of PTC, Rivera et al. demonstrated genotypic abnormalities in 11 of 28 encapsulated FVPTC tumors of which 26% of the invasive tumors and 0% of noninvasive tumors harbored a BRAF mutation. In comparison, 36% of encapsulated FVPTC harbored RAS mutations in contrast to 10% of invasive FVPTC tumors.

Given the recent description of the entity, the diagnostic criteria for NIFTP do not include a characteristic mutation, much like other thyroid tumors. Molecular studies are much more likely to play a critical role in guiding management at the time of FNA of these lesions. The presence of RAS mutations may contribute supportive evidence favoring a diagnosis of NIFTP, follicular adenoma, or follicular carcinoma, in contrast to BRAF mutations which are more commonly observed in association with classical papillary thyroid carcinoma. The presence of a BRAF V600E mutation would not be compatible with NIFTP.

Wong et al. reviewed a cohort of 63 cases that had been tested with the Afirma Gene Expression Classifier (GEC) in which FNA biopsies yielded diagnoses of atypia/follicular lesion of undetermined significance or suspicious for a follicular neoplasm and corresponding surgical resection specimens were reviewed. They found that NIFTP accounted for 64% of the carcinomas (“suspicious” test results) detected by the Afirma GEC. Valderrabano et al. assessed the performance of the ThryoSeq v2 at their institution by retrospectively reviewing results on Bethesda category III and IV specimens and extrapolated their results to predict the impact on the overall rate of malignancy presuming NIFTPs as a benign diagnosis. They estimated that the overall rate of malignancy would drop from 24% to 15%, the negative predictive value would increase from 88% to 94%, and the positive predictive value would decrease from 50% to 34% overall in both indeterminate categories. [6,7]

Differential Diagnosis

The main differential diagnosis for NIFTP is invasive encapsulated FVPTC as this lesion shares the well-circumscribed, often encapsulated structure, follicular architecture and papillary-like nuclear features with NIFTP and differs only with as much as a single focus of capsular or vascular invasion. Invasive encapsulated FVPTC harbors similar RAS-type mutations as NIFTP, follicular adenoma, and follicular carcinoma. In order to differentiate these diagnoses, the tumor capsule must be entirely submitted for microscopic examination to exclude invasion in the case of NIFTP .

Follicular adenoma is another entity that shares a similar morphological appearance and molecular genotype to NIFTP. Follicular adenomas are well-circumscribed, partially, or completely encapsulated and composed of follicles that can be arranged in various growth patterns (microfollicular, macrofollicular, trabecular, etc.) and lack nuclear features of papillary thyroid carcinoma. With a 94.3% classification accuracy reported for NIFTP using the nuclear scoring system, differentiating between NIFTP and follicular adenomas based on nuclear features may become more reproducible. [8]

MANAGEMENT

In patients with NIFTP, after its complete resection and in the absence of associated malignancy the need for and protocol of follow-up are matters of discussion. After the name change removing the term 'cancer', alteration of the nature of the lesion which is no longer'malignant', and definition of somehow strict diagnostic criteria designed exactly to rule out the possibility of metastases, maintaining patients with NIFTP under a similar follow-up as patients with PTC. It has been suggested that if patients with NIFTP continue to be followed up like those with lowrisk PTC, the practical impact promoted by these changes would have been minimal or none since noninvasive E-FVPTC was known to have an excellent prognosis after lobectomy and conservative treatment of this histological subtype was already recommended by the available guidelines. It is expected that specific protocols or recommendations for selective follow-up of subgroups of patients with NIFTP will be proposed. [9,10]

CONCLUSION

Clinicians must be aware of the ultrasonographic, cytological and molecular findings of nodules corresponding to NIFTP since this knowledge influences the definition of the extent of surgery. In addition, clinicians and pathologists must be familiar with the histological criteria for the diagnosis of NIFTP to spare patients with this tumor (without associated malignancy) from additional treatment and from the traditional follow-up recommended for differentiated thyroid cancer.

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