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Non-Invasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features – An Illustrative Case

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A 54-year-old woman underwent total thyroidectomy for a one-year history of anterior neck mass. The specimen was a 29.88–gram thyroid gland that on sectioning showed a single 2.0 x 1.5 x 1.5 cm encapsulated nodule with tan-brown solid cut surfaces noted on the right thyroid lobe. No gross lesions were noted on sectioning of the isthmus and left thyroid lobe.

Microscopic examination showed a thinly encapsulated nodule composed of tightly-packed follicles. *(Figure 1)* Examination of the entire capsule did not show capsular or vascular invasion. The follicles were lined by follicular cells that had crowded and enlarged nuclei with pale chromatin and some nuclear membrane irregularities such as grooving. *(Figure 2)* There were no papillae, psammoma bodies, necrosis, mitotic figures and solid or trabecular architecture seen. Based on these features, the diagnosis rendered was non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

NIFTP is a term adopted in 2016 to replace the nomenclature of a thyroid tumor previously termed "non-invasive encapsulated follicular variant of papillary thyroid carcinoma (FVPTC)".[1] In the most recent edition of the World Health Organization (WHO) Classification of Tumors, NITFP is considered a low-risk follicular cell-derived neoplasm whose definition also reflects the diagnostic criteria of this tumor.[2]

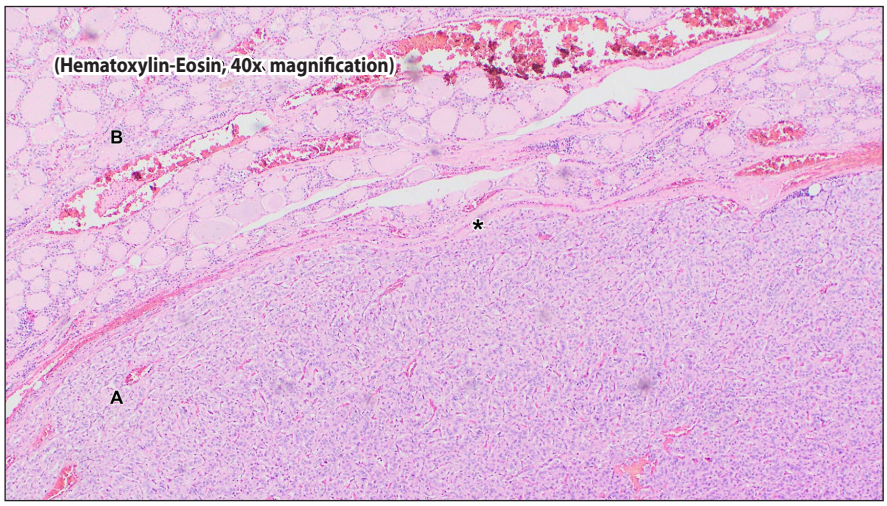

Figure 1. A nodule consisting of tightly-packed follicles **(A)** is separated from the surrounding non-neoplastic thyroid parenchyma **(B)** by a thin fibrous capsule (asterisk). No evidence of capsular or vascular invasion are identified. (Hematoxylin-Eosin, 40x magnification)

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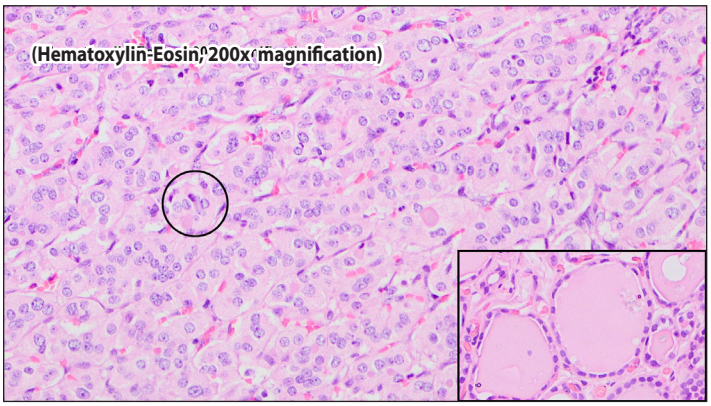

Figure 2. The neoplastic follicles are lined by cells with enlarged and pale nuclei resembling that of papillary thyroid carcinoma, in contrast to the small uniform nuclei of the non-neoplastic follicles at the same magnification (inset). Nuclear grooves are noted (encircled). (Hematoxylin-Eosin, 200x magnification)

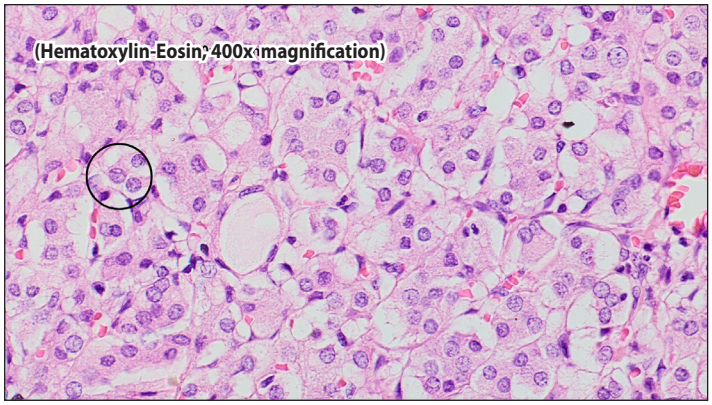

Figure 3. The follicular cells in oncocytic NIFTP have more abundant eosinophilic granular cytoplasm but still display nuclear enlargement, pale chromatin, and occasional nuclear membrane grooves (encircled). (Hematoxylin-Eosin, 400x magnification)

The original diagnostic criteria for NIFTP included a set of histopathologic features that can be assessed on routine Hematoxylin and Eosin-stained sections. These criteria included encapsulation or clear demarcation of the tumor; a predominantly follicular growth pattern with less than 1% papillae, no psammoma bodies, and less than 30% solid, trabecular, and insular growth pattern; moderate to complete expression of the nuclear features of papillary thyroid carcinoma (PTC); no evidence of capsular or vascular invasion after examination of the entire tumor interface; and no evidence of tumor necrosis or high mitotic activity.[1] Nuclear features characteristic of PTC include nuclear enlargement and elongation, nuclear membrane irregularities (e.g. irregular contours, nuclear grooving, and pseudoinclusions), and chromatin clearing.[1] These features are a very important point of distinction from a follicular adenoma – a similarly non-invasive follicular-patterned encapsulated neoplasm whose cells however lack these features.[3]

Minor revisions in the diagnostic criteria were made in 2018 on account of rare cases that were diagnosed as NIFTP but behaved like a classic PTC on follow-up.[4] The 2018 revised criteria modified the criterion of "less than 1% papillae" to "no well-formed papillae" and included a secondary diagnostic criterion that employed molecular or immunohistochemical assays to exclude a *BRAF* V600E or other high-risk mutations e.g., *TERT*, *TP53*. This criterion is helpful, but not requisite, such that the diagnosis may still be made following strict adherence to the morphologic criteria in settings where molecular testing is not available or limited.[2,4]

Two subtypes have been described - tumors measuring less than 10 millimeters are termed subcentimeter NIFTP while those in which at least 75% of the cells are oncocytes are called oncocytic NIFTP.[2] *(Figure 3)* In terms of underlying molecular drivers, *RAS*-like molecular alterations are the predominant mutation seen similar to follicular adenoma and follicular carcinoma, while *BRAF* V600E, which is more characteristic of classic PTC and its variants, is an exclusionary secondary criterion in the revised 2018 diagnostic criteria.[2]

The reclassification of this entity was made to reflect the very low incidence rate (less than 1% of cases) of adverse oncologic events such as metastasis to distant sites or recurrence associated with this tumor, with no reported mortality.[2] The avoidance of the term "carcinoma" was felt appropriate in order to obviate over-treatment given the indolent behavior of the entity.[1] Lobectomy without radioactive iodine therapy is the recommended treatment. Proper grossing technique - including submitting the entire tumor-capsule interface for histopathologic evaluation - and strict adherence to the set criteria are essential for a correct diagnosis and subsequent management. While avoiding overtreatment is the key goal, an accurate diagnosis is also crucial so as not to deprive a patient of radioactive iodine therapy and the appropriate surgery if the criteria are superficially or erroneously applied.

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