Follicular Neoplasm

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Manon Auger, Fabiano Callegari, Guido Fadda, Mitsuyoshi Hirokawa, and Lisa Rooper

Background

Since its first edition, The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has standardized the diagnostic terminology for the thyroid fine needle aspirates (FNAs) that suggest the possibility of a follicular neoplasm (FN), a diagnostic category that used to be reported with great variability, as demonstrated by a review of the literature published in 2008 [1]. In keeping with its overarching principle of a desired accrued simplification of the diagnostic categorization to ensure clear communication, the third edition of TBSRTC endorses only the terminology "FN" for the diagnostic category, which was also termed "Suspicious for FN" in the previous editions.

M. Auger (✉)
Department of Pathology, McGill University, QC, Canada
e-mail: manon.auger@mcgill.ca

F. Callegari
Department of Pathology, São Paulo Hospital, Federal University of São Paulo (EPM-UNIFESP), São Paulo, SP, Brazil
e-mail: fabcalleg@icloud.com

G. Fadda
Department of Pathology, University of Messina, Messina, Sicily, Italy
e-mail: gfadda@unime.it

M. Hirokawa
Department of Diagnostic Pathology and Cytology, Kuma Hospital, Kobe, Hyogo, Japan
e-mail: mhirokawa@kuma-h.or.jp

L. Rooper
Department of Pathology, The Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, Baltimore, MD, USA
e-mail: rooper@jhmi.edu

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Although it is acknowledged that there are overlapping cytologic features between various follicular-patterned lesions, including follicular nodular disease, follicular adenoma (FA), invasive follicular variants of PTC (FVPTC), follicular thyroid carcinoma (FTC), as well as the more recently described noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), there are nevertheless certain cytologic features that are very useful in raising the possibility of a neoplasm, and most importantly, those with the potential of being malignant. In this regard, FNA can be considered a screening test, selecting for surgery those nodules with a greater probability of malignancy. It is not the goal of FNA to identify all FN, because FA are clinically innocuous; in other words, the goal of the FN category is to identify all potential FVPTC, FTC, and NIFTP, and refer them for appropriate management [2]. The final diagnosis depends upon histologic examination of the surgical resection specimen because capsular and/or vascular invasion, the *sine qua non* of FTC and FVPTC, cannot be assessed by cytology. The majority of cases interpreted as FN will turn out to be FAs or follicular nodular disease on histologic follow-up (for more details, see section below "Cyto-Histologic Correlation").

The diagnostic terminology "FN" is recommended despite the fact that it is recognized that a certain proportion (up to approximately 30%) of cases that fulfill the criteria described herein prove not to be neoplasms but rather hyperplastic proliferations in the context of non-neoplastic conditions on cyto-histologic correlative studies; in view of these limitations, a facultative statement can be used to convey that uncertainty, if it is the preference of a laboratory (see Example 3) [3–5]. It is also important to point out that cytologic-histologic correlation is partly hindered by variability in the histopathologic classification of the follicular-patterned thyroid nodules [6–8].

The FN cytologic diagnosis is infrequent, accounting for only approximately 7% of the overall thyroid FNAs in most cytopathology laboratories [9].

Definition

The general diagnostic category "FN" refers to a moderately to markedly cellular aspirate that is comprised of follicular cells in which most are arranged in an altered architectural pattern characterized by microfollicle formation, and/or significant cell crowding, trabeculae, or single cells.

The majority of cases in the FN category consist of follicular cells without nuclear atypia: the nuclei are normal-sized and round, with clumpy or slightly hyperchromatic chromatin with absent or inconspicuous nucleoli. Nuclear grooves, intranuclear pseudoinclusions, and nuclear clearing are absent.

However, a minority of cases in the FN category consist of follicular-patterned aspirates with mild atypical nuclear changes, including increased nuclear size, nuclear contour irregularity (i.e., nuclear grooves), and/or chromatin clearing; such cases could still be classified as FN as long as true papillae are absent and intranuclear pseudoinclusions are either absent or very rare [10–13]. Such cases that exhibit the architecture pattern of typical FN but in which the subtle or focal nuclear

features are reminiscent of PTC raise the possibility of NIFTP or of FVPTC; as the latter two entities cannot be reliably distinguished prospectively by cytology, a facultative comment can be included in the report to alert the treating physicians of this diagnostic possibility (see Example 4) [14].

Exclusion from FN category-scenario #1

- The FNAs with the above-mentioned architectural pattern, but that are only sparsely cellular, are excluded from the FN category; they are best interpreted as "Atypia of Undetermined Significance (AUS)."

Exclusion from FN category-scenario #2:

- Cases with marked or unequivocal pronounced nuclear atypia (nuclear clearing and multiple nuclear pseudoinclusions) and/or presence of true papillae and/or psammoma bodies are excluded from the FN category and should be classified as "Malignant" or "Suspicious for Malignancy," depending on the quality or quantity of the changes (see Chaps. 7 and 8).

Criteria for FN Cases

Cellularity

Cytologic preparations are moderately or markedly cellular (Fig. 5.1a).

Architecture

There is a significant alteration in follicular cell architecture characterized by microfollicles and/or cell crowding, and less frequently, trabeculae or dispersed isolated cells (Fig. 5.1a–f).

Cytoplasm

The cytoplasm is scant or moderate.

Oncocytic changes should be absent, or present only focally (if present to any significant degree in a case exhibiting the above architectural features, the diagnostic category to consider is Follicular Neoplasm—Oncocytic Follicular Neoplasm (FN-OFN); see Chap. 6).

Nuclei

Most Common Scenario (i.e., The "Typical" FN Scenario)

The nuclei are normal-sized and round, with the chromatin clumpy/slightly hyperchromatic and an absent or inconspicuous nucleolus (Fig. 5.2a–c).

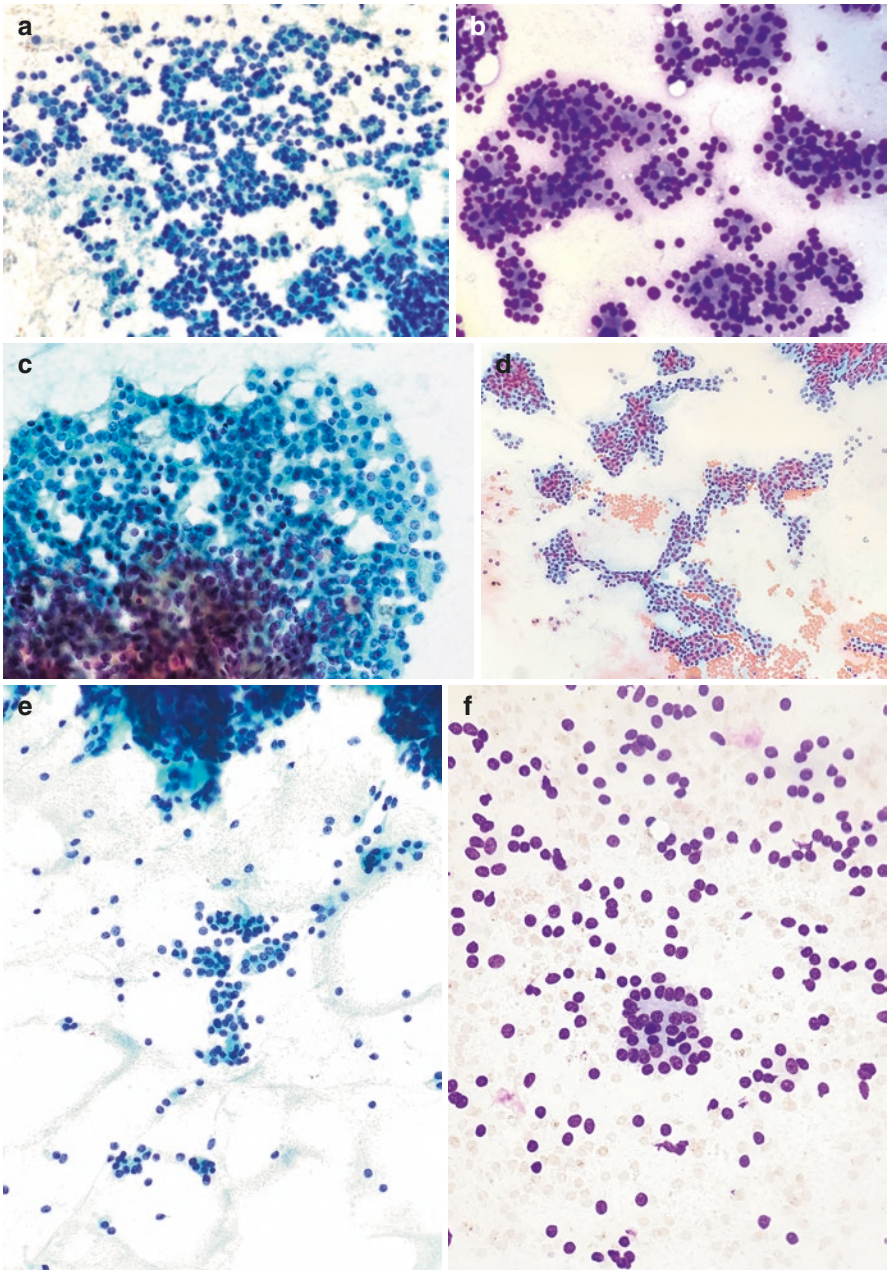

Fig. 5.1 Follicular neoplasm. Illustrating the various architectural alterations seen in FN. (**a**, **b**) Highly cellular aspirate composed of uniform follicular cells arranged in microfollicles (smears, **a**: Papanicolaou stain, **b**: Diff-Quik stain). (**c**) Follicular cells in crowded groups (smear, Papanicolaou stain). (**d**) Follicular cells in trabecular arrangement (smear, Papanicolaou stain). (**e**, **f**) Follicular cells in single cell pattern (smears, **e**: Papanicolaou stain, **f**: Diff-Quik stain)

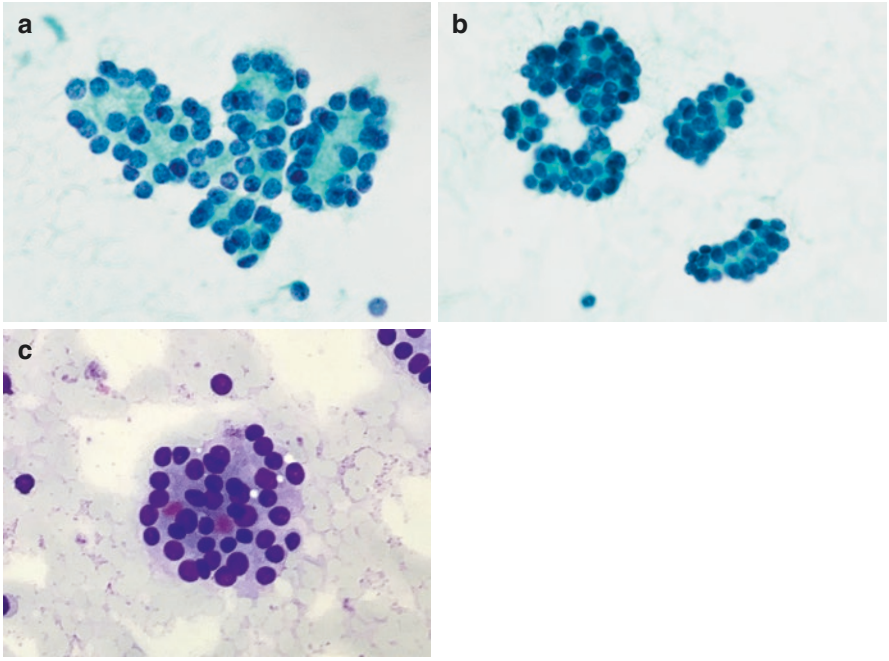

Fig. 5.2 Follicular neoplasm (*the "typical" FN scenario*). (**a**–**c**) The nuclei of the "typical" FN are normal-sized and round, with the chromatin clumpy/slightly hyperchromatic and an absent or inconspicuous nucleolus (the histologic follow-up for this case was follicular adenoma) (smears, **a**, **b**: Papanicolaou stain; **c**: Diff-Quik stain)

Infrequent Scenario (i.e., The "Potential NIFTP/FVPTC" Scenario)

Mild or focal nuclear atypia (papillary-like nuclear alterations) may be seen (Fig. 5.3a–d), manifested as either:

- Alterations of nuclear size and shape: enlargement, overlapping, and/or elongation.
- Nuclear membrane irregularities: irregular contours, grooves, and/or rare pseudo-inclusions.
- Alterations of chromatin characteristics: chromatin clearing, margination of chromatin to membrane, and/or glassy nuclei.
- A conspicuous nucleolus may be focally present.

Other Features

Colloid is scant or absent.

Cystic degeneration (i.e., foamy macrophages) may be present but is unusual; this is in contrast to FN-OFN, in which this feature is frequent.

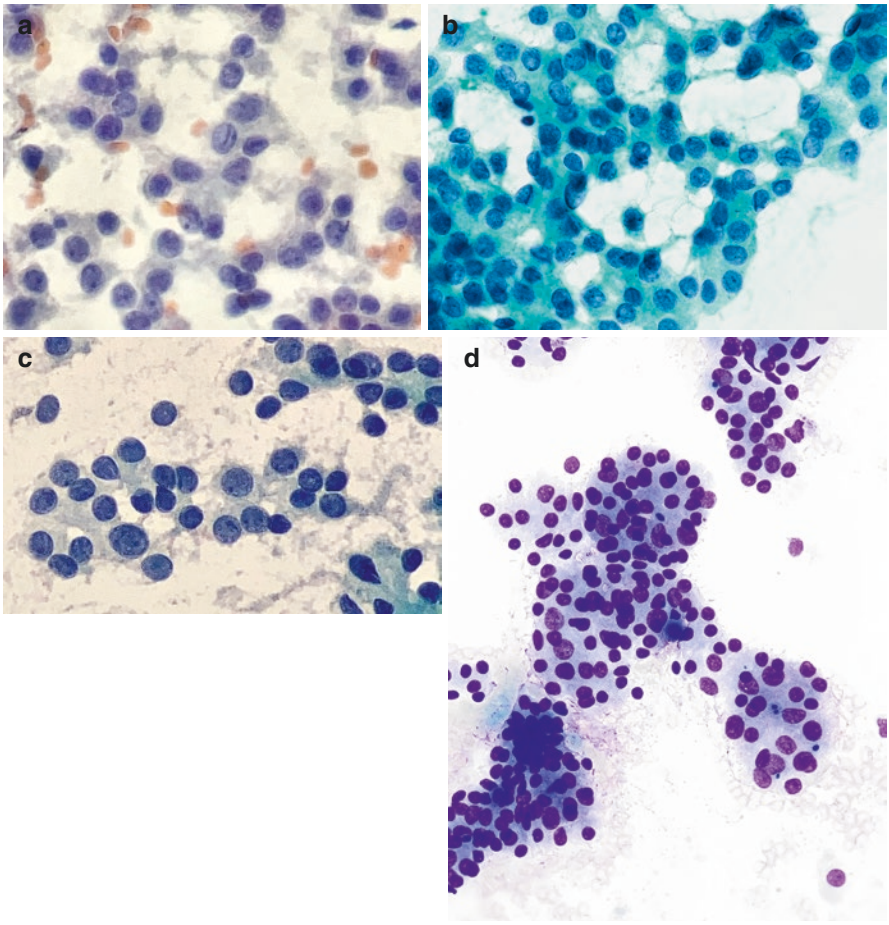

Fig. 5.3 Follicular neoplasm (*the "potential NIFTP/FVPTC" scenario*). (**a**–**d**) When the nuclei exhibit mild or focal nuclear atypia (i.e., papillary-like nuclear alterations), NIFTP/FVPTC comes into consideration (the histologic follow-up for this case was NIFTP) (smears, **a**–**c**: Papanicolaou stain; **d**: Diff-Quik stain)

Explanatory Notes

The hallmark of the FN case is the presence of a predominant microfollicular or crowded architectural pattern in the majority of the follicular cells in a moderately to markedly cellular specimen. Most commonly this is observed in the absence of nuclear atypia (no nuclear features reminiscent of PTC), or infrequently in the presence of mild/focal nuclear atypia (potential NIFTP/FVPTC scenario).

The microfollicles are composed of crowded and overlapping follicular cells (Figs. 5.1a and 5.2a–c). To improve reproducibility, it has been proposed that the designation of "microfollicle" be restricted to crowded, flat or 3-dimensional groups

with a circumference of less than 15 follicular cells arranged in a circle that is at least two-thirds complete [15]. A small amount of inspissated colloid may be present within the microfollicle (Fig. 5.2c). Microfollicles tend to be relatively uniform in size ("equisized"). Occasionally, crowded follicular cells form ribbons of overlapping cells ("trabeculae") that could be more prominent than the microfollicles (Fig. 5.1d). Although follicular cells can also be seen in a single cell pattern, it is infrequent (Fig. 5.1e, f); when present, the single cell pattern usually does not predominate, and the single cells are admixed with microfollicles, or less commonly trabeculae. In fact, when an aspirate exhibits a predominantly single cell pattern, other diagnostic entities (e.g., FN-OFN, medullary thyroid carcinoma, or even follicular nodular disease) should be considered instead, depending on the presence of other features (see Chaps. 6, 9, and 3, respectively).

It is important to recognize that rare macrofollicles may be present in FN specimens; however, if macrofollicles are easily identified in a specimen leading to a "mixed" macro- and micro-follicular architectural pattern, a diagnosis of FN should not be used; instead, either the "Benign" or "AUS" category should be considered depending on the other features seen (see Chaps. 3 and 4, respectively).

Although most FN are highly cellular, cellularity alone is insufficient to merit this designation. If the majority of follicular cells are arranged in macrofollicular fragments or honeycomb sheets (variably sized fragments without nuclear overlap or crowding), or if there is a significant mixture of both macrofollicles and/or honeycomb sheets along with microfollicles, the sample can be considered Benign. Of note, 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. Indeed, when a honeycomb sheet (which corresponds to a collapsed macrofollicle) is disrupted or fragmented, it may appear as a small fragment; however, in contrast to a "true" microfollicle, the nuclei of such a fragment should not be crowded or overlapping when looking at those that are located in the same focal plane (Fig. 5.4a–c).

A frequent dilemma is the sparsely cellular sample composed predominantly of microfollicles. Because of the low cellularity, it is more prudent to refrain from diagnosing such specimens as FN, and best to interpret them as "AUS" (see Chap. 4). In such cases, a repeat FNA to improve sampling and cellularity is a reasonable approach and is likely to resolve the discrepancy.

The majority of cases in the FN category consist of follicular cells exhibiting no nuclear atypia. The nuclei are normal-sized and round, the chromatin clumpy/slightly hyperchromatic with an absent or inconspicuous nucleolus. There are no nuclear grooves, intranuclear inclusions, nor nuclear clearing. In other words, there are no nuclear features reminiscent of PTC (Fig. 5.2a–c).

However, a minority of cases are those that exhibit an architectural pattern concerning for a FN, but in which the subtle/mild or focal nuclear features are concerning for PTC; such cases should also be diagnosed in the FN category as long as true papillae are absent and that intranuclear pseudoinclusions are either absent or very rare [10–13] (Fig. 5.3a–c). Such cases raise the possibility of NIFTP or FVPTC (see section below, for more details about NIFTP). Importantly, if the follicular cells

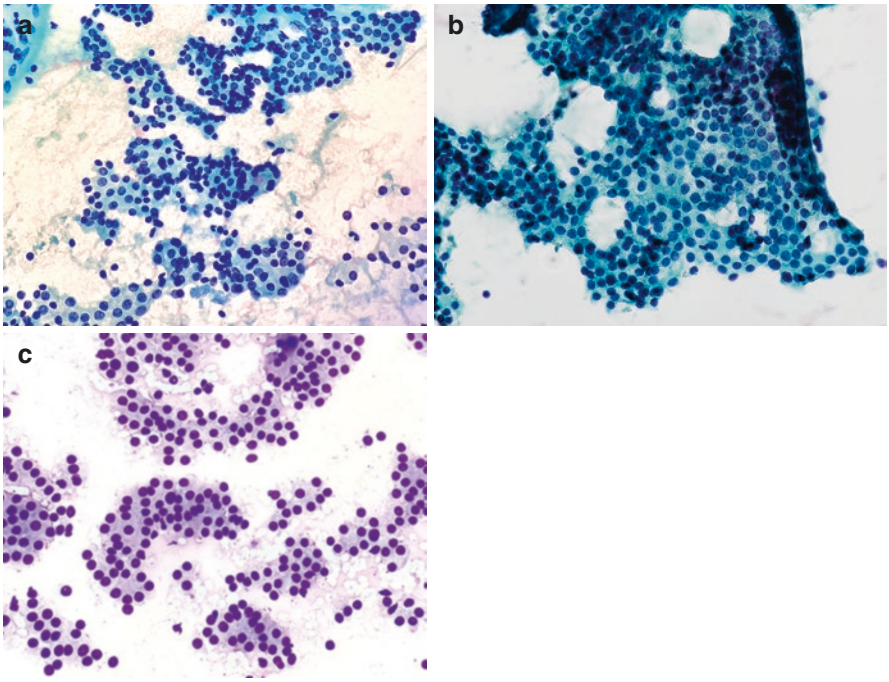

Fig. 5.4 Contrasting "true" microfollicle versus a "pseudofollicle." (**a**) A "true" follicle (with nuclei overlapping) from a follicular neoplasm (smear, Papanicolaou stain). (**b**, **c**) Pseudofollicles from a hyperplastic nodule (smears, **b**: Papanicolaou stain; **c**: Diff-Quik stain)

show definite or suspicious nuclear features of PTC, including frequent pseudoinclusions, and there are at least focal elements associated with classical PTC (psammoma bodies and/or true papillae), the specimen should not be interpreted as FN but rather as "Malignant—PTC," or "Suspicious for PTC," depending on the quality and quantity of the cytologic changes (see Chaps. 8 and 7, respectively). For lesions deemed borderline between FN and "Suspicious for malignancy," it may be more prudent to opt for the FN designation because the FN diagnosis is more likely to prompt a limited surgical approach (lobectomy).

More About NIFTP (and FVPTC)

NIFTP was originally described in 2016 in response to the increasing recognition that this well-demarcated or encapsulated follicular-pattern tumor has an indolent clinical behavior and should no longer be considered malignant nor labeled as "carcinoma" as it previously had been under the terminology of "encapsulated FVPTC" [7, 8]. Because a definitive diagnosis of NIFTP requires surgical excision for complete examination of the entire interface or capsule of the tumor with the

surrounding thyroid tissue to exclude capsular and/or vascular invasion, the distinction between NIFTP and FVPTC cannot be achieved by cytology.

Although now considered a non-cancer, NIFTP has an approximate prevalence of 9–10% of all retrospectively reviewed PTC cases worldwide; this percentage, however, shows significant geographic variation, ranging between 0.5% and 5% in Asia versus 13–20% in Western countries [16, 17].

The prospective cytologic diagnosis of NIFTP is problematic. In most series, the majority (approximately 75–80%) of FNAs of NIFTP cases are classified in the indeterminate diagnostic categories of TBSRTC; of those, approximately 50–75% are diagnosed as AUS, 25–30% as FN, while a minority are classified as suspicious or more rarely as malignant [7, 9, 13, 18]. A goal of this third edition is to increase awareness of diagnostic clues to a potential diagnosis of NIFTP. When such NIFTP are suspected, they should be put in the FN diagnostic category, with a facultative comment in the report raising this diagnostic possibility (see Example 4) [14].

Several studies have reported the cytological features of NIFTP [11–14, 18–22]. Although rare studies state that certain cytologic criteria can distinguish between NIFTP and FVPTC, the overall consensus is that there is too much overlap cytologically, but also ultrasonographically and molecularly, between the two entities to reliably distinguish them prospectively on cytology [11, 21]. However, there is general agreement that it is possible to distinguish most cases of NIFTP/FVPTC from benign follicular nodules and from conventional PTC on the basis of their cytological features. It is the nuclear, but not the architectural, features that allow the distinction of NIFTP/FVPTC from the benign nodules in a follicular pattern; although mild PTC-like nuclear changes will be seen in NIFTP/FVPTC, no nuclear atypia should be seen in benign nodules (with the exception of the context of lymphocytic thyroiditis) [13, 23]. At the other end of the spectrum, when trying to distinguish NIFTP/FVPTC from conventional PTC, the presence of marked/unequivocal pronounced nuclear atypia (nuclear clearing and multiple nuclear pseudoinclusions) and/or of any true papillae and/or psammoma bodies excludes NIFTP and strongly favors PTC [11, 12, 23, 24].

The ultrasonographic (US) features of most NIFTP are "benign," including wider than tall shape, well-circumscribed solid (hypo- or iso-echoic) nodules, and absence of microcalcifications; however, overall, these features are not specific and overlap with those of FA, FVPTC (more specifically, the invasive encapsulated subtype), and minimally invasive FTC. In contrast, US findings of thyroid malignancy including marked hypoechogenicity, taller-than-wide shape, micro-calcifications, and blurred or micro-lobulated margins argue against the diagnosis of NIFTP [14, 18, 25].

Short Notes About the Molecular Features of FN and NIFTP

Herein is a summary of the most pertinent molecular features of the FN category; more details are found in Chap. 14.

The follicular-patterned thyroid neoplasms, including FA, FTC, NIFTP, and FVPTC share many molecular alterations. The most common somatic mutations found are point mutations in the *RAS* gene family and *PPARG* rearrangements. In histologically proven cases, approximately 10% and 30–50% of FA and FTC respectively harbor mutations in the *RAS* genes, whereas *PAX8::PPARG* rearrangements occur in approximately 8% and 20–30% of FA and FTC, respectively [8, 21, 26, 27].

Molecular testing in thyroid FNAs diagnosed as FN reveals variation between studies in the percentage of cases exhibiting mutations, presumably partly due to inter-institutional differences in the type of thyroid FNA cases classified as FN. For example, using the same 7-gene panel test (*BRAF*, *RAS*, *RET::PTC*, and *PAX8::PPARG*), mutation rate in FN varied from 8.8% to 27.2.% between studies [26]. One constant in most series, however, is that *BRAF* V600E mutations and *RET::PTC* rearrangement (grouped together as *BRAF*-like mutations) are highly specific for malignant outcomes; similarly, *TERT* promoter mutations are usually associated with malignancy [27]. In contrast, *RAS* and *RAS*-like mutations (*PAX8::PPARG* without *BRAF* V600E alterations) are not malignant-specific since they are also detected in FA and low-risk neoplasms such as NIFTPs [21, 28].

NIFTP is characterized by alterations in either *RAS* (in up to 60% of cases), *PAX8::PPARG* (in up to 30% of cases), and *THADA* (in up to 30% of cases) gene fusions, or more rarely (in <10% of cases) by *BRAF* K601E, *EIF1AX*, *EZH1*, *DICER1*, *PTEN*, or *TSHR* mutations; however, *BRAF* V600E mutations and *RET* fusions (characteristic of conventional PTC) should be absent in NIFTPs [17, 21, 27–29]. The molecular profile of NIFTPs overlaps too much with that of other *RAS*-like tumors to allow a definitive preoperative identification.

Molecular testing of FN cases can be helpful to refining management decision-making. Molecular testing using a wider panel of genes (e.g., ThyroSeq® V3) can provide more refined risk stratification than pure cytomorphology, attributing different risk associated with different molecular signatures in the indeterminate nodules, including those classified as FN [30]. For example, in a study including FNAs categorized as AUS or FN, *PAX8::PPARG* fusion, or mutations in *BRAF*, *TERT*, and *PIK3CA* all carried a ROM of 100%; in contrast, *PTEN*, *DICER1*, *E1F1AX*, *TSHR*, and *TP53* genes were associated with benign pathologic follow-up, and the negative predictive value (NPV) for the FN cases was 95.5% [30]. In one study, the molecular-derived ROM for FN, when using Thyroseq v.3, was 32.6% [31]. The *Afirma*® Gene Sequencing Classifier (GSC) can also be used for risk stratification for FN, with a NPV of 95.8% for those classified as "benign" by *Afirma* GSC [32].

Risk of Malignancy

The re-classification of NIFTP as non-malignant has had an impact on the ROM of the indeterminate diagnostic categories, including the FN category, but the magnitude of the impact that the NIFTP has had on malignancy rates varies by institution. The range reported for the ROM of the FN category ranges from 20% to 50% with

an average of 30%, though this range can be 0.2–30% lower if excluding NIFTP in ROM calculations (see Chap. 1: Tables 1.2 and 1.4) [3–5, 9, 33]. Of note, the impact has been more significant in the West than in Asia where NIFTP is diagnosed much more sparingly; in one meta-analysis, the average relative decrease of the ROM for the FN category was 22% and 32% for Asian and Western studies, respectively [34].

Finally, although some studies have reported a higher ROM for the FN category in the pediatric population as compared to the adult one, meta-analytic data has shown no statistically significant difference between the two groups (see Chap. 1, Table 1.3) [35].

Differential Diagnosis of FN

A variety of relatively rare lesions (paraganglioma, hyalinizing trabecular tumor) and metastatic low-grade carcinomas from other primary sites can mimic FN; only parathyroid lesions are covered here.

Fine needle aspirations of parathyroid lesions (adenomas or hyperplasia) are composed of cells that resemble crowded and overlapping follicular cells, often in microfollicular arrangement, therefore mimicking FN (Fig. 5.5a). 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 if the parathyroid gland is located within the thyroid parenchyma or thyroid capsule. When submitted as a "thyroid FNA" specimen, parathyroid samples are often misinterpreted as FN. If there is a clinical suspicion that the lesion may be parathyroid (such as in the context of hypercalcemia), or if there are cellular features suggesting that possibility (e.g., prominent "salt and pepper" chromatin, crowded trabeculae in an aspirate lacking colloid, or triangular clusters—the so-called "wedge pattern"), then the possibility of a parathyroid lesion may be suggested in the report (see Example 5) [36, 37]. Immunocytochemistry can be instrumental in reaching the correct diagnosis, in particular GATA3 and parathormone (PTH); parathyroid lesions are also usually positive for chromogranin, synaptophysin, and CD56, but are negative for

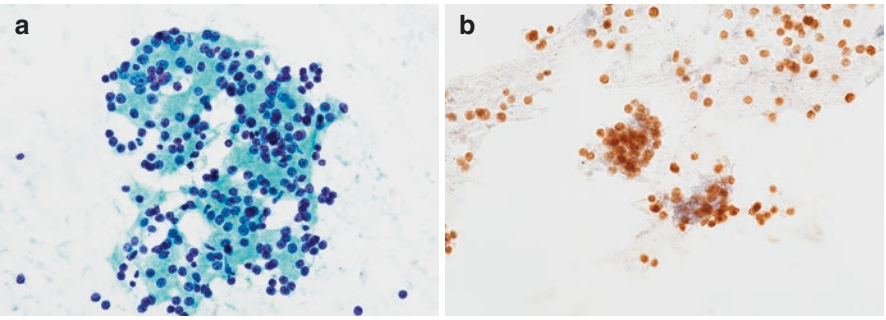

Fig. 5.5 Fine needle aspirate of a parathyroid adenoma, mimicking a follicular neoplasm (**a**: smear, Papanicolaou stain; **b**: Immunocytochemistry for GATA3)

thyroglobulin, TTF-1, and calcitonin [36, 37]. Assessment of PTH in the needle washout of FNA is also a powerful tool to rule in or rule out parathyroid lesions. The Afirma® GSC, which can be used as an adjunct to cytology for FN cases, includes a cassette that recognizes the gene expression profile of parathyroid neoplasms.

Cyto-Histologic Correlation

There are robust data on the predictive value of the FN interpretation because most patients with this FNA diagnosis undergo surgery. In most series, the most common histopathological diagnosis is FA, followed by adenomatous nodule/hyperplasia (follicular nodular disease), and much less frequently by FVPTC, NIFTP, and FTC. With the revised diagnostic criteria in the second and third editions of TBSRTC, however, it should be expected that the proportion of FVPTC and NIFTP would increase among cases diagnosed as FN. FA and follicular nodular disease account for approximately 40–45% and 30–35% respectively of the cases on follow-up [3–5]. The likelihood that the nodule is neoplastic (i.e., the risk of neoplasia, RON) is 65–75%, while the ROM is significantly lower (see section above "ROM," and Chap. 1: Tables 1.2 and 1.4) [3–5, 9, 33].

Management

According to the 2015 American Thyroid Association management guidelines, surgical excision (lobectomy) is the long-established standard of care for this diagnosis [2]. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery; informed patient preference and feasibility should be considered in clinical decision-making [2]. The extent of surgery may be expanded if the molecular testing results are considered high risk for malignancy. Conversely, a conservative approach could be chosen in patients who do not want surgery if the molecular data are of low suspicion for malignancy. Geographic variations on the use of molecular testing exist depending on availability and preferences; for example, in Japan, some FN cases are preferentially followed up without the use of molecular testing when a variety of triaging criteria/parameters (including ultrasonographic findings, tumor size, tumor volume doubling rate) suggest a low-risk FN (see Chaps. 13 and 14) [38].

Sample Reports

If an aspirate is interpreted as FN, it is implied that the sample is adequate for evaluation (i.e., an explicit statement of adequacy is optional). The general category FN is a self-sufficient interpretation and narrative comments that follow are optional; however, such comments are certainly suggested when there is concern for NIFTP/FVPTC. An educational note specifying the risk of malignancy for this interpretation, derived from the laboratory itself or from the literature, is optional.

Example 1
FOLLICULAR NEOPLASM.

Example 2
FOLLICULAR NEOPLASM.
Cellular aspirate of follicular cells with a predominantly microfollicular architecture, scattered isolated cells, and scant colloid. No nuclear features of papillary thyroid carcinoma are identified.

Example 3
FOLLICULAR NEOPLASM.
Cellular aspirate of follicular cells with a predominantly microfollicular architecture, scattered isolated cells, and scant colloid.
Note: Although the cytologic features are in keeping with a follicular neoplasm (FN), approximately 30% of cases diagnosed as Follicular Neoplasm (Bethesda IV) on FNA turn out to be benign follicular nodular disease on surgical resection. Potential histologic follow-up on resection include most commonly follicular adenoma, and less commonly (in decreasing order of frequency) hyperplastic nodules, follicular thyroid carcinoma, and much less likely NIFTP or FVPTC.

Example 4
FOLLICULAR NEOPLASM.
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 indolent counterpart, NIFTP; definitive distinction among these entities is not possible on cytologic material.

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

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