Ear, Nose & Throat Journal
1–3

DOI: 10.1177/0145561319890162
journals.sagepub.com/home/ear
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Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features

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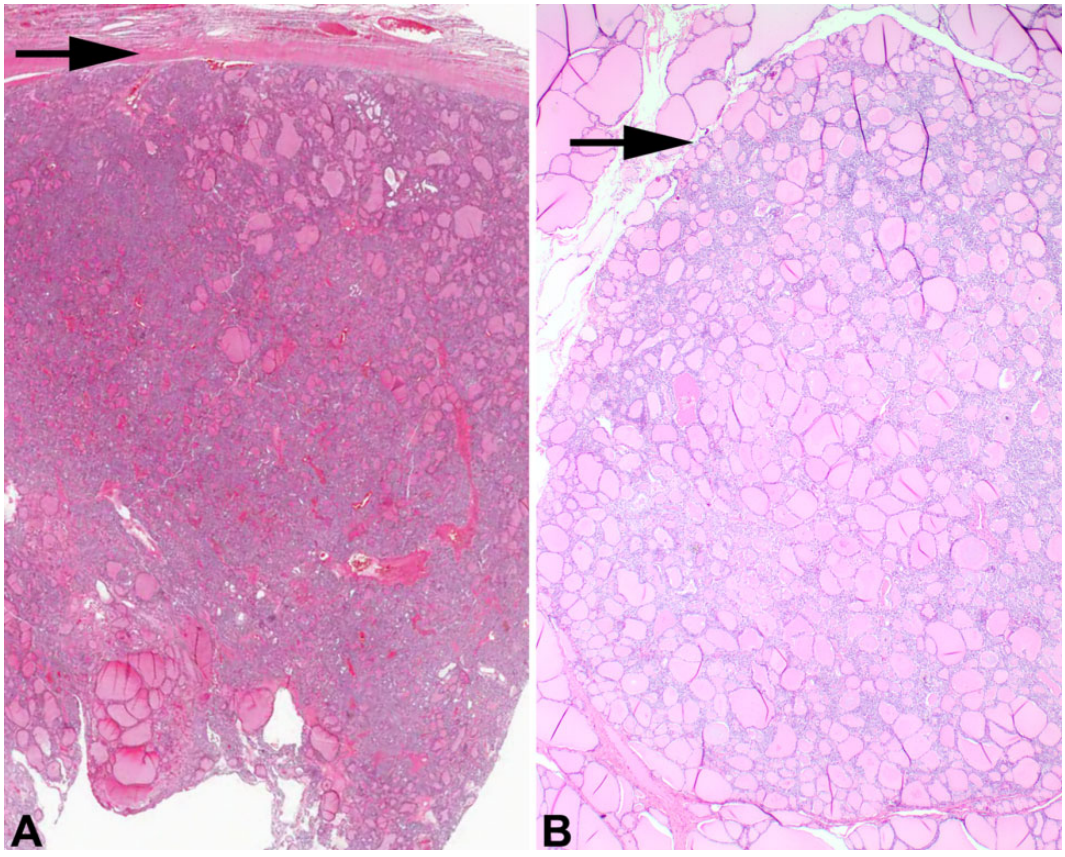

Figure 1. A, This follicular patterned tumor is surrounded by a well-formed fibrous connective tissue capsule (black arrow). B, This tumor is well demarcated and circumscribed (black arrow) but is not encapsulated.

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a recently recognized indolent neoplasm separated from invasive follicular variant of papillary thyroid carcinoma (FVPTC). NIFTP is a noninvasive, partially to completely encapsulated thyroid follicular neoplasm arranged in almost exclusively follicular architecture, showing papillary carcinoma-like nuclear features in an adequately sampled tumor. In order to qualify for placement in this category, several inclusion and exclusion criteria must be met.

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Received: October 14, 2019; revised: October 19, 2019; accepted: November 1, 2019

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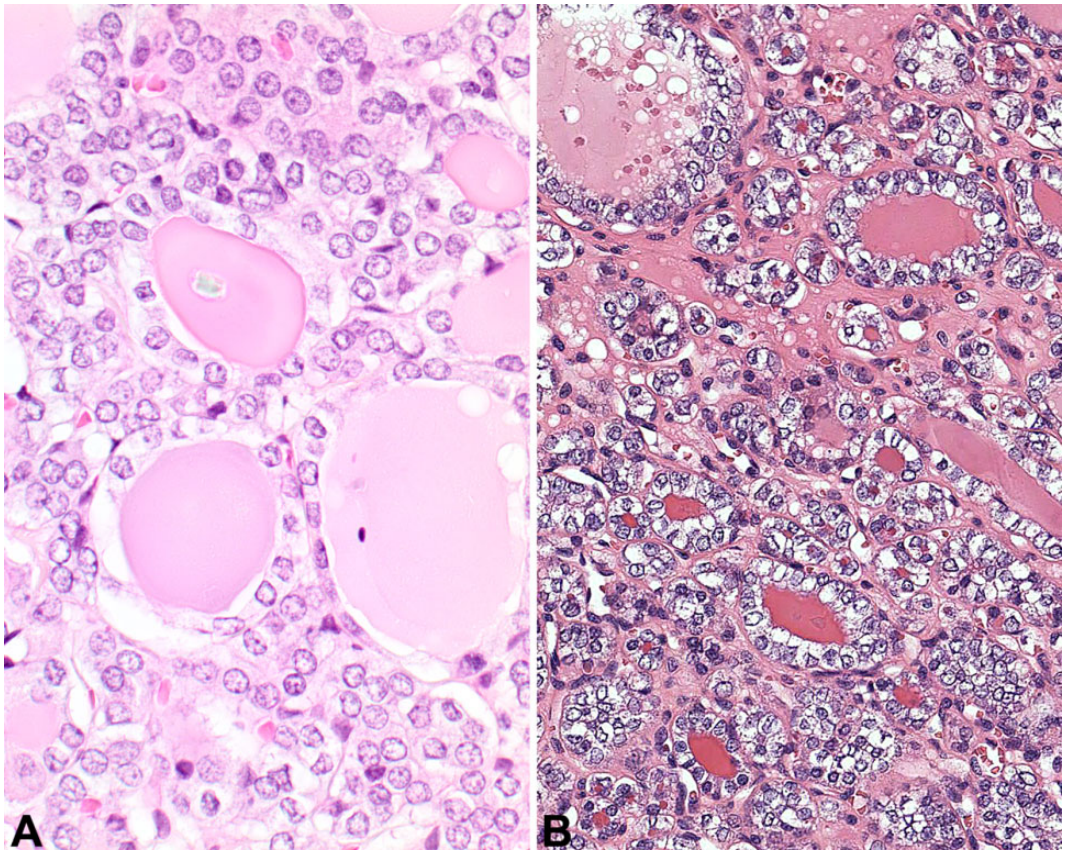

Figure 2. A, The nuclear features of papillary carcinoma are easily identified in this follicular patterned tumor, with increased nuclear to cytoplasmic ratio, nuclear overlapping, and nuclear contour irregularities. B, This tumor shows enlarged nuclei, nuclear overlapping, nuclear contour irregularities, and nuclear chromatin clearing.

Importantly, there can be no invasion at the tumor periphery (ie, usually the capsule) that has been completely sampled for histologic review. There cannot be another recognized pattern of papillary carcinoma, and no more than 30% of the tumor should be solid, trabecular, or insular. There cannot be any tumor necrosis and no increased mitoses of $\geq$4 mitoses/2 mm^2. Finally, there cannot be any true papillary structures.

When strictly defined, about 30% of papillary thyroid carcinoma (PTCs) are follicular patterned. However, when invasion is present, papillary structures are identified, or there is tumor necrosis, a NIFTP cannot be diagnosed, and other categories would be employed. Most patients are in the fifth decade of life, with females affected more often than males (4:1). Patients present with a usually unicentric, slowly growing nodule, although bilateral and multicentric tumors are recognized. Lobectomy or the treatment that generated the specimen in which the diagnosis was rendered, is sufficient, without completion thyroidectomy or radioablative iodine. Retrospective analysis identifies no recurrences or biochemical evidence of disease in tumors meeting diagnostic criteria.

When fine needle aspiration is performed, most NIFTP are classified in Bethesda categories III, IV or V, and thus, the risk of malignancy within these categories has been altered by the introduction of NIFTP. Most NIFTP demonstrate *RAS* mutations (*NRAS* mutation is most common), while *BRAF* K601E mutations along with *THADA/IGF2BP3* and *PAX8*/*PPARγ* gene fusions are identified in about 5% each, respectively, of NIFTP. By definition, *BRAF* V600E mutations; *RET, NTRK1-3*, or *ALK* fusions; and *TERT* promoter mutations are not identified in this tumor. Frozen sections are not meaningful and should not be performed, as the entire capsule/periphery must be evaluated in order to definitively render this diagnosis.

The tumors are circumscribed and usually well encapsulated, with a distinctly different appearance from the adjacent parenchyma (Figure 1). Tumors range from 1 to 10 cm, with a mean of 3 cm (tumors <1 cm should only be diagnosed when identified by imaging, subjected to cytology examination, and/or are the reason for the surgery). There is no invasion (capsular or lymphovascular), with easily identified colloid and no necrosis or increased mitoses. The tumor shows a follicular architecture, usually exhibiting small, tight, well-formed follicles (Figures 1 and 2). Papillae are absent. Intratumoral, acellular, eosinophilic fibrosis is frequently present. The cells are enlarged with an increased nuclear to cytoplasmic ratio. The nuclear features of papillary carcinoma must be identified (based on nuclear size and shape, nuclear membrane

irregularities, folds and grooves, and nuclear chromatin clearing/margination; Figure 2), although they are often patchy or multifocal within the tumor nodule (at least 3 high-power field foci per centimeter of tumor diameter).

NIFTP needs to be separated from a follicular adenoma, encapsulated FVPTC with invasion, encapsulated classical PTC, follicular thyroid carcinoma, Plummer nodule (toxic adenoma), and cellular adenomatoid nodules.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Suggested Reading

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