Thyroid

13

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Contents

Frequently Asked Questions

1. How is thyroid FNA used as a screening test for clinically or ultrasound-detected thyroid nodules?

As:

The prevalence of thyroid nodules is high in the general population, up to 50–60% [1]. However, the malignancy rate is only 5% [1]. The fine needle aspiration (FNA) serves as a minimal invasive test and as a gatekeeper for further management, as well as to select the appropriate surgical candidates. Based on ultrasonography (US), the thyroid nodules are categorized into three groups: low malignancy risk, intermediate malignancy risk, and high malignancy risk. The current American Thyroid Association (ATA) guidelines recommend FNA of thyroid nodules that are >10 mm diameter and lack of suspicious US and/or clinical findings but are not completely benign appearing (intermediate US risk thyroid nodules). FNA should be considered in thyroid nodules 5–10 mm diameter only when suspicious US signs are present (high US risk thyroid lesions). It is recommended that thyroid nodules <5 mm should be monitored with US (Table 13.1).

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2. What are the key procedure steps of thyroid aspiration and slide preparation?

As:

The FNA remains the gold standard for evaluation of thyroid nodules. The thyroid aspiration can be performed under ultrasound or palpation guidance. Ultrasound-guided thyroid fine needle aspiration can reduce the unsatisfactory rate, especially for those thyroid nodules with the following features, such as non-palpable, cystic, or unsatisfactory from previous aspiration. Aspiration nodules less than 1 cm are not recommended unless with suspicious features such as microcalcifications or lesion with heterogeneous cystic component (>25%) [3].

The key steps of the aspiration techniques are the same in both palpated and US-guided procedure. The skin should be cleaned by alcohol swab. Local anesthesia with lidocaine is optional. Regarding the aspiration needle, guidelines recommend the small size 25- or 27-gauge needle to avoid damaging the vessels. The needle should not go through gel if under US guidance; otherwise, it will interfere the cytomorphology. The aspiration can be performed with or without suction according to patient's condition and operator's preference and depending on the nodule structure and vascularization. When using suction, it should be released before the needle comes out. The number of aspiration needle passes varies, depending on the nature of the lesion, the expertise of the performer, and the availability of on-site evaluation, usually 2–5 passes [4].

Based on individual practice setting, a variable number of smear slides are prepared for alcohol fixed Papanicolaou stained smears, H&E smears, or air-dried and Romanowsky-

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Table 13.1 US rating system of the risk of malignancy and the indications for US-guided FNA [2]

	US classification systems	US features	Risk of malignancy	Indications for US-guided FNA
Class I	Low-risk thyroid lesion	Isoechoic spongiform appearance Simple cyst with thin margins Mostly cystic (>50%) nodules with comet-tail sign (colloid) Regular "eggshell" calcification	1%	>20 mm and increasing in size or associate with a risk history and before thyroid surgery or minimally invasive ablation therapy
Class II	Intermediate-risk thyroid lesion	Isoechoic or hyperechoic nodule with hypoechoic halo Mild hypoechoic nodule with smooth margin Peripheral vascularization Intranodular macrocalcification	5–15%	>20 mm
Class III	High-risk thyroid lesion	Marked hypoechogenicity Spiculated or microlobulated margins Microcalcifications Taller-than-wide shape Evidence of extrathyroidal growth or pathologic adenopathy Intranodular vascularization and well-defined halo	50–90%	≥10 mm Thyroid incidentalomas detected by positron emission tomography (PET)

type stained smears. As an adjunct to the smears, rinsing the needle in the cyto-collection fluid to make a cell suspension is a common practice. The cell suspension solution can be used for liquid-based preparation (either SurePath or ThinPrep), and cytospin and cellblock preparation. Additional passes may be required to rinse in a second tube for molecular studies (e.g., the Afirma Gene Expression Classifier, ThyroSeq, and ThyGenX) [5].

The Papanicolaou stain is used in liquid-based cytology (SurePath and ThinPrep) slides and other conventional alcohol fixed slides. It usually gives better nuclear features, such as inclusions, grooves, and chromatin texture. The Romanowsky-type stain is used in conventional air-dried slides and allows better evaluation of extracellular material (colloid and amyloid) and cytoplasmic granules. In some labs, an H&E stain is used for conventional alcohol fixed slides too. The advantage of the H&E stain is that the cytomorphology is comparable to the routine histology stain.

For the key procedures/steps, please also refer to the clinical management guidelines.

Table 13.2 Compare the cytomorphological features of colloid in thyroid FNA with different stains

	PAP (smear)	DQ (smear)	H&E (smear or cellblock)
Colloid (thin/watery)	A thin layer of blue, light green, or pink amorphous material with linear cracking artifact, lost on touch-prep slide	A thin layer of pink to purple amorphous material with linear cracking artifact, lost on touch-prep slide	Thin pink homogenous material
Colloid (thick/dense)	Round- or irregular-shaped chips displaying cracking artifact on the side with blue color. Two-tone color (pink/orange in the central area and blue/purple on the edge)	Round- or irregular-shaped chips displaying cracking artifact on the side with homogeneous pink/purple color	Dense pink homogenous material

3. What are the cytomorphological differences of colloid among different staining methods in thyroid FNA?

As:

Colloid, a sticky fluid, is present at the core of a thyroid follicle. It is basically a collection of large glycoprotein – thyroglobulin. It is synthesized by thyroid follicular cells under the stimulation of thyroid-stimulating hormone (TSH). The texture and quantity of the colloid reflect the metabolism status of the thyroid gland and the nature of the thyroid nodule. The cytomorphological features (Table 13.2) and quantity of colloid are among the key diagnostic criteria to determine the nature of the FNA targeted thyroid lesion. In general, benign thyroid nodule has abundant colloid, and the texture can be thin, watery, or thick. Some of the follicular lesions have balls of inspissated (bubble gum)-like colloid. And most of malignant lesions have scant thick colloid.

4. What are the complications of thyroid FNA?

As:

There is no general contraindication for thyroid FNA. Universal precautions are necessary to prevent the complications of thyroid FNA. Patients need to be prescreened and

given prophylaxis if there is history of bleeding disorder, uncontrollable coughing, infectious disease, mental disorder, etc. Complications are uncommon. Subcutaneous transient hematoma, local tissue or thyroid swelling, abscesses formation, and post-aspiration thyrotoxicosis can occur in some patients. Other uncommon ones are infarction of the nodule, tracheal injury, and damage to the local nerve and blood vessels. Seeding of neoplastic cells along the needle track after aspiration is very rare, mostly seen in papillary carcinoma, followed by follicular carcinoma and anaplastic carcinoma. [6].

5. What is the diagnostic accuracy of thyroid FNA? What are the main factors to cause false positive and false negative diagnosis?

As:

The sensitivity of thyroid FNA ranges from 65% to 98%. And the specificity ranges from 72% to 100%. The recent application of ancillary molecular tests has significantly increased both sensitivity and specificity.

False positive diagnosis is usually caused by overinterpretation of reparative changes, especially in the background of chronic inflammation or changes related to previous biopsy. In a hypercellular specimen, benign papillary hyperplasia could be overcalled as papillary thyroid carcinoma. These will result in the increase of unnecessary surgical rates or total thyroidectomy surgical rates. The false positive rate ranges from 0% to 7%.

False negative diagnosis rate is about 1–11%. Inadequate sampling, poor sample collection, lack of options of ancillary molecular test, diagnostic error, and sampling error due to occult small lesion, or heterogeneous cystic lesion, are the main reasons.

6. What is the relationship between Bethesda diagnostic categories and risk of malignancy (%)?

As:

The Bethesda reporting system for classifying thyroid cytology was proposed in 2007 by Dr. Edmund Cibas and Dr. Syed Ali at the meeting hosted by the National Cancer Institute and provides diagnostic categories with accompanying risk stratification and recommended clinical management. This standardized reporting system improves the communication between laboratories, surgeons, radiologists, cytopathologist, and clinicians toward management of patient [7, 8]. In 2017, a revised version was published by adding new knowledge in recent thyroid research advancement. Two major changes are added. One is applying ancillary molecular testing to assist cytomorphological diagnosis. The other is reclassifying the noninvasive follicular variant of papillary thyroid carcinoma as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), to improve clinical management. In Table 13.3, the differences in risk of malignancy and recommended clinical management between 2010 and 2017 Bethesda System for Reporting Thyroid Cytopathology are listed.

7. What are the current ancillary studies available with thyroid FNA fluid specimen?

As:

The current ancillary studies include the following: thyroid hormone measurement on FNA washout (Table 13.4), immunocytochemistry (Table 13.5), and molecular testing [5].

The molecular testing in general is to complement, not replace, cytomorphological evaluation and to assist clinical

Table 13.3 The differences in risk of malignancy and recommended clinical management between 2010 and 2017 Bethesda System for Reporting Thyroid Cytopathology

Bethesda categories	Interpretation	Risk of malignancy (%) 2010	Risk of malignancy if NIFTP not CA (%) 2017	Risk of malignancy if NIFTP = CA (%) 2017	Decreased risk of malignancy after NIFTP reclassification (%)	Usual management 2010	Usual management 2017
I	Nondiagnostic or unsatisfactory	1–4	5–10	5–10	Not significant	Repeat FNA with US guidance	Repeat FNA with US guidance
II	Benign/negative	0–3	0–3	0–3	0.3–3.5	Clinical F/U	Clinical F/U
III	Atypical (AUS/FLUS)	5–15	6–18	10–30	5.2–13.6	Repeat FNA	Repeat FNA or molecular testing
IV	Follicular neoplasm or suspicious for a follicular neoplasm	15–30	10–40	25–40	9.9–15.1	Surgical lobectomy	Lobectomy or molecular testing
V	Suspicious for malignancy	60–75	45–60	50–75	17.6–23.4	Near-total thyroidectomy or surgical lobectomy	Near-total thyroidectomy or surgical lobectomy
VI	Malignant	97–99	94–96	97–99	2.5–3.2	Near-total thyroidectomy	Near-total thyroidectomy or surgical lobectomy

Adapted from Ali and Cibas [7, 9] with permission of Springer

Table 13.4 Utilization of hormone measurement in thyroid FNA washout

Hormone measurement	Indications	Comments
Thyroglobulin level	Recurrence of thyroid carcinoma s/p radical thyroidectomy Rule-out lymph node with metastatic thyroid carcinoma	*Fine needle aspiration thyroglobulin* (*FNA-Tg*) test increases FNA accuracy of lymph nodes which are suspicious for metastatic well-differentiated thyroid cancer Overall FNA-Tg sensitivity (95%) and specificity (94.5%) are good However the technique is not fully standardized and definite cutoff levels have not been validated
Calcitonin level	Clinical suspicion of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2), screening lymph nodes with patients history of MTC	A diagnosis of MTC is highly indicated when the elevation of calcitonin is >100 pg/ml. The degree of calcitonin elevation correlates well with tumor volume.
Parathyroid hormone (PTH) level	Rule-out parathyroid adenoma	It has not been validated and definite cutoff values have not been established

Table 13.5 Utilization of immunocytochemistry (ICC) studies on thyroid FNA cellblock and smears

ICC studies	Indications	Comments
Markers include galectin-3, HBME-1, fibronectin-1, CITED-1, and cytokeratin-19	Differentiate thyroid lesions from nonfollicular origin (e.g., parathyroid gland, medullary thyroid carcinoma, lymphoma, metastasis from another organ origin)	These markers have not been adopted entirely to improve the DD of indeterminate nodules, due to absence of method standardization and overlap between follicular adenomas and differentiated thyroid carcinomas. The use of panels of IHC markers may reach a sensitivity and specificity of up to 90% if enough tissue is present in cellblock
PTH positive and TTF-1 negative	To confirm parathyroid gland origin	Need good quality of specimen
Positive: calcitonin, CEA, chromogranin, synaptophysin, TTF-1, and Congo red (amyloid component) Negative: thyroglobulin	To confirm medullary thyroid carcinoma	Need good quality of specimen
Lymphoma IHC panel	To confirm and classify lymphoma	Need good quality of specimen

management. It is not recommended in benign and malignant nodules with characteristic cytomorphological features. The uncertainty of incidental thyroid nodules (ITNs) can be resolved by molecular tests that are able to rule-in or rule-out malignancy. This ability to rule in and rule out depends on the test's PPV and NPV. BRAF, RET/PTC, PAX8/PPARG, and RAS mutations are often used to detect mutations in cytological indeterminate nodules. $BRAF^{V600E}$ is almost 100% PPV for papillary thyroid carcinoma. In Table 13.6, common mutations associated with thyroid neoplasia are listed.

One of the most exciting advancements in molecular studies is applying clinical utilization of next-generation sequencing platform (Table 13.7) [5].

8. How will changes in the new 8th edition AJCC cancer staging manual potentially affect our cytology reporting?

As:

In the 8th edition AJCC staging book [11, 12], the pN0 designation is clarified as one or more cytologically or histologically confirmed benign lymph node(s). This requisite will result in an increase in neck lymph node FNA or thyroid bed lymph node FNA for restaging. The challenge or the pitfall will be to differentiate between a metastatic tumor deposit and residual normal thyroid follicles, chronic thyroiditis versus metastatic lymph nodes, and normal parathyroid gland cells. Therefore, a definitive cytology diagnosis is important for further staging of the resected surgical specimen.

9. Can we diagnose NIFTP in thyroid cytology?

As:

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a recently proposed terminology for thyroid neoplasms which used to be called noninvasive encapsulated follicular variant of papillary thyroid carcinoma (PTC) [13].

The Endocrine Pathology Society performed a 10–25-year clinical follow-up study for patients with NIFTP diagnosis. This clinical study shows that this tumor has very low risk of recurrence and nodal metastasis. More conservative therapy like lobectomy only is recommended.

The diagnostic criteria for NIFTP are as follows:

- Encapsulation or clear demarcation.
- Follicular growth pattern with <1% true papillae formation; no psammoma bodies; <30% solid/trabecular /

Table 13.6 Common mutations in thyroid neoplasia [10]

	PTC, classical and tall cell	PTC, follicular variant	Follicular carcinoma	Poorly differentiated carcinoma	Anaplastic carcinoma	Follicular adenoma
BRAF V600E	+++			+	+	
BRAF K601E		+++	+			+
NRAS		+++	++	+	+	++
HRAS		++	+			+
KRAS	+	++	+			++
PTEN			+			++
TSHR			+			++
GNAS						++
RET/PTC	++ (PTC1/CCD6)					+ (PTC3/ NCOA4)
PAX8/PPARG		++	+++			+
ALK FUSIONS	+	+		++	++	
BRAF FUSIONS	+	+				
ETV6/NTRK	++					
NTRK FUSIONS	++					

Note: Number of "+" indicates reported frequency ranges in genetic mutations

Table 13.7 Utilization of next-generation sequencing platform on thyroid FNA specimen

Next-generation sequencing	Indications	Comments
Afirma (Veracyte): Gene expression classifier (GEC) test based on microarray technology used to analyze the mRNA expression of 167 different genes	Good as "rule-out test" with a NPV of 95% (Bethesda III) and 94% (Bethesda IV) categories (if the test is "benign" in ITN category, the patient could be followed up clinically with no need for surgery) Hurthle cell lesion specificity is high (58.8%)	Lower performance in lesions of Bethesda V (suspicious for malignancy) category; the NPV is only 85%, leaving a 15% risk of malignancy Lower performance as a "rule-in" test with a PPV of 38% for Bethesda II and 37% for Bethesda IV categories
ThyroSeq v.2. (new expanded version of the original ThyroSeq): next-generation sequencing-based gene mutation and fusion panel of DNA alterations (14 genes and >1000 mutations) and RNA alterations (42 fusions, 16 genes)	In the lesions with pretest probability of malignancy (14–34%), ThyroSeq has shown a reported PPV of 83% and NPV of 96% suggesting that it may potentially function as both "rule-out" and rule-in" test for nodules with indeterminate cytology A detection of a mutation highly predictive of malignancy (BRAFV600E, TERT, TP53, PIK3CA, gene rearrangement) could direct patients toward total thyroidectomy	In the lesions with a low pretest probability of malignancy (5–15%), although ThyroSeq v.2. would remain an effective "rule-out" test (good NPV of 98–99%), a relatively low PPV (40–69%) would make it an unsatisfactory "rule-in" test in indeterminate nodules There is an increased chance of detecting "false positive" molecular abnormalities with the expanded NGS-based mutational profile
ThyGenX (thyroid oncogene panel): using a next-generation sequencing (NGS) platform to identify more than 100 genetic alterations across 8 genes associated with thyroid malignancy	Only cases with Bethesda III and IV categories are accepted for ThyGenX analysis	ThyGenX requires only one dedicated FNA pass (50 ng of cellular material) More recently used in combination with the ThyraMIR test
ThyraMIR: based on the analysis of 10 different microRNAs	In conjunction with ThyGenX when the ThyGenX result is negative	A combination of ThyGenX and ThyraMIR demonstrated a NPV of 94% (good rule-out test) and PPV of 74% (good rule-in test) When both ThyGenX and ThyraMIR tests are negative, the residual risk of cancer is very low (6%)

insular growth pattern; no tall cell, columnar, or cribriform-morular morphology; and no necrosis.

- Nucleus with 2 or 3 following features (1-enlarged and elongated nucleus, nuclear overlapping; 2-nuclear membrane with irregular contours, grooves, and pseudoinclusions; 3-chromatin clearing with margination and glassy nuclei).
- No vascular or capsular invasion.
- No high mitotic activity (<3 mitotic figures per 10 HPF).

- NIFTP are BRAF V600E mutation negative; instead they often have RAS mutations like follicular adenoma/carcinoma [14].

However, it is not possible to make a definitive cytologic diagnosis of NIFTP on cytology FNA specimens. Studies show that NIFTP tumors have been diagnosed as all six categories of the Bethesda System for Reporting Thyroid Cytopathology. But most of them are clustered in the indeterminate categories: atypia of undetermined significance/follicular lesion of undetermined significance (BS III – AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (BS IV – FN/SFN), and suspicious for malignancy (BS V – SFM) [8, 15].

The cytologic features of NIFTP are as follows[16]:

- Groups of follicular cells showing nuclear crowding/overlapping
- Some of the PTC nuclear features (1-enlarged and elongated nucleus, nuclear overlapping; 2-nuclear membrane with irregular contours, grooves, and rare pseudoinclusions; 3-chromatin clearing with margination and glassy nuclei)

If the following cytologic features are noticed, a NIFTP diagnosis should be excluded:

- Papillary architecture, such as true papillae, branching groups, capillaries, or psammoma bodies
- Frequent intranuclear pseudoinclusions

The thyroid FNA is still a screening test. A NIFTP lesion should be suspected on a cytology FNA specimen with a predominantly microfollicular pattern and some nuclear features of PTC. The possibility should be raised on a cytology report. So far there is no consensus as to what Bethesda category a NIFTP should be assigned to. The best approach is to make a comment [17].

In the current guidance of the management of indefinite thyroid FNAs, the molecular testing for rule-in or rule-out NIFTP is not very helpful. It usually harbors similar mutations such as RAS or PAX8/PPARγ to other follicular lesions (follicular adenoma and follicular carcinoma). PTC-associated BRAF V600E mutations and RET fusions are usually absent. Patients most likely will receive hemithyroidectomy alone [18].

10. What are the clinical practice guidelines of thyroid nodules?

As: Since the Bethesda System for Reporting Thyroid Cytopathology is linked to a malignancy risk, the clinical management of thyroid nodules is directed by the thyroid cytology reporting with six Bethesda diagnostic categories. The current clinical practice guidelines are listed in (Table 13.8).

Table 13.8 Clinical management of thyroid nodules [19]

FNA Diagnosis	Clinical management
Nondiagnostic – **Bethesda category I**	If the nodule is solid, repeating the FNA with US guidance is recommended If repeat FNA is inadequate, performing a US-guided CNB is recommended If FNA inadequacy is persistent, surgery may be considered in a minority of solid nodules with favorable clinical and US features If the nodule is predominantly cystic (>50%) with benign clinical and US features, follow up with US
Benign – **Bethesda category II**	Clinical follow-up Repeat FNA only if clinically symptomatic, having suspicious clinical or US features, or in nodules with an increase >50% in volume Medical treatment is not recommended in general Consider surgery if there is presence of local pressure symptoms, having suspicious US features Percutaneous ethanol injection (PEI) for thyroid cysts and complex nodules with a large fluid components, relapsing benign cystic lesions Consider laser or radiofrequency ablation, if the nodules are solid or complex, progressively enlarge, symptomatic, or having cosmetic concern Consider radioiodine therapy for hyperfunctioning and/or symptomatic goiter, high-risk surgical candidate
Indeterminate lesions (low risk) – **Bethesda III (AUS/FLUS)**	Consider conservative management if the clinical criteria are favorable Repeat FNA and review with experienced cytopathologist CNB may be considered Routine use molecular markers for ancillary testing is under investigating
Indeterminate lesions (high risk) – **Bethesda IV (FN/SFN)**	Consider surgery for most of the lesions Thyroid lobectomy plus isthmectomy is recommended; total thyroidectomy may be performed depending on clinical setting and patient preference Consider close clinical follow-up in a minority of cases with favorable clinical and US features
Suspicious nodules – **Bethesda V**	Surgical treatment is recommended Repeat FNA in cases (such as anaplastic thyroid carcinoma, metastatic lesions, and thyroid lymphoma) with inadequate cellularity or require more cellular material for further diagnostic work-up (such as anaplastic thyroid carcinoma, metastatic lesions, and thyroid lymphoma) Intraoperative frozen section may be considered
Malignant – **Bethesda VI**	Surgical treatment is recommended in the case of differentiated thyroid carcinoma Preoperative evaluation of concomitant suspicious nodule or lymph node with FNA/B

Case Presentation

Case 1

Learning objectives:

1. To become familiar with cytologic features of benign thyroid cytology
2. To generate a differential diagnosis

Case history:

- A 31-year-old female was found left neck mass incidentally on regular physical examination. Imaging studies show a 3 cm left thyroid nodule with solid and cystic US features. The patient, otherwise healthy, did not have any other clinical symptoms.

Specimen source:

- Ultrasound-guided fine needle aspiration was performed on the left thyroid nodule. A Pap-stained smear and SurePath smear were made from the aspiration. Corresponding surgical resection specimen was obtained 6 months later.

Cytomorphological findings:

- Adequate cellular specimen.
- The follicular cells arranged in clusters with microfollicular and macrofollicular patterns (Fig. 13.1a, c).
- Some follicular fragments show three-dimensional structure.
- Some colloid and scattered macrophages are seen in the background (Fig. 13.1b, c).

Differential diagnosis:

- Benign follicular nodule
- Follicular lesion
- Papillary thyroid carcinoma

Cytology final diagnosis:

- Benign (Bethesda category II)

- Multinodular goiter with cystic degeneration

Histological findings:

- Benign hyperplastic nodule with pseudopapillary hyperplastic changes (Fig. 13.1d)

Take-home messages:

1. Benign follicular lesion usually presents with variable proportion of colloid, microfollicles and macrofollicles, and some scattered macrophages.
2. Increased degenerative changes, stromal fragments, and foamy macrophage suggest of lesion with cystic degeneration.
3. In some benign hypercellular nodules, decreased colloid and abundant follicular cells can be present. Most of the follicular cells form monolayers, rosettes, microfollicles, or three-dimensional structure (pseudopapillary hyperplastic changes), but with bland nuclear features and without PTC-like nuclear features (such as nucleus enlargement, overlapping, and pseudoinclusions).
4. Very low false negative rate (<3%).

References: [20, 21].

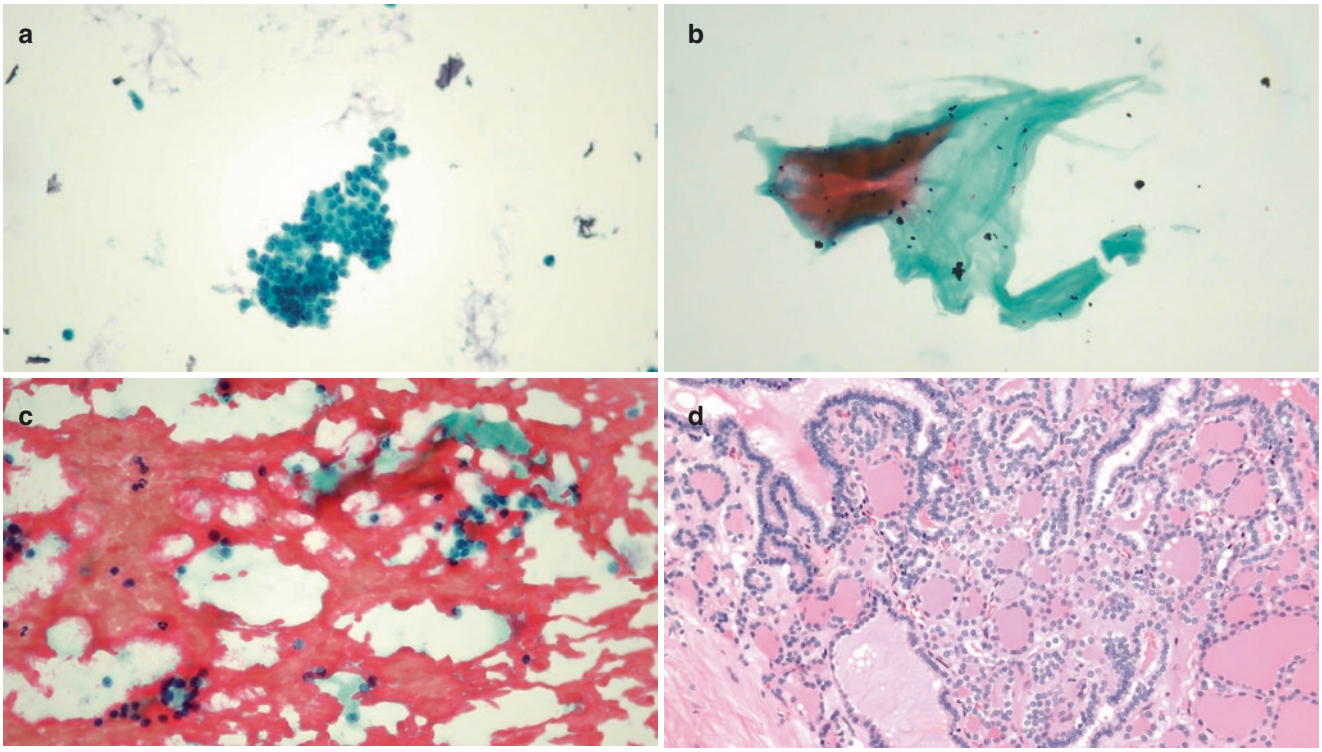

Fig. 13.1 Case 1. (**a**) Mixed microfollicles and macrofollicles (SurePath, Papanicolaou stain 400×). (**b**) Thin and thick colloid material (conventional smear, Papanicolaou stain 200×). (**c**) Mixed microfollicles and macrofollicles, some colloid and foamy macrophages (conventional smear, Papanicolaou stain 400×). (**d**) Benign hyperplastic thyroid nodule with focal papillary hyperplasia (histologic section, H&E stain 400×)

Case 2

Learning objectives:

1. To become familiar with the Bethesda System for Reporting Thyroid Cytopathology
2. To generate a differential diagnosis and recognize mimics of oncocytic follicular neoplasms
3. To become familiar with current clinical management guidelines

Case history:

- A 60-year-old male was found on imaging studies to have a 1.3 cm thyroid nodule in the right mid lobe. The patient, otherwise healthy, did not have any other clinical symptoms.

Specimen source:

- Ultrasound-guided fine needle aspiration was performed on the right thyroid nodule. A Pap-stained smear and SurePath smear were made from the aspiration. Corresponding surgical resection specimen was obtained 5 months later.

Cytomorphological findings (Fig. 13.2a–c):

- Hypercellular specimen with scant colloid.
- Follicular cells are arranged predominantly in microfollicular, trabecular, or syncytial sheet-like patterns.
- Some populations of microfollicles are arranged in crowded trabecular abnormal architectural groupings.
- Most of the follicular cells show oncocytic changes with finely granular cytoplasm, large and round central nuclei, and prominent nucleoli. Mild nuclear atypia and pleomorphism are noted.

Differential diagnosis:

- Hyperplastic proliferations of follicular cells in multinodular goiter
- Follicular lesions (follicular vs Hurthle cell)
- Chronic thyroiditis
- NIFTP
- Papillary thyroid carcinoma

Cytology final diagnosis:

- Follicular neoplasm or suspicious for a follicular neoplasm (Bethesda category IV)
- Hurthle cell (oncocytic) type

Histological Findings:

- Hurthle cell adenoma (Fig. 13.2d).
- There is no evidence of capsular or lymphovascular invasion.

Take-home messages:

1. The Bethesda category IV (follicular neoplasm or the synonymous term suspicious for a follicular neoplasm) is to identify a nodule that might be a follicular or Hurthle cell carcinoma and subject to surgical (lobectomy) follow-up. Distinction between a follicular adenoma and follicular carcinoma, which diagnostic criteria are based on capsular and/or vascular invasion, is not possible diagnosed on cytologic material.
2. It is important to differentiate the follicular lesions from the Hurthle cell lesions since they have different underlying genetics.
3. It is helpful to recognize the abnormal architectural patterns (predominantly single cells, syncytial-like sheets, and decreased colloid) which are suggestive of neoplasm instead of other benign mimics (e.g., Hurthle cell metaplasia in chronic lymphocytic thyroiditis and multinodular goiter).
4. If the lesion shows predominantly microfollicles and associated with mild focal nuclear changes, suspicious for FVPTC or NIFTP, it can be put in this Bethesda category.

References: [22–26].

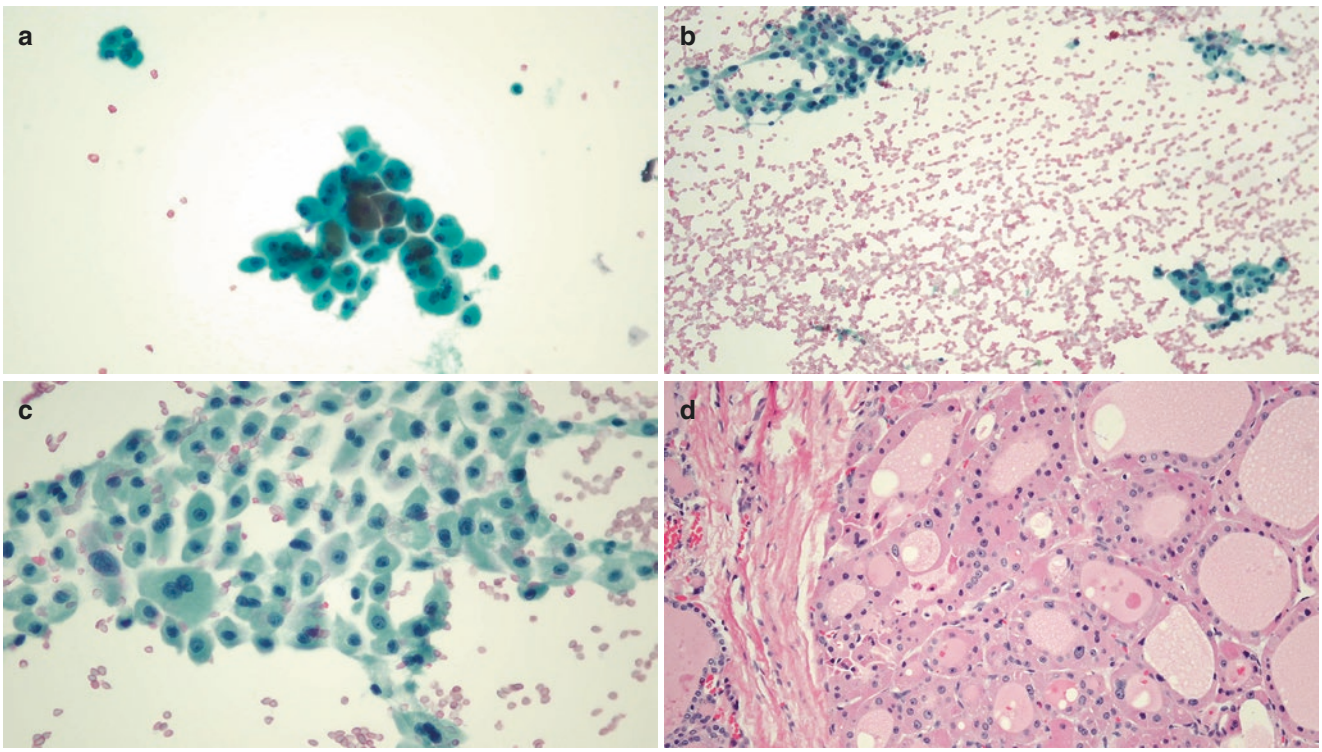

Fig. 13.2 Case 2. (**a**) Single and groups of Hurthle cells with predominantly microfollicular and trabecular patterns (SurePath, Papanicolaou stain 400×). (**b**) Some groups of the Hurthle cells show flat syncytial sheet-like pattern; other groups present slight overcrowded. Nuclei atypia and pleomorphism are present (conventional smear, Papanicolaou stain 200×). (**c**) Follicular cells form loose aggregate. The follicular cells show predominantly Hurthle cell changes with granular cytoplasm, well-defined cell border, centralized nuclei, and prominent nucleoli. Some cells show mild atypia with binucleation and nuclear pleomorphism (conventional smear, Papanicolaou stain 400×). (**d**) Hurthle cell adenoma, without capsular or vascular invasion (Histologic section, H&E stain 200×)

Case 3

Learning objectives:

1. To become familiar with the definition of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
2. To learn how to generate an appropriate cytologic diagnosis

Case history:

- A 61-year-old woman in whom an incidental thyroid nodule was detected on MRI. Ultrasound study showed that the nodule was 2.5 cm, mostly solid and replacing the right thyroid lobe. The left thyroid lobe was normal. The patient, otherwise healthy, did not have any other clinical symptoms.

Specimen source:

- Ultrasound-guided fine needle aspiration was performed on the left thyroid nodule. A Pap-stained smear and SurePath smear were made from the aspiration. Corresponding surgical resection specimen was obtained 6 months later.

Cytomorphological findings (Fig. 13.3a, b):

- The follicular cells form microfollicular groups with slightly enlarged nuclei, crowding and overlapping.
- The nuclear chromatin appears pale and has occasional grooves and pseudoinclusions.
- Three-dimensional papillary structures or psammoma bodies are not seen.

Differential diagnosis:

- Benign follicular hyperplasia
- Follicular adenoma
- Follicular variant of papillary thyroid carcinoma
- Classic variant of papillary thyroid carcinoma

Other ancillary study:

- BRAF mutation analysis: BRAF V600E mutation absent

Cytology final diagnosis:

- Suspicious for a follicular neoplasm (Bethesda category IV)
- 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.

Histological findings:

- The histologic sections of NIFTP at low power (Fig. 13.3c) and high power (Fig. 13.3d) show an encapsulated well-circumscribed lesion with no evidence of capsular invasion or invasion to the adjacent benign thyroid parenchyma. The lesion shows predominantly a microfollicular pattern, with no papillary architectures or psammoma bodies. The nuclear features are similar to those seen in a classic papillary thyroid carcinoma: nuclei are slightly enlarged or elongated, with nuclear crowding and overlapping, pallor chromatin, and irregular nuclear contour and/or grooves.

Final histological diagnosis:

- Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

Take-home messages:

1. Most noninvasive follicular variant of papillary thyroid carcinomas is reclassified as NIFTP after surgical resection with histologic evaluation of the entire tumor capsule. The difficulty lies in avoiding overcalling this tumor in the thyroid FNA specimen as Bethesda category VI (malignant). Indeterminate categories (atypia of undetermined significance BC III, follicular neoplasm or suspicious for a follicular neoplasm BC IV, and suspicious for malignancy BC V) are recommended for reporting potential NIFTP like thyroid cytology.
2. Ancillary BRAF mutation study is recommended if diagnostic cytologic material is available.

References: [8, 15, 16].

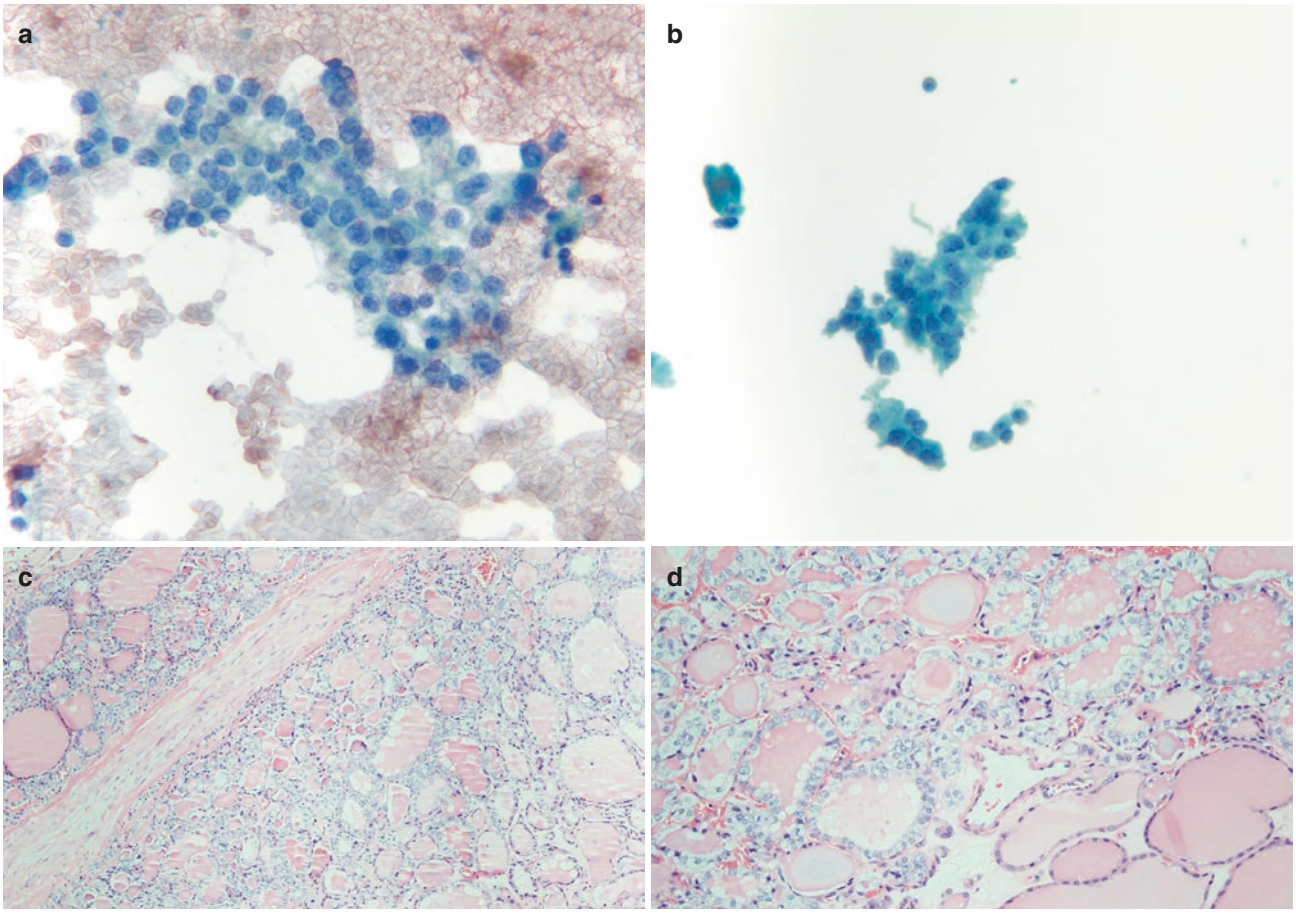

Fig. 13.3 Case 3. (**a**) Follicular cells form microfollicular groups with slightly enlarged, crowding, and overlapping nuclei. The nuclear chromatin appears pale with occasional grooves and pseudoinclusions. No three-dimensional papillary structures are seen (conventional smear, Papanicolaou stain 400×). (**b**) Follicular cells form microfollicular groups with slightly enlarged and overlapping nuclei. The nuclear chromatin appears pale. No true papillary structures are seen (SurePath smear, Papanicolaou stain 400×). (**c**) The lesion is encapsulated and well circumscribed. There is no evidence of capsular invasion or invasion to the adjacent benign thyroid parenchyma (histologic section, H&E stain 100×). (**d**) The lesion shows predominantly a microfollicular pattern, with no papillary architectures or psammoma bodies. The nuclei are slightly enlarged or elongated, with nuclear crowding and overlapping, pallor chromatin, and irregular nuclear contour and grooves (histologic section, H&E stain 200×)

Case 4

Learning objectives:

1. To become familiar with cytologic features of the thyroid carcinoma with neuroendocrine features
2. To generate a differential diagnosis

Case history:

- A 46-year-old male was found on imaging studies to have a 3.5 cm poorly defined right thyroid nodule. Further CT scan shows enlarged cervical lymph nodes.

Specimen source:

- Ultrasound-guided fine needle aspiration was performed on the right thyroid nodule. A Pap-stained smear and SurePath smear were made from the aspiration. Corresponding surgical resection specimen was obtained 1 month later.

Cytomorphological findings (Fig. 13.4a–e):

- Hypercellular specimen with scant colloid and some amorphous material which is positive for Congo red consistent with amyloid.
- Round or polygonal cells with mild pleomorphism form clusters, cords, or small follicles.
- Some of the tumor cells appear plasmacytoid and oncocytic with dense granular cytoplasm.
- The nuclei appear uniform round/oval with punctate chromatin.

Differential diagnosis:

- Benign adenomatous nodule
- Hurthle cell neoplasm
- Papillary thyroid carcinoma
- Medullary carcinoma of thyroid
- Metastatic neoplasm

Ancillary studies:

- Serum calcitonin is elevated.
- Positive IHC: calcitonin (Fig. 13.4e), TTF-1, chromogranin, and CEA.
- Negative IHC: thyroglobulin.
- Congo red staining is positive for amyloid component in the stroma.
- RET activation mutation is present.

Cytology final diagnosis:

- Malignant (Bethesda category VI)
- Medullary carcinoma of thyroid

Histological findings:

- Medullary carcinoma of thyroid.
- One lymph node is positive for metastatic medullary thyroid carcinoma (Fig. 13.4f).

Take-home messages:

1. The incidence of medullary thyroid carcinoma (MTC) is low, about 5–10% of all thyroid carcinoma. The tumor cell origin is the parafollicular cells or C-cells which produce calcitonin. About 90% of the MTCs are sporadic, and the rest have the background of familial genetic syndrome (such as MEN 2a, the Sipple syndrome). It is easy to miss the diagnosis if there is lack of clinical information of elevated serum calcitonin or no amyloid detected in the specimen. If cytologic features such as cord or nesting follicular cell groups with relative monomorphic nuclei and granular chromatin are present, a differential diagnosis of medullary thyroid carcinoma should be raised.
2. Sometimes normal follicular cells are entrapped in the lesion and can be sampled. The minor normal follicular component should not dissuade you including MTC as a differential diagnosis.
3. Ancillary studies such as immunohistochemistry studies and mutation analysis are helpful to characterize the lesion and confirm the diagnosis.

References: [27–31].

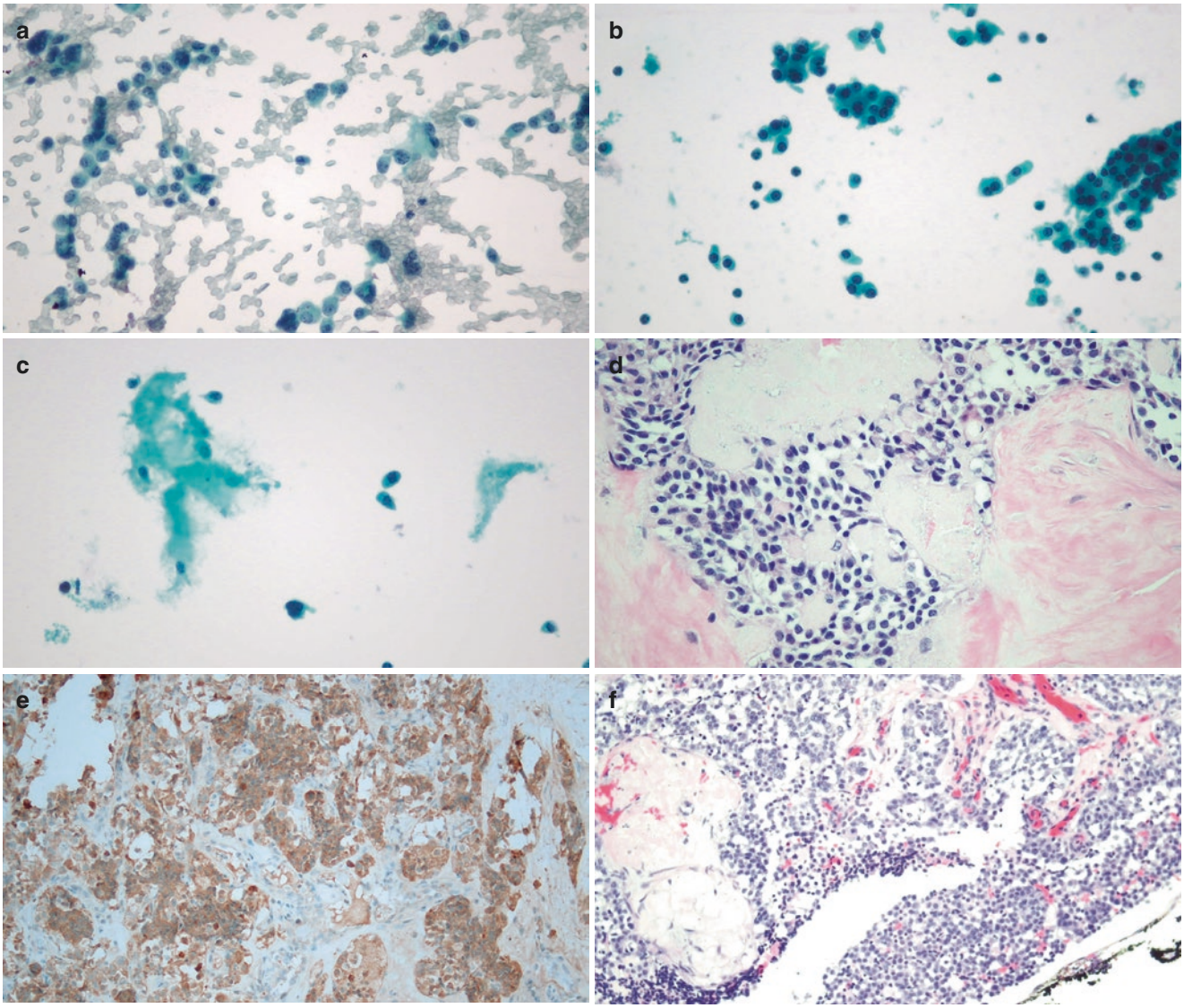

Fig. 13.4 Case 4. (**a**) Round or polygonal follicular cells with mild pleomorphism form clusters, cords, or small follicles (conventional smear, Papanicolaou stain 400×). (**b**) Some of the lesional cells appear plasmacytoid and oncocytic with dense granular cytoplasm (SurePath smear, Papanicolaou stain 400×). (**c**) Some of the lesional cells appear plasmacytoid and spindle. The nuclei are overall round/oval with punctate chromatin (SurePath smear, Papanicolaou stain 400×). (**d**) The cell-block shows pink amorphous material deposit in the stroma among the cords and ribbons of tumor cells. This material is positive for Congo red stain consistent with amyloid (histologic section, H&E stain 200×). (**e**) The lesional cells are positive for calcitonin immunostaining (histologic section, immunohistochemistry stain 200×). (**f**) Cervical lymph node is positive for metastatic medullary thyroid carcinoma. The tumor deposit shows similar cytomorphology as previous FNA specimen, fibrous band, and amyloid deposition are also noted (histologic section, H&E stain 100×)

Case 5

Learning objectives:

1. To become familiar with cytologic features of reactive atypia versus atypical malignancy
2. To generate a differential diagnosis of poorly differentiated thyroid tumor

Case history:

- A 59-year-old male was found on ultrasound to have a large heterogeneous but isoechoic right thyroid mass, more than 6 cm. The nodule showed minimal grade 2 peripheral vascular flow. No microcalcifications were noted. Otherwise, he was asymptomatic.

Specimen source:

- Ultrasound-guided fine needle aspiration was performed on the right thyroid mass. A Pap-stained smear and SurePath smear were made from the aspiration. Corresponding surgical resection specimen was obtained 1 month later.

Cytomorphological findings (Fig. 13.5a–c):

- Hypercellular specimen with scant colloid.
- Follicular cells are arranged in single and clusters; some groups have three-dimensional papillary structure.
- Most of the follicular cells are slightly enlarged; nuclear overlapping with pale, powdery chromatin; intranuclear pseudoinclusion; and nuclear groove. Follicular cells on some smear slides are predominantly singly and show slight pleomorphism, focal necrotic debris, and increased mixed inflammatory cells in the background.

Differential diagnosis:

- Chronic thyroiditis
- Papillary thyroid carcinoma
- Poorly differentiated carcinoma
- Lymphoproliferative disorder
- Metastatic carcinoma

Cytology final diagnosis:

- Malignant (Bethesda category VI)
- Poorly differentiated carcinoma

Histological findings (Fig. 13.5d):

- Poorly differentiated thyroid carcinoma with well-differentiated thyroid carcinoma component and areas of necrosis

Take-home messages:

1. When the cytological appearance is variable from field to field, or slide to slide, there is a possibility of different histologic patterns present in the same lesion.
2. When a greater degree of nuclear atypia or necrosis is present focally in a background of more differentiated carcinoma, poorly differentiated thyroid carcinoma component should be raised in the differential diagnosis.
3. Poorly differentiated thyroid lesion can be missed; our cytology report should alert the clinician to follow up with a surgical consult as the next step management as well as planning multimodality treatment.

References: [32–35].

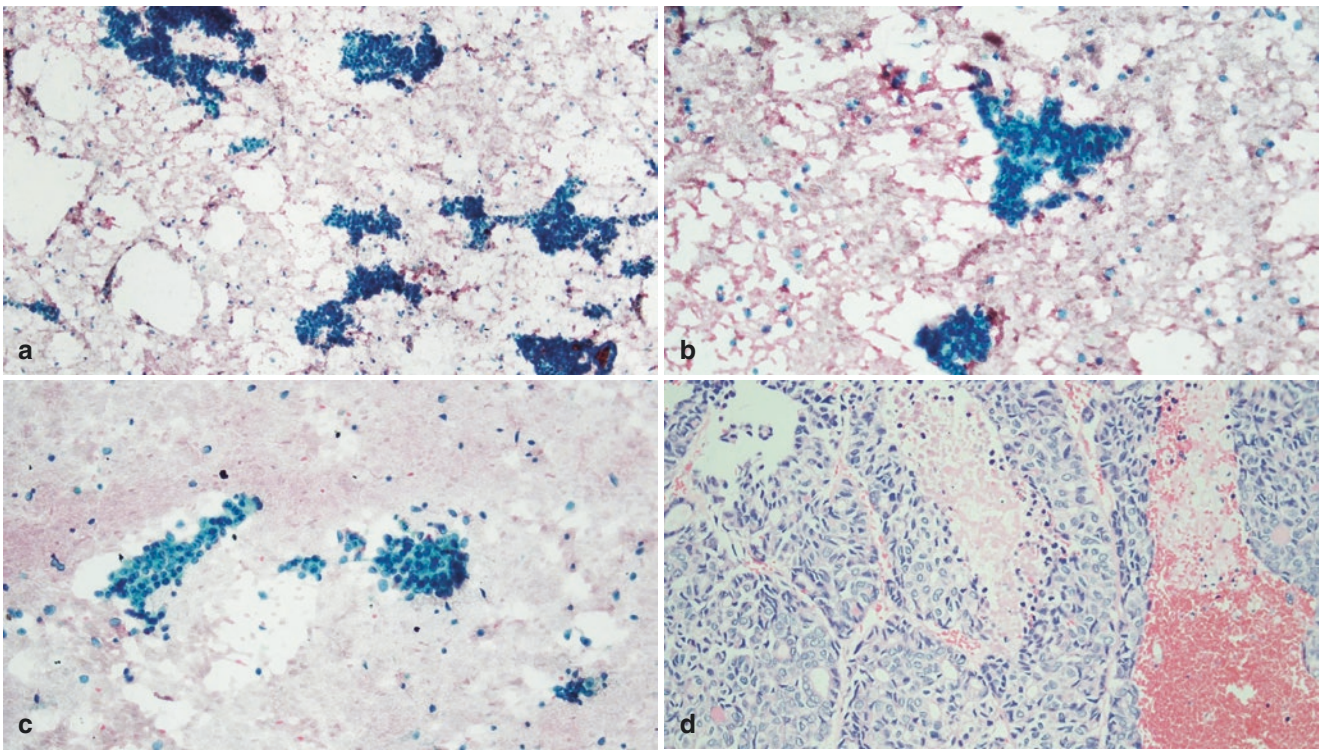

Fig. 13.5 Case 5. (**a**) Hypercellular specimen, follicular cells are arranged in single and clusters with trabecular and three-dimensional structures (conventional smear, Papanicolaou stain 100×). (**b**) Some follicular cells form three-dimensional papillary structure; the nuclei are slightly enlarged; overlapping with pale, powdery chromatin; pseudoinclusions; and nuclear groove (conventional smear, Papanicolaou stain 200×). (**c**) Follicular cells are either in loose aggregate or singly. Some cells show high N/C ratio and some degree of nuclear pleomorphism. Increased mixed inflammatory cells and cellular debris suggestive of necrosis are present (SurePath smear, Papanicolaou stain 200×). (**d**) Poorly differentiated thyroid carcinoma associated with necrosis and adjacent area with more differentiated papillary thyroid carcinoma coexist in this lesion (Histologic section, H&E stain 200×)

Case 6

Learning objectives:

1. To become familiar with cytologic features of the postsurgical and treatment-related changes and malignant tumor cell changes
2. To generate the differential diagnosis
3. To utilize ancillary studies in the cytologic diagnosis

Case history:

- A 48-year-old male with history of papillary thyroid carcinoma was status post total thyroidectomy, followed by radioactive iodine treatment. Posttreatment PET scan showed a thyroid bed mass with increased uptake around central left paratracheal area. The mass was about 1.1 × 1.0 cm. Serum test for thyroglobulin was elevated. A fine needle aspiration was performed on this mass lesion.

Specimen source:

- Ultrasound-guided fine needle aspiration was performed on the thyroid bed mass. A Pap-stained smear and SurePath smear were made from the aspiration.

Cytomorphological findings (Fig. 13.6a–d):

- Large sheets and three-dimensional groups of cells are present in a background of scattered histiocytes and small lymphocytes.
- Three-dimensional groups of lesional cells show crowed nuclei, nuclear membrane-bounded nucleoli, and pseudoinclusions. Psammoma bodies are present associated with the group of lesional cells.
- Cellblock tissue sections show fragments of lesional cells with typical cytologic features of papillary thyroid carcinoma.

Differential diagnosis:

- Parathyroid adenoma
- Reactive lymph node
- Reparative stromal tissue
- Lymph node with metastatic thyroid carcinoma
- Recurrent papillary thyroid carcinoma

Ancillary studies:

- BRAF V600E mutation is present.
- Thyroglobulin level is elevated in the FNA aspirate fluid.
- PTH is not detected in FNA aspirate fluid.

Cytology final diagnosis:

- Malignant (Bethesda category VI)
- Other: recurrent papillary thyroid carcinoma of the thyroid bed

Take-home messages:

1. FNA is a very important and practical diagnostic tool in monitoring changes in the thyroid bed for the recurrent thyroid carcinoma.
2. Clinical history is also very important to help us to reach the correct diagnosis. Changes induced by drugs, surgical or radiation treatments need to be included in the differential diagnosis.
3. Ancillary studies and aspiration fluid test for thyroglobulin and/or PTH are helpful.
4. The positive predictive value of thyroid bed FNA is very high in papillary and medullary thyroid carcinoma and less in follicular cell carcinoma.
5. False negative FNA results are usually due to low cellularity and lack of diagnostic tissue.

References: [36–38].

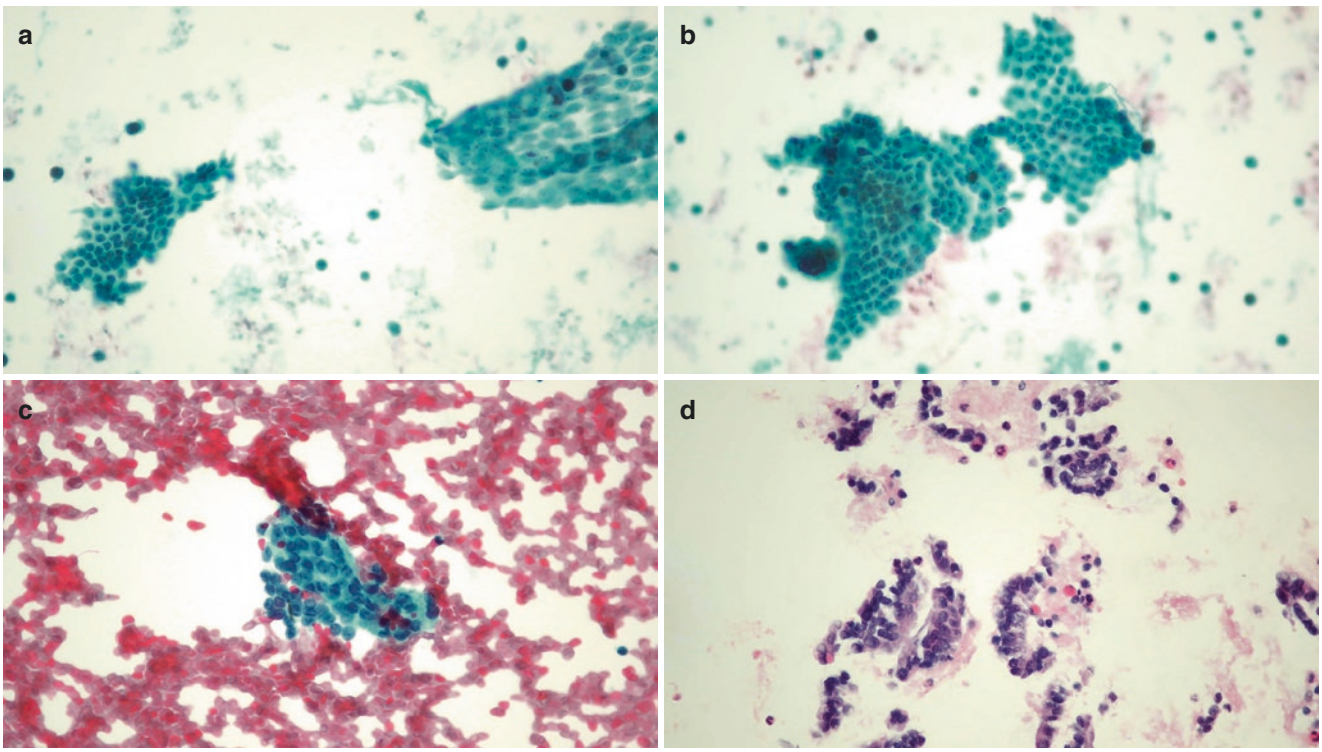

Fig. 13.6 Case 6. (**a**) Big sheets and three-dimensional groups of cells are present in a background of scattered histiocytes and small lymphocytes (SurePath smear, Papanicolaou stain 400×). (**b**) Follicular cells form three-dimensional papillary structure; the nuclei are slightly enlarged and overlapping. Psammoma bodies are present adjacent to the lesional cells (SurePath smear, Papanicolaou stain 400×). (**c**) Lesional cells form papillary structure, and the nuclei show overlapping, pseudoinclusions, and grooving (conventional smear, Papanicolaou stain 400×). (**d**) Aggregates of tissue fragments show partially fragmented papillae or epithelium lined by cuboidal cells with overlapping nuclei and clear chromatin consistent with papillary thyroid carcinoma (cellblock histologic section, H&E stain 400×)

Case 7

Learning objectives:

1. To become familiar with cytologic features of benign changes
2. To generate a differential diagnosis

Case history:

- A 53-year-old female was found on ultrasound to have a 4.9 cm mass/nodule in the posterior to left thyroid lobe. Serum test for PTH is elevated.

Specimen source:

- Ultrasound-guided fine needle aspiration was performed on the posterior left thyroid nodule. A Pap-stained smear and SurePath smear were made from the aspiration. Corresponding surgical resection specimen was obtained 2 months later.

Cytomorphological findings (Fig. 13.7a):

- Monomorphic lesional cells form microfollicular pattern.
- Scattered mixed inflammatory cells present in the background.

Differential diagnosis:

- Follicular lesion (follicular thyroid adenoma, parathyroid gland/adenoma)
- Reactive lymph node
- Lymph node with metastatic thyroid carcinoma

Ancillary studies

- PTH and calcium serum level is elevated.
- Thyroglobulin level is low.
- ThyroSeq v.2. study confirmed the presence of parathyroid follicular cells.

Cytology final diagnosis:

- Suspicious for a follicular neoplasm (Bethesda category IV)
- Favor parathyroid adenoma

Histological findings (Fig. 13.7b):

- Hypercellular parathyroid gland tissue consistent with parathyroid adenoma

Take-home messages:

1. It is challenging to distinguish parathyroid lesions from thyroid lesions. Based on characteristic cytologic features of parathyroid lesion, combined with clinical history, ancillary studies, or sestamibi scans, it is possible to reach the correct diagnosis.
2. Cytomorphology is important to generate the differential diagnosis. In this case, the FNA shows small uniform epithelial cells and some with oncocytic features and bare oval nuclei. The findings may represent parathyroid cells. However, the specimen is hypocellular. This interpretation cannot be confirmed without immunophenotyping or molecular studies. We feel that it is better to put this lesion in Bethesda category IV with a note. Surgical intervention is recommended.
3. Ancillary studies such as ThyroSeq v.2. and aspiration fluid test for thyroglobulin and/or PTH are helpful. Positive PTH and negative thyroglobulin confirm the diagnosis of parathyroid adenoma.

References: [39, 40].

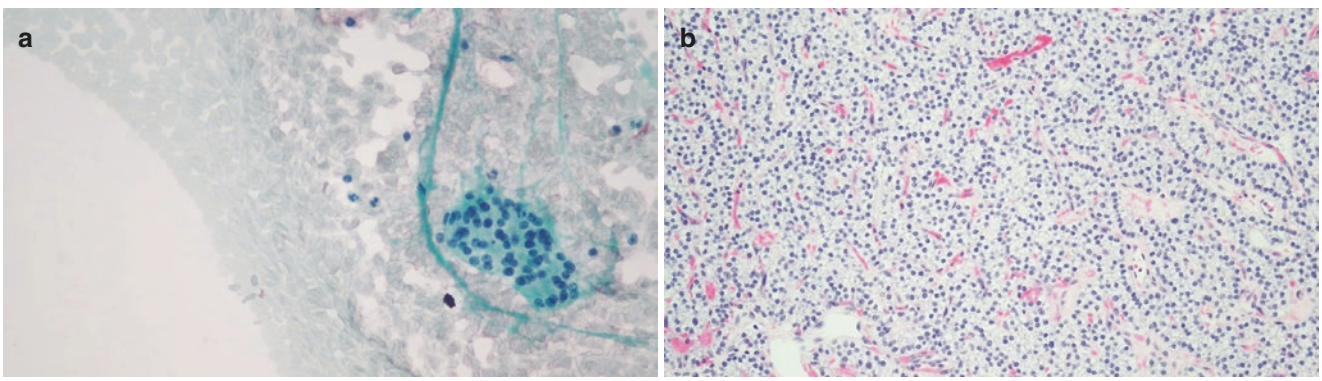

Fig. 13.7 Case 7. (**a**) Monomorphic follicular cells with microfollicular pattern (conventional smear, Papanicolaou stain 400×). (**b**) Hypercellular parathyroid gland tissue consistent with parathyroid adenoma (histologic section, H&E stain 200×)

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