Follicular Neoplasm/Suspicious for a Follicular Neoplasm

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Michael R. Henry, William H. Westra, Jeffrey F. Krane, and Fernando Schmitt

Background

Prior to the introduction of the Bethesda System for Reporting Thyroid Cytopathology, there was great variability in the way thyroid aspirates that are suspicious for a follicular neoplasm were reported, as demonstrated by a review of the literature compiled for the National Cancer Institute (NCI)-sponsored Thyroid Fine-Needle Aspiration State of the Science Conference in 2007 [1]. The terminology used ranged from broad terms like "follicular lesion," "follicular proliferation," and "indeterminate" to the more specific terms like "rule out/suggestive of/suspicious for follicular neoplasm" or "follicular neoplasm" [2–10]. Much of this variability resulted from the fact that the so-called follicular lesions, comprised of nodular goiter (nodular hyperplasia), follicular adenoma, follicular variant of papillary carcinoma, follicular carcinoma, and the recently described noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), have overlapping cytomorphologic features and cannot be accurately distinguished by FNA alone. Nevertheless, certain cytologic features are very useful in raising the

M.R. Henry (✉)
Department of Laboratory Medicine, Mayo Clinic, Rochester, MN, USA
e-mail: henry.michael@mayo.edu

W.H. Westra
Department of Pathology, The Johns Hopkins Hospital/The Johns Hopkins University School of Medicine, Baltimore, MD, USA

J.F. Krane
Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

F. Schmitt
Department of Pathology and Oncology, Medical Faculty of Porto University and IPATIMUP, Porto, Portugal

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possibility of a neoplasm, most importantly the possibility of a carcinoma. In this regard, FNA can be considered a screening test, selecting for surgery those nodules with a greater probability of malignancy. The final diagnosis depends upon lobectomy because capsular and/or vascular invasion is the sine qua non of follicular carcinoma. In 2016 an international panel convened to review the 2007 terminology and criteria and proposed changes based on current knowledge [11]. The panel preferred having just one term for this category but recognized that, for practical purposes, the terms "follicular neoplasm" and "suspicious for a follicular neoplasm" are equally acceptable. A laboratory should choose the one it prefers and use it exclusively for that category. These synonymous terms should not be used separately to denote two distinct and different interpretations. "Suspicious for a follicular neoplasm (SFN)" is preferred over "follicular neoplasm (FN)" by some laboratories because a significant proportion (up to 35%) of cases that fulfill the criteria described herein prove not to be neoplasms but rather hyperplastic proliferations in nodular goiter [3–5, 12, 13]. The term SFN acknowledges this limitation, provides a rational framework for cytologic-histologic correlation, and preserves the credibility of cytopathologists with their clinical colleagues and the patients they serve. The goal of this category is to identify all potential follicular carcinomas and refer them for appropriate follow up, most often a diagnostic lobectomy [14]. It is not the goal of FNA to identify all follicular neoplasms, because adenomas are clinically innocuous, and there is little if any evidence to suggest progression from adenoma to carcinoma in the thyroid. Nevertheless, the terms FN and SFN are preferred over "suspicious for follicular carcinoma" for several reasons. Both FN and SFN have an established tradition in many laboratories; the terms recognize the impossibility of distinguishing adenoma from carcinoma by FNA; and both terms recognize that the majority of cases interpreted as FN/SFN turn out to be follicular adenomas simply because follicular adenomas outnumber follicular carcinomas in the population.

It is important to point out that cytologic-histologic correlation for the follicular-patterned thyroid nodules is hindered somewhat by the imperfect reproducibility among histopathologists in the diagnosis of nodular hyperplasia, follicular adenoma, follicular carcinoma, the follicular variant of papillary carcinoma, and the recently recognized noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [15–17].

Definition

The general diagnostic category "follicular neoplasm" or "suspicious for a follicular neoplasm" refers to a cellular aspirate comprised of follicular cells, most of which are arranged in an altered architectural pattern characterized by significant cell crowding and/or microfollicle formation. The sample should be at least moderately cellular; sparsely cellular aspirates are excluded from this category and could be interpreted as *atypia of undetermined significance* or *follicular lesion of undetermined significance* (see Chap. 4). Cases that demonstrate suspicious or definitive nuclear features for papillary carcinoma are excluded from this category and should be classified as *suspicious*

for malignancy or *malignant*, respectively. Follicular-patterned aspirates with mild nuclear changes, such as increased nuclear size, nuclear contour irregularity, and/or chromatin clearing, can be classified as FN/SFN so long as true papillae and intranuclear pseudoinclusions are absent; a note that some nuclear features raise the possibility of an invasive follicular variant of papillary carcinoma or the more indolent noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) can be included [18, 19].

Criteria

Cytologic preparations are moderately or markedly cellular (Fig. 5.1a, b).
There is a significant alteration in follicular cell architecture, characterized by cell crowding, microfollicles, and dispersed isolated cells (Fig. 5.2a, b).
Follicular cells are normal-sized or enlarged and relatively uniform, with scant or moderate amounts of cytoplasm.
Nuclei are usually round and slightly hyperchromatic, with inconspicuous nucleoli (Fig. 5.2a, b).
Some nuclear atypia may be seen, either enlarged, variably sized nuclei, and prominent nucleoli (Fig. 5.3a, b) or enlarged nuclei with nuclear contour irregularity and mild and/or focal chromatin clearing.
Colloid is scant or absent.

Explanatory Notes

The hallmark of the FN/SFN specimen is the presence of a significant architectural alteration in the majority of the follicular cells. The altered architecture takes the form of crowded and overlapping follicular cells (Fig. 5.4a, b), some or most of which are arranged as microfollicles. To improve reproducibility, it has been

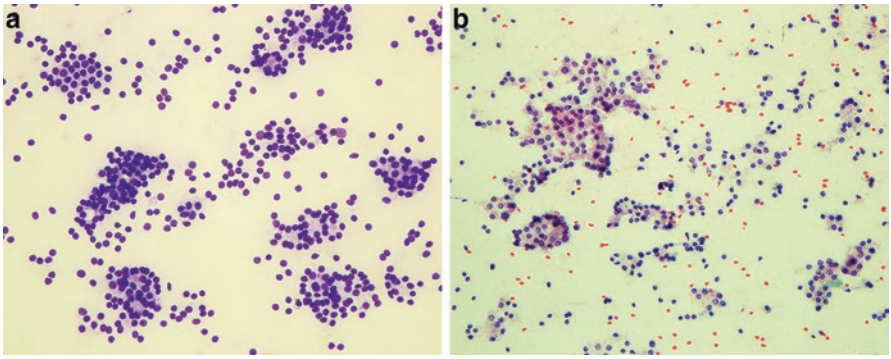

Fig. 5.1 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**, **b**) Low magnification shows a highly cellular aspirate composed of uniform follicular cells arranged in crowded clusters and microfollicles (**a** smear, Diff-Quik stain; **b** smear, Papanicolaou stain).

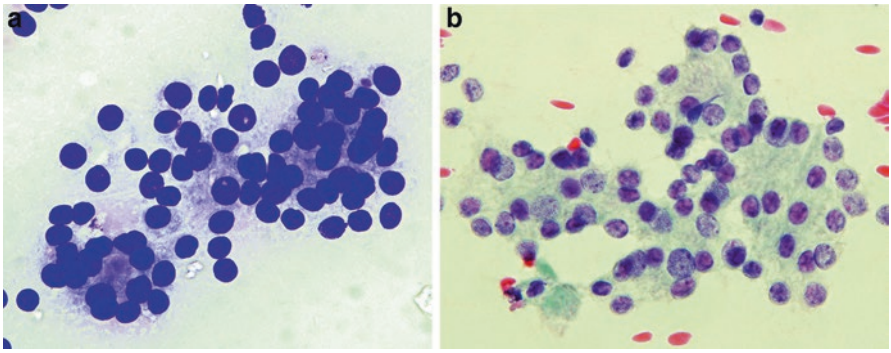

Fig. 5.2 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**) The crowded follicular cells have round nuclei of similar size and faint cytoplasm (smear, Diff-Quik stain). (**b**) Follicular cells are arranged as microfollicles and have round nuclei, evenly dispersed, granular chromatin, and small nucleoli (smear, Papanicolaou stain).

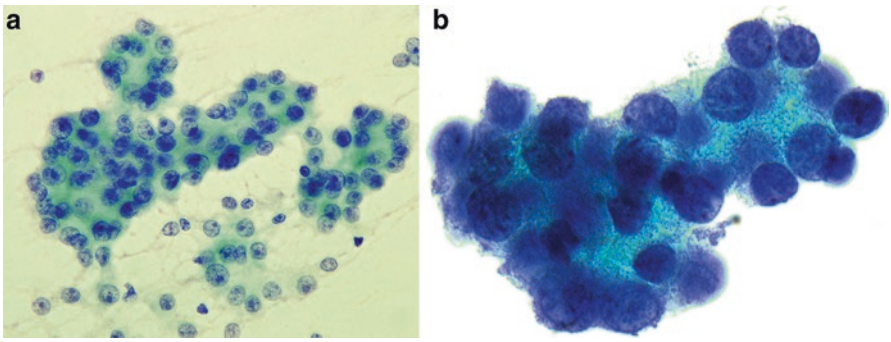

Fig. 5.3 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**, **b**) Follicular cells in crowded, microfollicular arrangements show slight size variation, chromatin that is more "open" (less granular), and enlarged nucleoli (**a** smear, Papanicolaou stain; **b** ThinPrep, Papanicolaou stain).

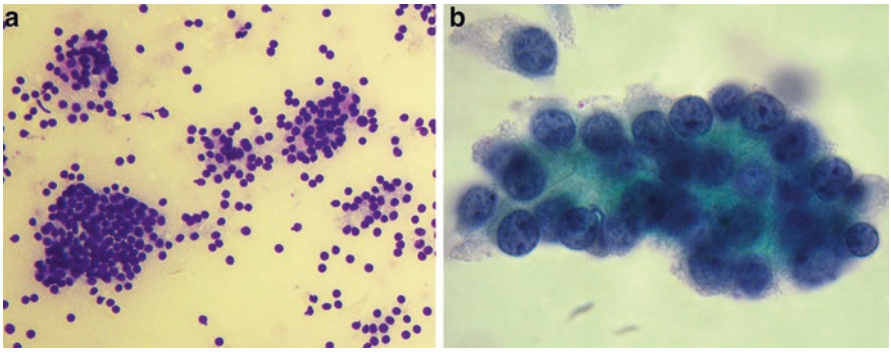

Fig. 5.4 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**, **b**) Microfollicles demonstrate nuclear overlap. Some are loosely cohesive clusters, and there are dispersed, isolated cells (**a** smear, Diff-Quik stain; **b** ThinPrep, Papanicolaou stain).

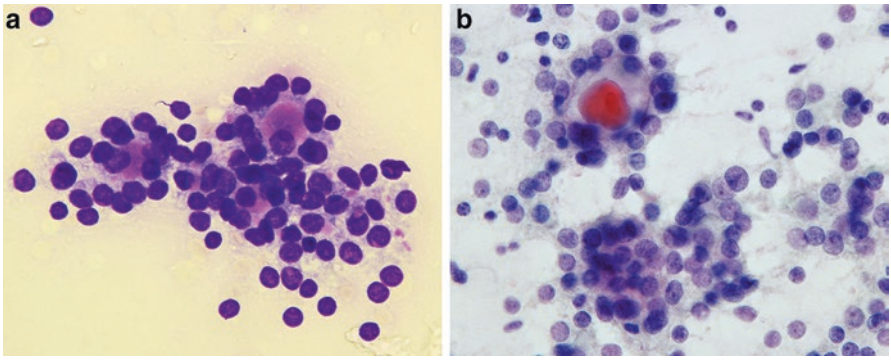

Fig. 5.5 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**, **b**) Microfollicles may contain small amounts of colloid (**a** smear, Diff-Quik stain; **b** smear, Papanicolaou stain).

proposed that the "microfollicle" designation must be limited to crowded, flat groups of less than 15 follicular cells arranged in a circle that is at least two-thirds complete [15], but this recommendation has not been tested in a prospective study. A small amount of inspissated colloid may be present within the microfollicle (Fig. 5.5a, b). Microfollicles tend to be relatively uniform in size ("equisized"). In some cases, crowded follicular cells form ribbons of overlapping cells ("trabeculae") that are more prominent than the microfollicles (Fig. 5.6).

It is important to recognize that rare macrofollicle fragments as well as some background colloid may be present in FN/SFN specimens. A small fragment of follicular cells is not necessarily a microfollicle: an important defining feature of the microfollicle is the crowding and overlapping of the follicular cells.

Cystic change is not common unless the neoplasm is large, at which point it may undergo central degenerative change with associated findings (foamy and hemosiderin-laden macrophages).

Although most FN/SFNs are highly cellular specimens, cellularity by itself is not sufficient to merit this designation [20]. If the majority of follicular cells are arranged in macrofollicle fragments (variably sized fragments without overlap or crowding), the sample can be considered benign. Similarly, nuclear atypia by itself is not diagnostic of malignancy or even neoplasia, as hyperplastic nodules and follicular adenomas can demonstrate nuclear enlargement and hyperchromasia [21–23].

An occasional dilemma is the sparsely cellular sample composed predominantly of microfollicles. Most cytologists are reluctant to make an FN/SFN interpretation on a sparsely cellular sample because of the discrepancy between the cellularity and the cell pattern. It is reasonable to interpret such cases as *atypia of undetermined significance* (or *follicular lesion of undetermined significance*) (see Chap. 4). In such cases, a repeat aspiration and/or molecular testing is a reasonable approach and is likely to resolve the discrepancy.

In some instances, both architectural features concerning for a follicular neoplasm and nuclear features concerning for papillary carcinoma are present.

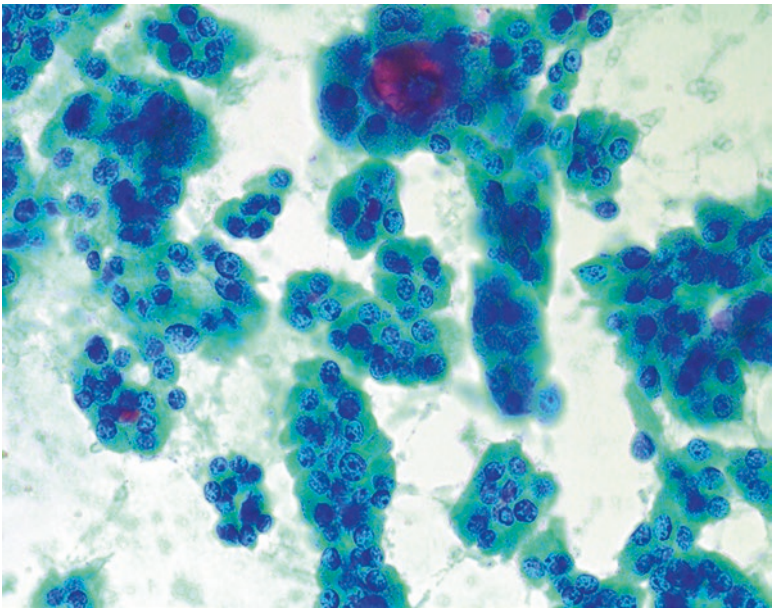

Fig. 5.6 Follicular neoplasm/suspicious for a follicular neoplasm. In some cases, trabeculae of crowded follicular cells are more conspicuous than microfollicles (smear, Papanicolaou stain).

If the follicular cells show definitive nuclear features of papillary thyroid carcinoma, including frequent intranuclear pseudoinclusions, and if there are at least focal elements associated with classical papillary carcinoma (psammoma bodies and/or true papillae), the specimen should not be interpreted as FN/SFN but rather as "*malignant*, papillary thyroid carcinoma" [18, 24, 25]. If nuclear features of papillary carcinoma are not definitive or architectural features of classical papillary carcinoma are absent, such aspirates raise concern for invasive follicular variant of papillary carcinoma or NIFTP. Whether such aspirates are better classified as FN/SFN or "*suspicious for malignancy*, suspicious for papillary thyroid carcinoma" will be dictated by the quality and quantity of the cytologic changes. In either instance, an explanatory note regarding concern for NIFTP/invasive follicular variant of papillary carcinoma is warranted [17]. (See section "Sample reports," Example 4.) For lesions deemed borderline between FN/SFN and *suspicious for malignancy*, it may be more prudent to opt for the FN/SFN designation because the FN/SFN diagnosis is more likely to prompt a limited surgical approach (lobectomy).

Fine needle aspirations of parathyroid adenomas are composed of cells that resemble crowded and overlapping follicular cells (Fig. 5.7). Even when the FNA is performed with ultrasound guidance, it may not be clear to the aspirator that the lesion arises from a parathyroid gland rather than the thyroid, particularly for

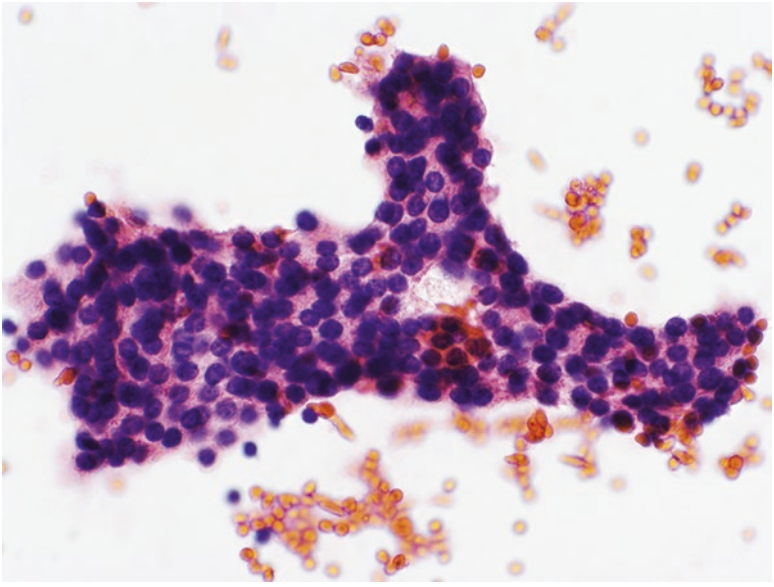

Fig. 5.7 Follicular neoplasm/suspicious for a follicular neoplasm. These crowded, uniform cells are arranged in thick trabeculae mimicking neoplastic follicular cells. Lobectomy revealed an unsuspected parathyroid adenoma (smear, hematoxylin, and eosin stain).

parathyroid glands located within the thyroid parenchyma or thyroid capsule. When submitted as a "thyroid FNA" specimen, parathyroid adenomas are often misinterpreted as FN/SFN. If there is a clinical suspicion that the lesion may be parathyroid, or if there are cellular features suggesting that possibility (e.g., crowded trabeculae in an aspirate lacking colloid), then the possibility of a parathyroid lesion might be suggested in the report [26]. (See section "Sample reports," Example 5.) The gene expression classifier Afirma (Veracyte, Inc.), which can be used as an adjunct to cytology for FN/SFN cases, includes a cassette that recognizes the gene expression profile of parathyroid neoplasms [27, 28].

There are robust data on the predictive value of the FN/SFN interpretation because most patients with this FNA result undergo surgery [3, 4, 9, 12]. The likelihood that the nodule is neoplastic is 65–85%. The rate of malignancy is significantly lower, at 25–40% (see Table 1.2, Chap. 1). Moreover, not all the malignancies prove to be follicular carcinomas: many if not most of the malignancies (27–68%) are interpreted histologically as papillary thyroid carcinoma [3, 4, 9, 12]. There are a number of explanations for this discrepancy. Some tumors, particularly the follicular variant of papillary carcinoma and NIFTP, may have cellular features of papillary carcinoma that are not fully developed throughout the entire nodule and thus may not be appreciated in the FNA sample. In other cases, however, the discrepancy may be due to the imperfect reproducibility of the histologic diagnoses of follicular carcinoma and follicular variant of papillary carcinoma [15].

Management

According to the 2015 American Thyroid Association management guidelines, diagnostic surgical excision (lobectomy) is the long-established standard of care for this diagnosis [14]. After consideration of clinical and sonographic features, however, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery [14, 29, 30].

Sample Reports

If an aspirate is interpreted as FN/SFN, it is implied that the sample is adequate for evaluation. (An explicit statement of adequacy is optional.) The general category FN/SFN is a self-sufficient interpretation; narrative comments that follow are optional. An educational note specifying the risk of malignancy for this interpretation, derived from the laboratory itself or from the literature, is optional.

Example 1
SUSPICIOUS FOR A FOLLICULAR NEOPLASM.

Example 2
FOLLICULAR NEOPLASM.

Example 3
SUSPICIOUS FOR A FOLLICULAR NEOPLASM.
Cellular aspirate of follicular cells with a predominantly microfollicular architecture, scattered isolated cells, and scant colloid.

Example 4
SUSPICIOUS FOR FOLLICULAR NEOPLASM (*SEE NOTE*).

Note: Although the architectural features suggest a follicular neoplasm, some nuclear features raise the possibility of an invasive follicular variant of papillary carcinoma or its recently described indolent counterpart, NIFTP; definitive distinction among these entities is not possible on cytologic material.

Example 5
SUSPICIOUS FOR A FOLLICULAR NEOPLASM.
Cellular aspirate composed predominantly of crowded uniform cells without colloid. The features suggest a follicular neoplasm, but the possibility of a parathyroid lesion cannot be excluded. Correlation with clinical, serologic, radiologic, and molecular test findings (if any) should be considered.

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