Thyroid and Parathyroid Glands

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Summary of Pearls and Pitfalls

- Based on the *Bethesda System for Reporting Thyroid Cytopathology*, the terminology "follicular lesion" is no longer recommended in routine practice. Instead, a distinct subcategory of "Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance" (AUS/FLUS) was recommended.
- Focal nuclear pleomorphism of the follicular cells is frequently seen in a lymphocytic/Hashimoto's thyroiditis; one should avoid overdiagnosing this change as "Atypia of Undetermined Significance."
- When a fine-needle aspiration (FNA) smear is composed of a mixture of epithelioid and spindle cells singly and in loosely cohesive groups, and absence of colloid, regardless of the cellularity, a medullary carcinoma should be included in the diagnostic consideration.
- Hyalinizing trabecular neoplasm is an uncommon lesion and shares many important cytological features with papillary carcinoma of the thyroid, including nuclear grooves and intranuclear pseudoinclusions. When the follicular cells appear to be elongated and a hyaline matrix-like material between cellular components is present, it is necessary to exclude a hyalinizing trabecular neoplasm before a definitive diagnosis of papillary carcinoma is rendered. An immunostain for mindbomb E3 ubiquitin protein ligase 1 (MIB-1 clone[Ki-67]) with distinctive membranous staining pattern is useful in confirming the diagnosis.
- If abundant acute inflammation is present, in addition to an acute inflammatory process, undifferentiated (anaplastic) carcinoma of the thyroid should be included in the diagnostic consideration. Paired box gene 8 (PAX8) is positive in 50% of the tumors; in contrast, both thyroid transcription factor 1 (TTF1) and thyroglobulin are usually negative.
- The vast majority of cystic lesions of the thyroid are benign; however, cystic papillary carcinoma of the thyroid or metastatic squamous cell carcinoma with cystic degeneration may mimic a benign cystic lesion.
- Parathyroid adenoma/neoplasm should be excluded if colloid is absent and numerous small naked nuclei and vascular-rich stroma are seen. Clear cell or oncocytic changes are common.
- If the neoplastic cells are morphologically unlike follicular cells and colloid is absent in the background, a rare primary tumor or a metastasis should be considered. The most common metastases in the thyroid are renal cell (clear cell) carcinoma, melanoma, and adenocarcinoma of the lung, breast, and stomach.
- If a mixture of histiocyte-like cells and lymphoid cells is present, Langerhans cell histiocytosis, follicular dendritic cell tumors, and other rare histiocytic lesions should be considered.

Modified from the 2004 World Health Organization (WHO) Classification of Thyroid and Parathyroid Tumors[1]

Thyroid

Benign Nonneoplastic Lesions

- Acute thyroiditis
- Granulomatous thyroiditis/subacute thyroiditis

[1]Modified with permission from DeLellis RA, Williams ED. Tumors of the thyroid and parathyroid. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C, editors. WHO classification of tumours. Pathology and genetics tumours of endocrine organs. Lyon, France: IARC Press; 2004:49–136.

F. Lin et al., *Handbook of Practical Fine Needle Aspiration and Small Tissue Biopsies*, DOI 10.1007/978-3-319-57386-1_3

- Hashimoto's thyroiditis/lymphocytic thyroiditis
- Nodular goiter
- Graves' disease

Neoplasms

Follicular Neoplasms

- Follicular adenoma
- Follicular carcinoma

Hurthle Cell Neoplasms

- Hurthle cell adenoma
- Hurthle cell carcinoma

Other Neoplasms

- Papillary carcinoma
- Medullary carcinoma
- Poorly (insular) differentiated carcinoma
- Undifferentiated (anaplastic) carcinoma
- Hyalinizing trabecular neoplasm

Uncommon and Rare Lesions

Squamous cell carcinoma
Mucoepidermoid carcinoma
Sclerosing mucoepidermoid carcinoma with eosinophilia
Mucinous carcinoma
Spindle cell tumor with thymus-like differentiation
Carcinoma showing thymus-like differentiation
Lymphoma and plasmacytoma
Angiosarcoma
Smooth muscle tumor
Peripheral nerve sheath tumor
Solitary fibrous tumor
Follicular dendritic cell tumor
Langerhans cell histiocytosis
Teratoma
Ectopic thymoma
Second tumors

- Kidney
- Skin (melanoma)
- Lung adenocarcinoma
- Breast carcinoma
- Gastric adenocarcinoma
- Squamous cell carcinoma of the head and neck

Parathyroid

Parathyroid adenoma
Parathyroid carcinoma

The Bethesda System for Reporting Thyroid Cytopathology

FNA biopsy plays a crucial role in the assessment and triage of a thyroid nodule, and it has resulted in a significant reduction in unnecessary surgeries for patients with a benign lesion. However, some of the diagnostic categories and terminologies are inconsistent from one laboratory to another, which has created ambiguity and confusion among pathologists and clinicians. To clarify the potential misunderstanding and improve clarity of communication, the *Bethesda System for Reporting Thyroid Cytopathology* was introduced and published as an atlas in 2010. Six diagnostic categories and the associated risk of malignancy and recommended clinical management for each category were recommended as summarized in Table 3.1 below.

Perhaps the most important change was to introduce a distinct subcategory of "Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance." This subcategory of lesions was defined as cellular components (follicular cells, lymphoid cells, and others) with architectural and/or nuclear atypia that is not sufficient to be classified as suspicious for a follicular neoplasm/Hurthle cell neoplasm, suspicious for malignancy, or malignancy. Also, the atypia cannot be confidently classified as benign change. The risk of malignancy in this category is about 5–15%, and a repeat FNA in a reasonable interval was suggested.

Normal Thyroid

Colloid

Colloid is the key diagnostic component for thyroid disease. Colloid appears to be light blue or blue-purple on a Diff-Quik (DQ)-stained slide (Fig. 3.1) and light purple to pink on Papanicolaou (Pap) stain (Fig. 3.2). Comparing the two staining methods, colloid is easier to observe on DQ stain. In the presence of blood and the absence of follicular cells, thin colloid can be difficult to differentiate from serum. The finding of even few follicular cells is an important clue to confirm the presence of thin or watery colloid. In general, two types of colloid are seen: one is thin or watery colloid (Fig. 3.3) and the other is thick or inspissated colloid (Fig. 3.4). When watery colloid falls off the slide, it resembles a spider web (Fig. 3.5).

Table 3.1 Summary of the Bethesda System for Reporting Thyroid Cytopathology

Diagnostic category	Diagnosis	Risk of malignancy (%)	Recommended management
Non-diagnostic or unsatisfactory	Cyst fluid only [a]Virtually acellular specimen	–	Repeat FNA with ultrasound guidance
Benign	Benign follicular nodule Lymphocytic (Hashimoto's) thyroiditis Granulomatous thyroiditis	0–3	Clinical follow-up
Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance	Atypical follicular cells	5–15	Repeat FNA
Follicular neoplasm or suspicious for follicular neoplasm	Follicular neoplasm Hurthle cell neoplasm	15–30	Lobectomy
Suspicious for malignancy	Suspicious for papillary carcinoma, medullary carcinoma, metastatic carcinoma, lymphoma, and others	60–75	Lobectomy or near-total thyroidectomy
Malignant	Papillary thyroid carcinoma (PTC) Medullary thyroid carcinoma Poorly differentiated thyroid carcinoma Anaplastic thyroid carcinoma Squamous cell carcinoma Non-Hodgkin's lymphoma Metastatic carcinoma Others	97–99	Near-total thyroidectomy

Used with permission from Ali SZ and Cibas ES, editors. The Bethesda System for Reporting Thyroid Cytopathology. New York: Springer Science+Business Media; 2010

[a]In general, an adequate specimen should contain a minimum of six groups of well-visualized follicular cells with at least ten cells per group, preferably on a single slide, with the exception of these special circumstances: (1) colloid nodule, (2) solid nodules with cytologic atypia, and (3) solid nodules with inflammation such as lymphocytic thyroiditis or abscess

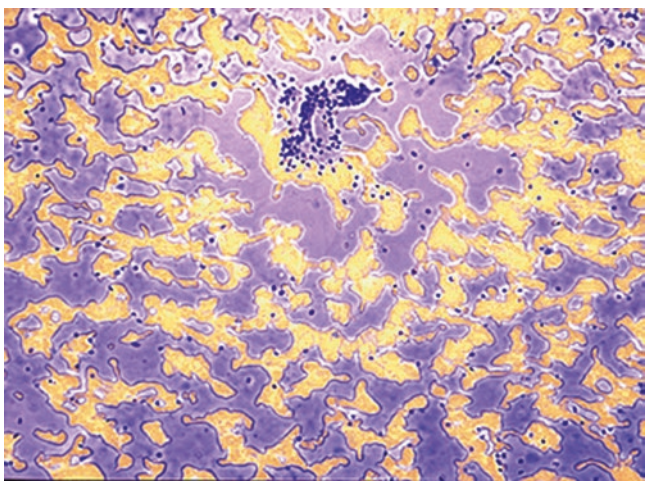

Fig. 3.1 Watery colloid on DQ stain

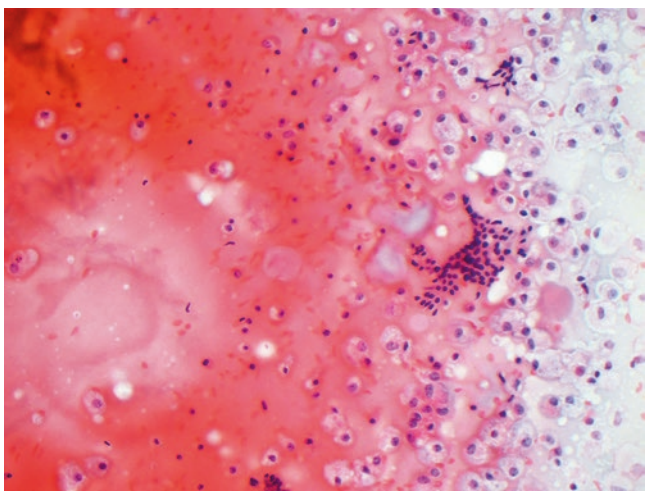

Fig. 3.2 Watery colloid on Pap stain

Follicular Cells

Follicular cells are cuboids and uniform in size, with a honeycomb arrangement. Nuclei are round, 6–9 um, with small to inconspicuous nucleoli, fine nuclear chromatin with even distribution, and a smooth nuclear contour (Fig. 3.6).

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Hurthle Cells

A subtype of follicular cells, slightly larger than normal follicular cells, with abundant granular cytoplasm, small to conspicuous nucleoli, and binucleation; they appear light purple on DQ stain and orange to pink on Pap stain (Fig. 3.7).

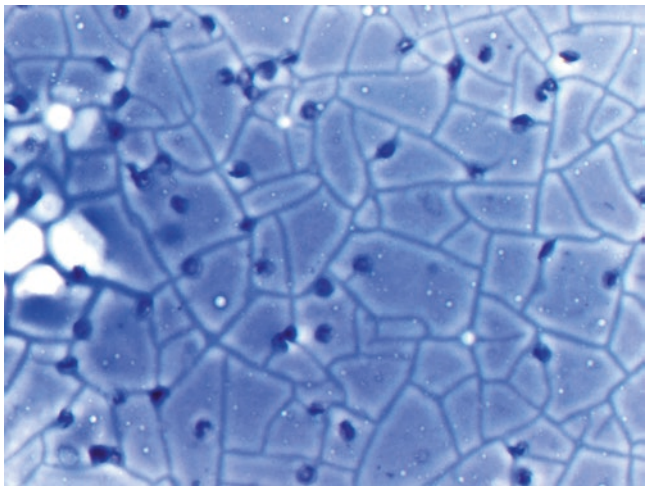

Fig. 3.3 Colloid on DQ stain with cracked glass window appearance

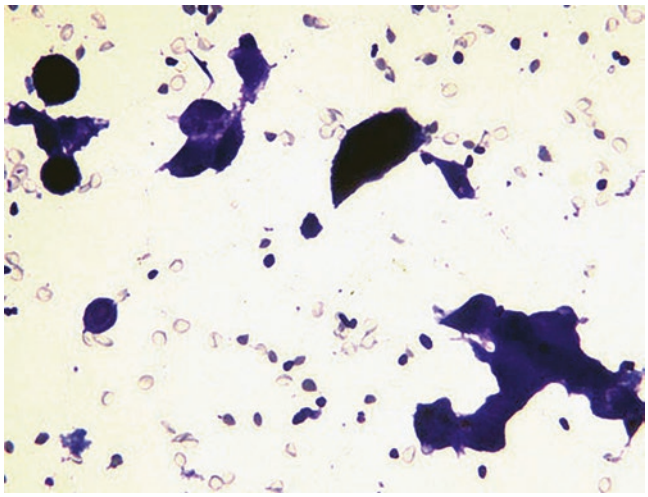

Fig. 3.4 Thick colloid with *dark blue* staining on DQ stain

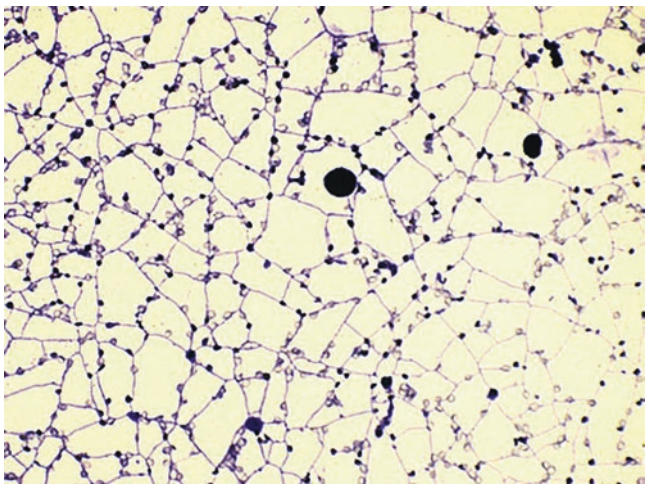

Fig. 3.5 Colloid fell off the slide, with spiderweb appearance on DQ stain

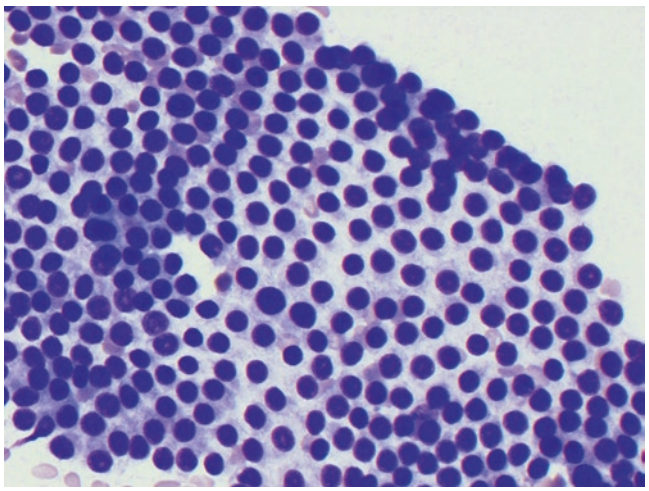

Fig. 3.6 Benign follicular cells with uniform size and orderly arrangement on DQ stain

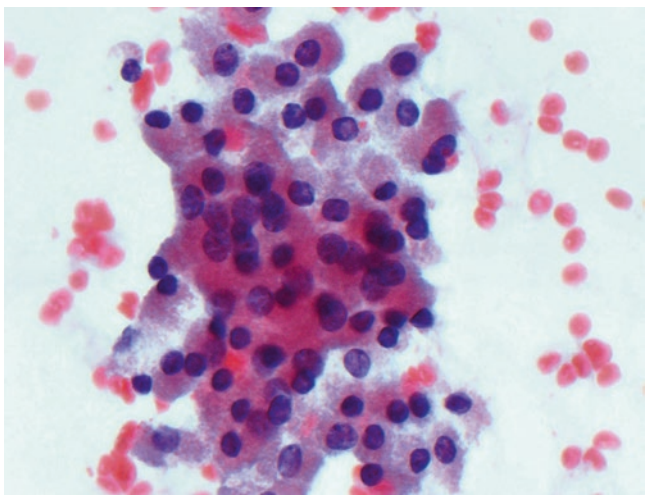

Fig. 3.7 Hurthle cells with large nuclei and abundant eosinophilic granular cytoplasm

Flame Cells

A subtype of follicular cells, with abundant cytoplasm with cytoplasmic fine vacuoles; they appear purple-pink on DQ stain (Fig. 3.8). They reflect the hyperfunctional status of the thyroid, such as in Graves' disease. They can be seen in nodular goiter and subacute thyroiditis as well.

Respiratory Epithelial Cells

During the aspiration procedure, the needle may accidentally enter the trachea, and the aspirate may contain respiratory epithelial cells (Fig. 3.9).

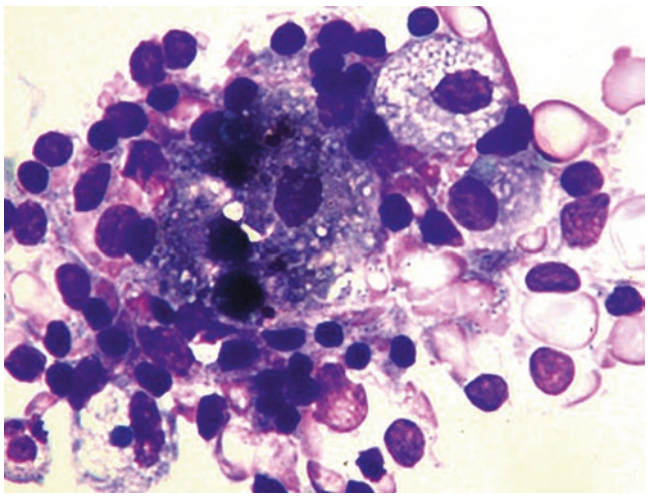

Fig. 3.8 Flame cells frequently seen in nodular goiter with hyperthyroid function

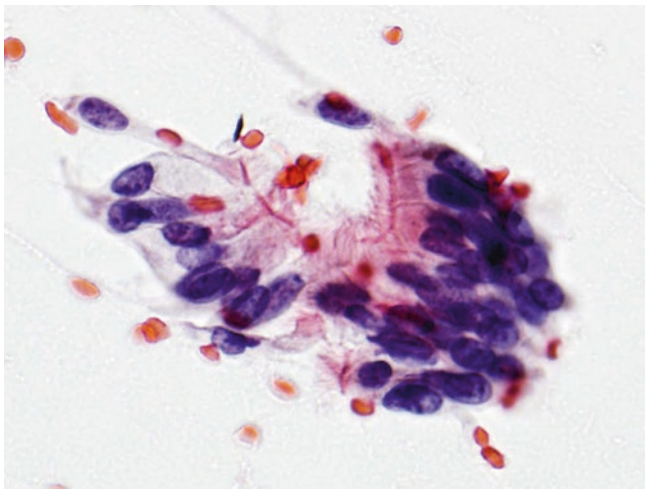

Fig. 3.9 Ciliated columnar respiratory epithelial cells when a needle accidentally enters the trachea

Benign Thyroid Lesions

Acute Thyroiditis

Clinical Features

- Rare, caused by bacteria and fungus.
- Fever and neck pain.
- Biopsy is generally unnecessary because of the obvious clinical presentation. If a nodular lesion is formed, then a neoplastic lesion, especially an anaplastic carcinoma, should be included in the diagnostic consideration.

Cytological Features

- Numerous acute inflammatory and histiocytes (Fig. 3.10a, b)
- Only few follicular cells
- Necrotic debris or granulomatous inflammation
- Fungus or bacteria can be seen on a special stain (Fig. 3.11)

Histologic Features

- Acute inflammation with abscess formation and tissue necrosis

Differential Diagnosis

- Anaplastic carcinoma

Granulomatous (de Quervain) Thyroiditis/ Subacute Thyroiditis

Clinical Features

- Caused by viral infection and a self-limiting process
- More common in young female
- Painful or painless diffuse thyroid enlargement

Cytological Features

- Granulomatous inflammation with multinucleated giant cells; some giant cells may engulf colloid.
- Many giant cells may contain many nuclei (many more nuclei than multinucleated giant cells seen in PTC).
- Acute and chronic inflammatory cells.
- Few follicular cells.

Histologic Features

- Usually multiple non-caseating granulomas associated with marked inflammation
- Granulomas containing foreign-body giant cells, which may engulf colloid (Figs. 3.12 and 3.13)
- Thyroid follicles surrounded by granulomas and inflammation
- Patchy fibrosis

Differential Diagnosis

- Tuberculosis
- Sarcoidosis
- Mycoses

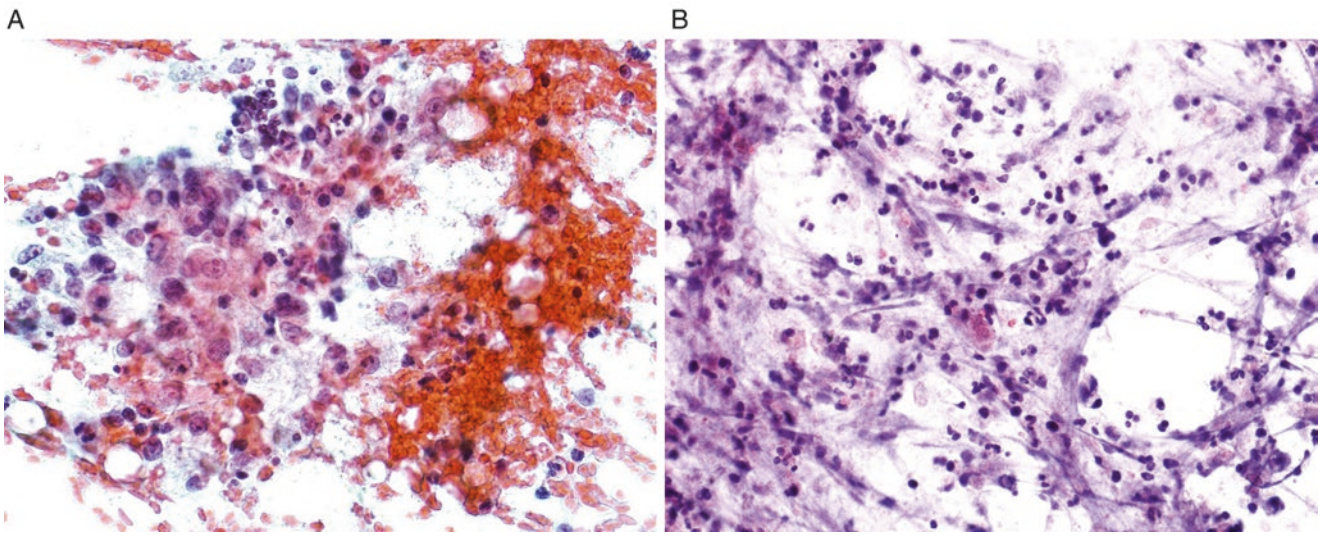

Fig. 3.10 Acute inflammatory cells, histiocytes, and necrotic debris in acute thyroiditis (Pap stain)

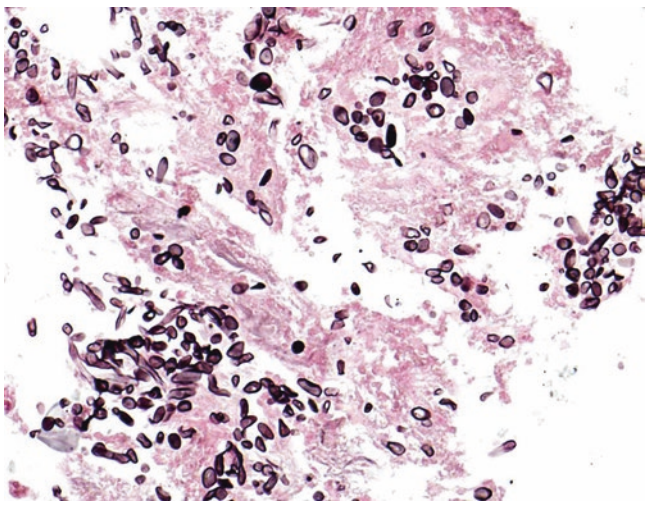

Fig. 3.11 Fungal elements in acute thyroiditis (Grocott's methenamine silver [GMS] stain)

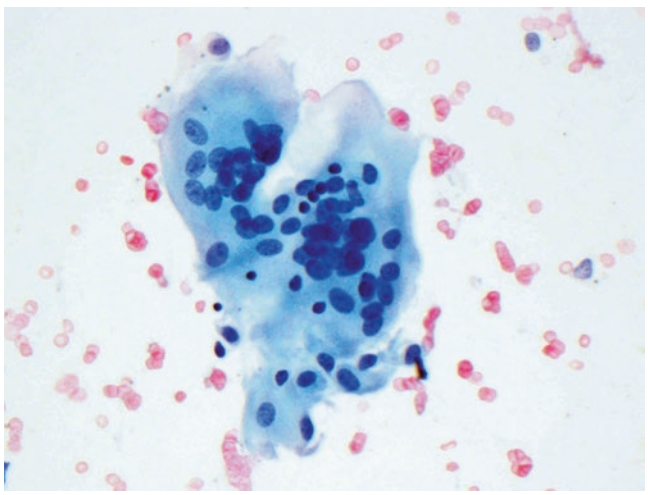

Fig. 3.12 A large multinucleated giant cell in subacute thyroiditis

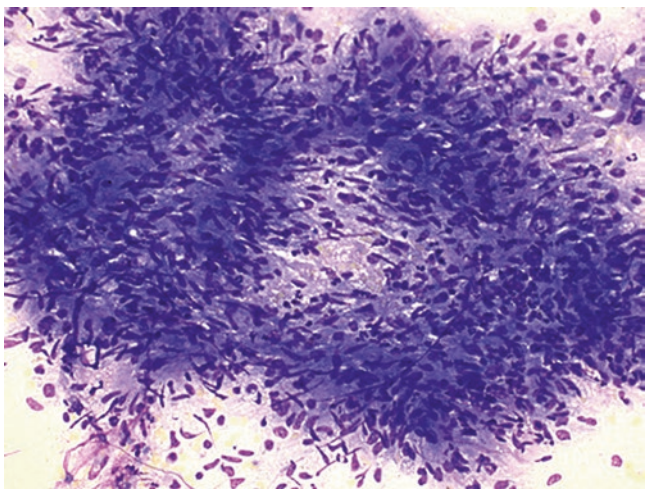

Fig. 3.13 Epithelioid histiocytes in chronic granulomatous inflammation (DQ stain)

Hashimoto's Thyroiditis/Lymphocytic Thyroiditis

Clinical Features

- An autoimmune-related disease.
- More common in middle-aged women.
- Present with firm and diffuse enlargement of the thyroid.
- Normal thyroid function in early stage and hypothyroidism in late stage.
- Serological tests are positive for anti-thyroglobulin, anti-mitochondrial antibody, and anti-oxidase antibody.

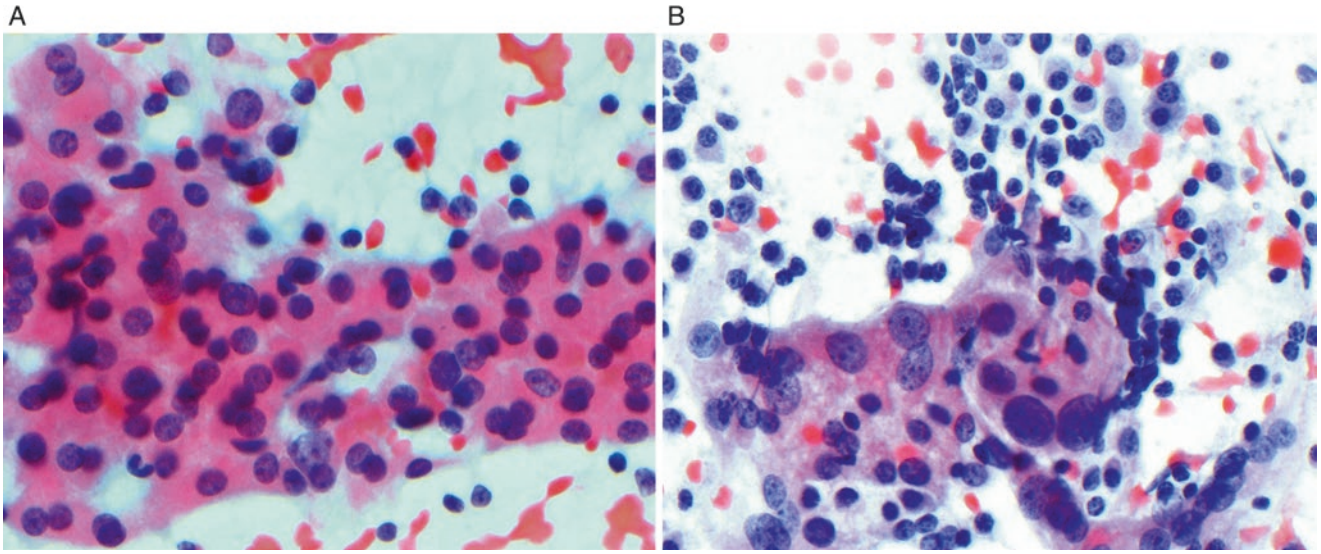

Fig. 3.14 Infiltration of lymphoid cells within Hurthle cells in Hashimoto's thyroiditis (Pap stain and DQ stain)

Cytological Features

- Infiltration of lymphocytes in Hurthle cells (Fig. 3.14a, b).
- Acute and chronic inflammatory cells with plasma cells.
- Multinucleated giant cells.
- Granulomatous inflammation.
- Reduced numbers of follicular cells dependent upon of the stage of the disease. It can be divided into three phases: (1) florid lymphoid phase, predominately a mixed population of lymphoid cells with sparse Hurthle cells and follicular cells; (2) cellular phase, proliferation of Hurthle cells; and (3) fibrotic phase, fibrotic tissue, scant Hurthle cells and lymphoid cells, and squamous cells (squamous metaplasia).
- Reactive atypical follicular cells/Hurthle cells; may mimic papillary carcinoma.
- May coexist with papillary carcinoma, especially papillary microcarcinoma.

Histologic Features

- Typically diffuse involvement of the thyroid both grossly and microscopically but can be a localized process with a distinct nodular involvement.
- Thyroid follicles with oncocytic changes and epithelial atrophy.
- Lymphoplasmacytic infiltration of the stroma with many large lymphoid follicles, which contain prominent germinal centers (Fig. 3.15a–c).
- Lymphoplasmacytic cells infiltrating oncocytic follicular cells.
- Lymphoid cells, plasma cells, histiocytes, and scattered granulomas.
- Patchy fibrosis or extensive fibrosis with dense hyaline-type collagens.
- Squamous metaplasia is common.
- Cystic formation may be present.
- Reactive atypical follicles, which may mimic PTC (Fig. 3.15d).

Immunohistochemistry

- Reactive oncocytic follicular cells may be positive for galectin-3 and Hector Battifora mesothelial epitope-1 (HBME-1) but usually negative for cytokeratin (CK) 19 and tumor-associated calcium signal transducer 2 (TROP2).

Differential Diagnosis

- Papillary carcinoma
- Hurthle cell neoplasm
- Lymphoma
- Riedel's thyroiditis

Nodular Goiter

Clinical Features

- The most common benign lesion
- More common in middle-aged women

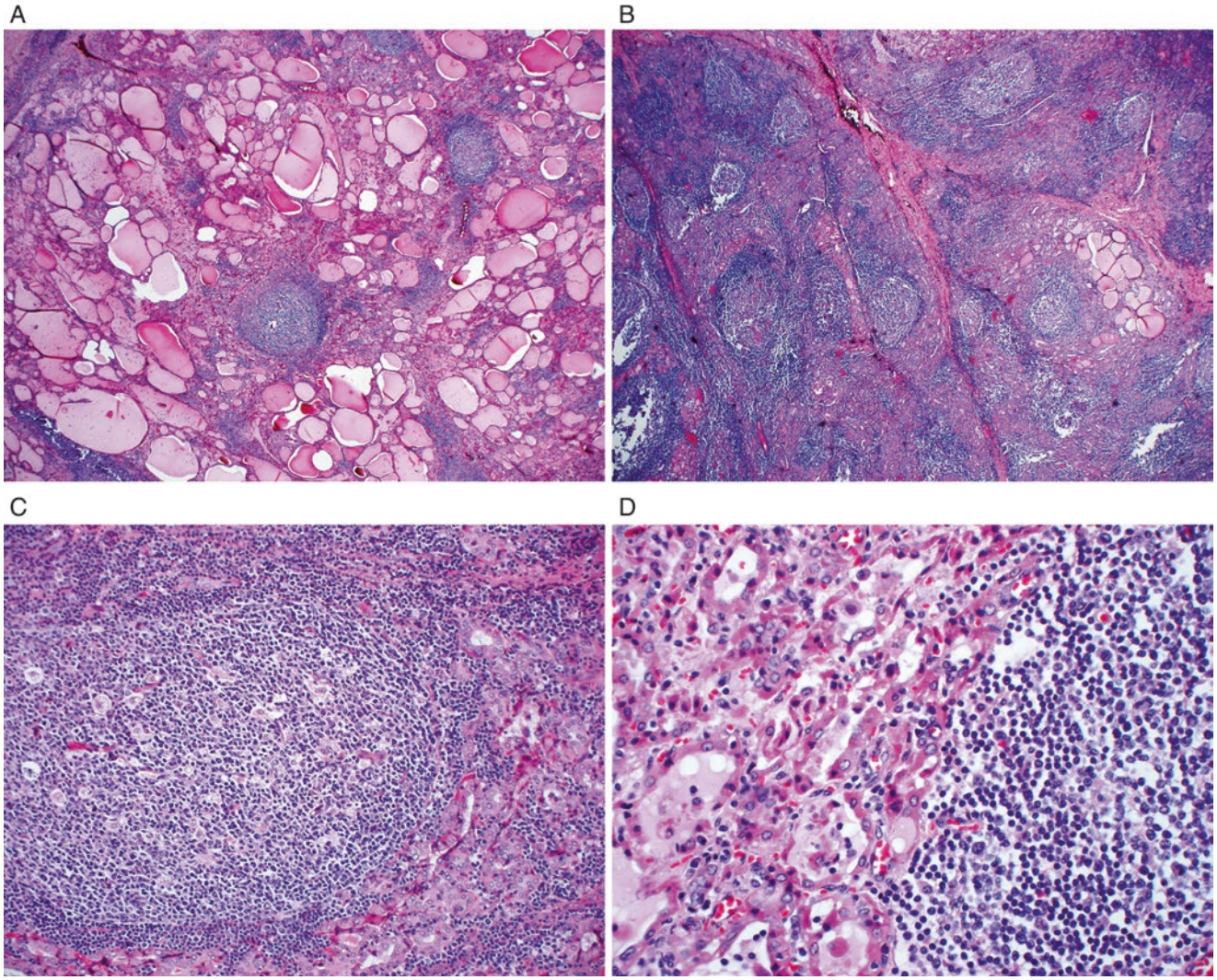

Fig. 3.15 Histologic sections of Hashimoto's thyroiditis with oncocytic follicular cells with lymphoid cell infiltration (**a**, **b**), prominent germinal center (**c**) and Hurthle cell/follicular cells with reactive atypia (**d**)

- Normal thyroid function; sometimes hyper- or hypothyroidism
- Goiter with multiple nodules

Cytological Features

- Abundant colloid and small amount of follicular cells (Figs. 3.16, 3.17, 3.18, 3.19, 3.20, and 3.21).
- Mixed population of follicular cells, Hurthle cells, and histiocytes.
- Pigment-laden histiocytes, foamy histiocytes, and stromal cells.
- Follicular cells are arranged in a honeycomb pattern with follicles of variable sizes.
- Focal reactive atypical follicular cells can be seen.

Histologic Features

- A wide spectrum of histologic changes can be seen (Fig. 3.22a–c).
- Multiple nodules, some surrounded by partial or even complete capsules.
- Huge follicles lined by flattened follicular epithelium, a mixture of follicles of variable sizes, cellular nodules with microfollicles, or cellular nodules with hyperplastic changes, including papillary formations.
- Focal or diffuse Hurthle cell changes.
- Secondary changes such as hemorrhage, cystic degeneration, fibrosis, calcification, or even ossification.
- Rupture of follicles with granulomatous reaction, foreign body-type multinucleated giant cells, and variable numbers of chronic inflammatory cells.

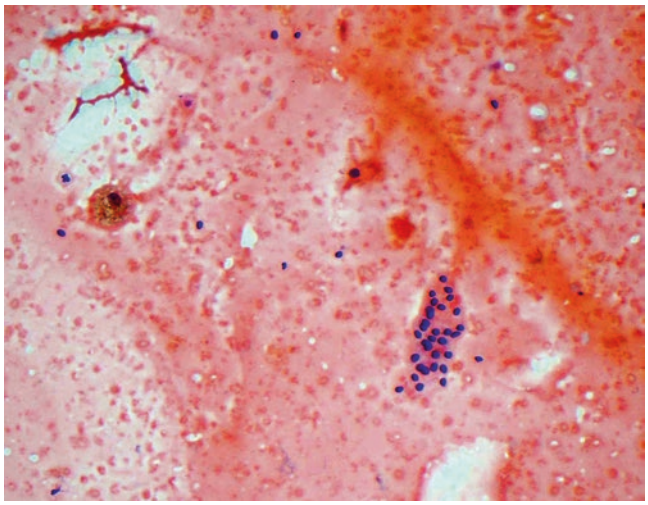

Fig. 3.16 Nodular goiter/hyperplasia with abundant watery colloid, benign follicular cells, and histiocytes (Pap stain)

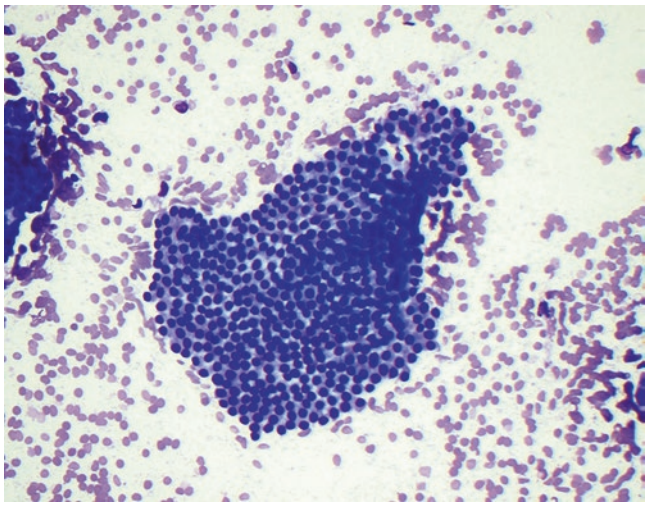

Fig. 3.17 Benign follicular cells in a nodular goiter/hyperplasia (DQ stain)

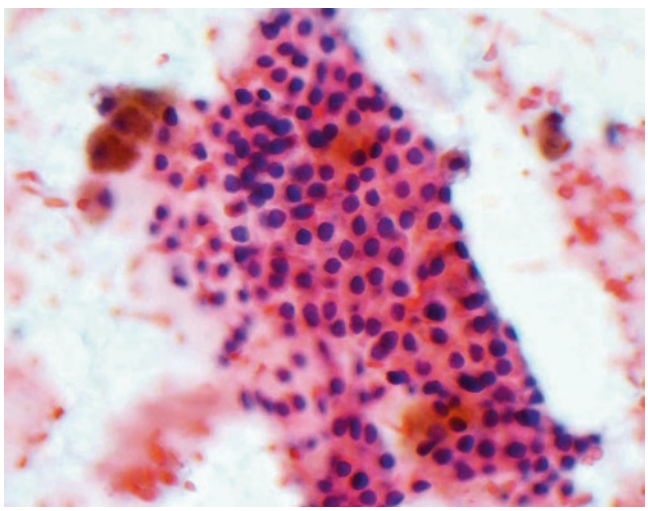

Fig. 3.18 Hurthle cells in a nodular goiter/hyperplasia (Pap stain)

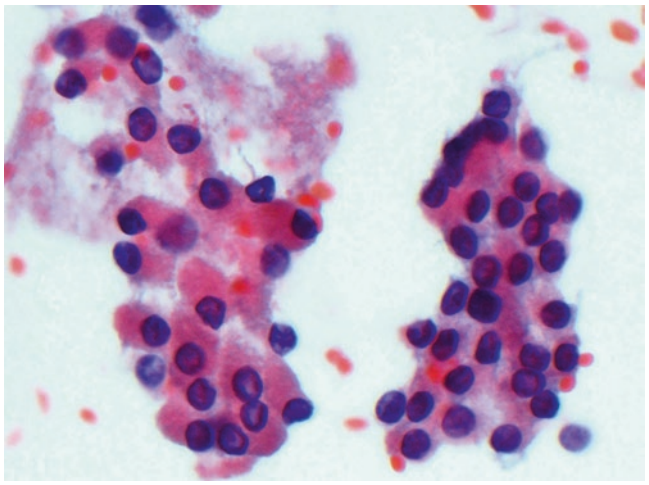

Fig. 3.19 Hurthle cells in a nodular goiter (Pap stain)

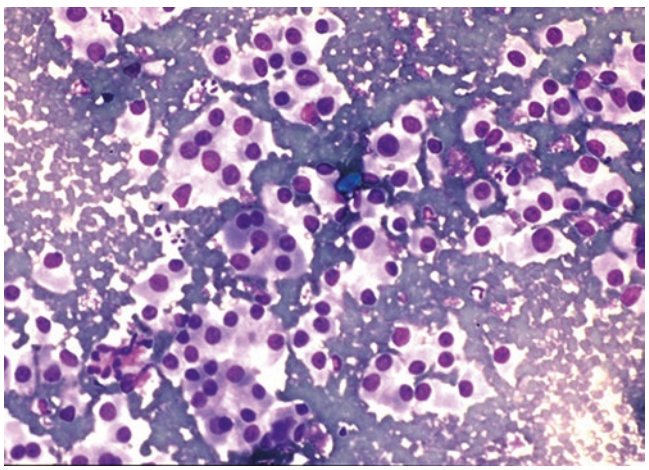

Fig. 3.20 Hurthle cells in a nodular goiter/hyperplasia (DQ stain)

Differential Diagnosis

- Follicular neoplasm
- Hurthle cell neoplasm
- Papillary carcinoma

Neoplastic Thyroid Lesions

Follicular Neoplasm

- Including follicular adenoma and follicular carcinoma

Follicular Adenoma

Clinical Features

- Common benign neoplasm
- More common in women
- Usually present with a solitary, well-circumscribed, mass

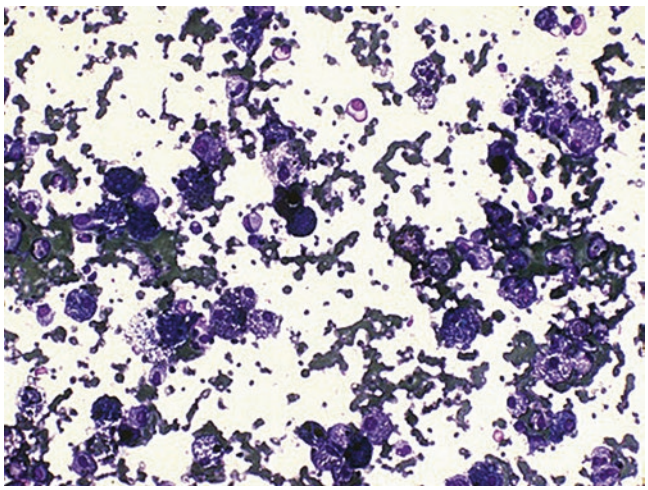

Fig. 3.21 Histiocytes in a nodular goiter/hyperplasia with degenerative change (DQ stain)

Cytological Features

- Hypercellular specimen with numerous groups of follicular cells and little or no colloid (Figs. 3.23 and 3.24).
- Microfollicular growth pattern (defined as 6–12 crowded follicular cells in a ring or rosette-like structure, with or without colloid in the center).
- Relatively uniform population of follicular cells without other types of cells, such as Hurthle cells and histiocytes.
- Follicular cells are enlarged in size with round nuclei.
- Focal nuclear atypia can be present.

Histologic Features

- A follicular nodule enclosed by a fibrous capsule of variable thickness (Fig. 3.25a).
- Absence of capsular or vascular invasion.

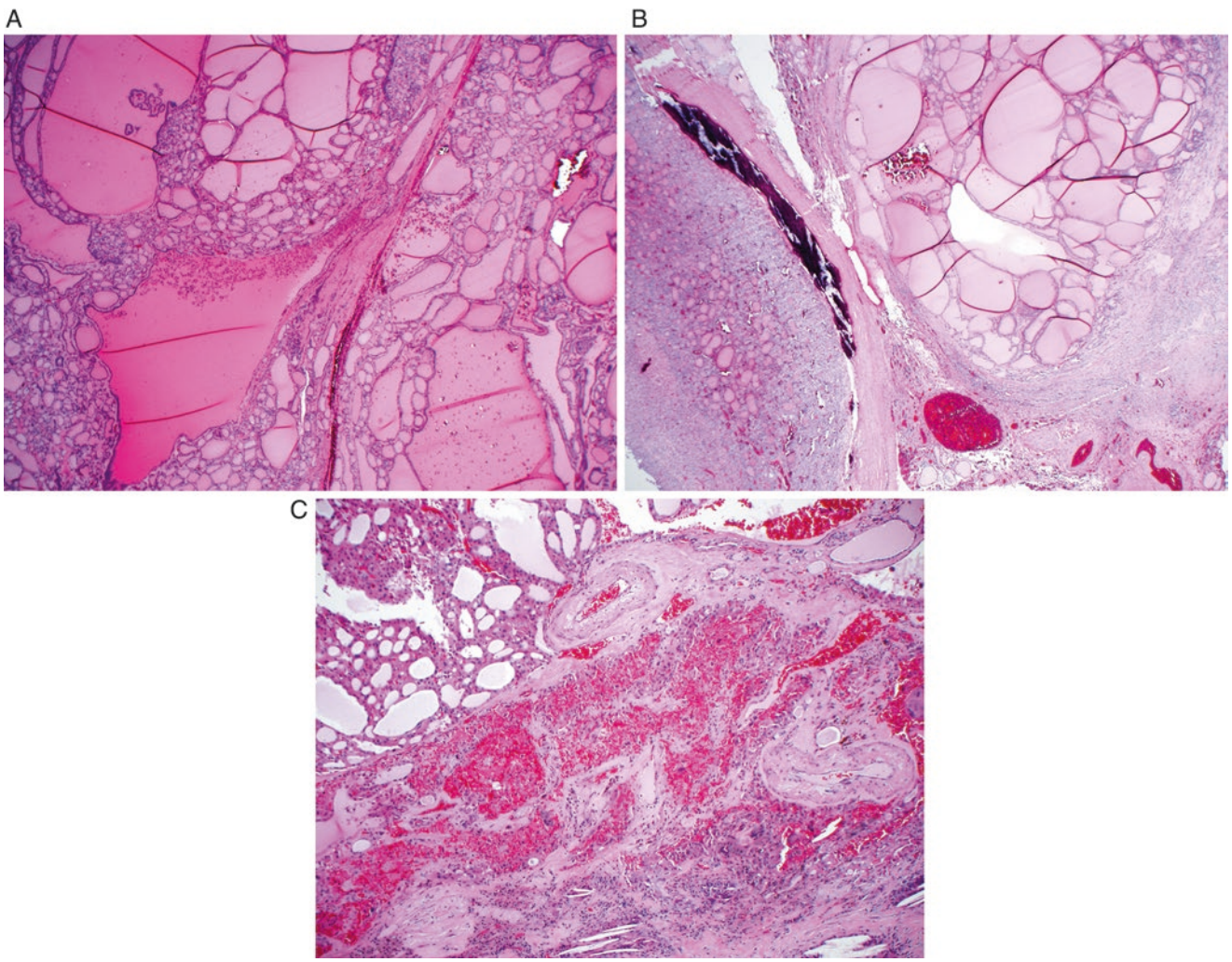

Fig. 3.22 Histologic sections of nodular goiter with Hurthle cells changes, calcification, and degenerative and regenerative changes

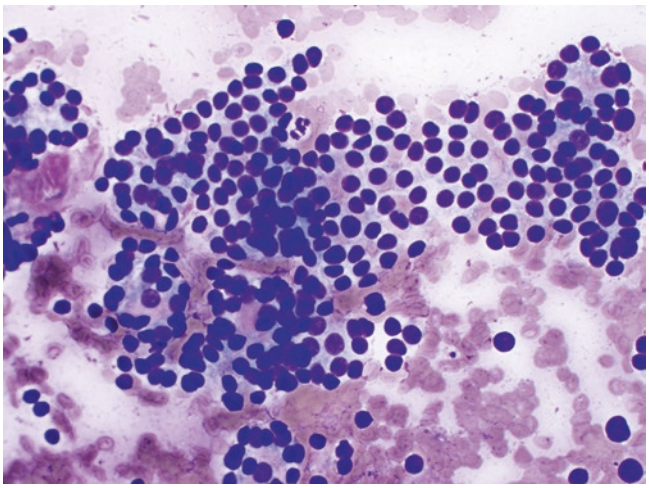

Fig. 3.23 Follicular neoplasm (DQ stain) with microfollicular growth pattern and lack of colloid in the background

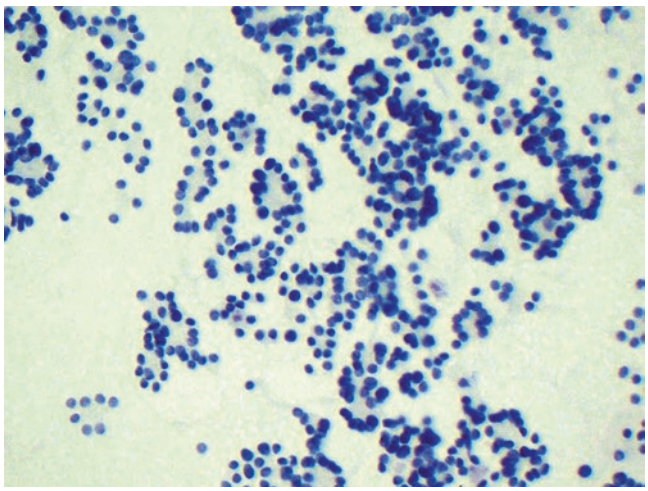

Fig. 3.24 Follicular neoplasm (DQ stain) with microfollicular growth pattern, nuclear enlargement, and nuclear crowding

- The architectural patterns may include microfollicular and solid (Fig. 3.25b), trabecular (Fig. 3.25c), normofollicular, and macrofollicular architectures (Fig. 3.25d).
- The tumor cells are cuboidal, columnar or polygonal, and frequently with uniform, dark, round nuclei.
- Foci of large nuclei or atypical nuclei with degenerative changes can be seen.
- Mitotic figures are rare.
- Many histologic variants have been described, such as clear cell follicular adenoma (Fig. 3.25e), oncocytic follicular adenoma, signet-ring cell follicular adenoma, lipoadenoma, mucinous follicular adenoma, follicular adenoma with bizarre nuclei (Fig. 3.25f), follicular adenoma with papillary hyperplasia, and hyperfunctioning follicular adenoma.
- Secondary changes, such as myxoid change, cyst formation, fibrosis, hyalinization, hemorrhage, cartilaginous metaplasia, ossification, and calcifications, can be seen.

Immunohistochemistry

- Positive for TTF1, PAX8, and thyroglobulin
- Negative for calcitonin and neuroendocrine markers
- Can be positive for HBME-1 and galectin-3; usually negative for CK19 and TROP2

Differential Diagnosis

- Cellular nodular goiter
- AUS/FLUS
- Follicular variant of papillary carcinoma

Follicular Carcinoma

Clinical Features

- More common in 40- to 60-year-old women.
- Accounts for 10% of thyroid carcinomas.
- A slow-growing neoplasm.
- Can be divided into two types: minimally invasive type which is rarely going for distant metastasis; another type is widely invasive type which is frequently goes for a distant metastasis and has a worse prognosis than papillary carcinoma of the thyroid.

Cytological Features (Figs. 3.26, 3.27, and 3.28)

- In general, there are no definitive criteria to separate follicular adenoma from follicular carcinoma on an FNA sample.
- Crowded and three-dimensional follicular structures.
- Microfollicles with irregular shapes and many single cells.
- Nuclear pleomorphism.
- Nuclear enlargement (three to four times that of normal follicular cells).
- Coarse and irregular nuclear chromatin.
- High nuclear-to-cytoplasmic ratio.
- Prominent and multiple nucleoli.
- Mitoses can be seen.

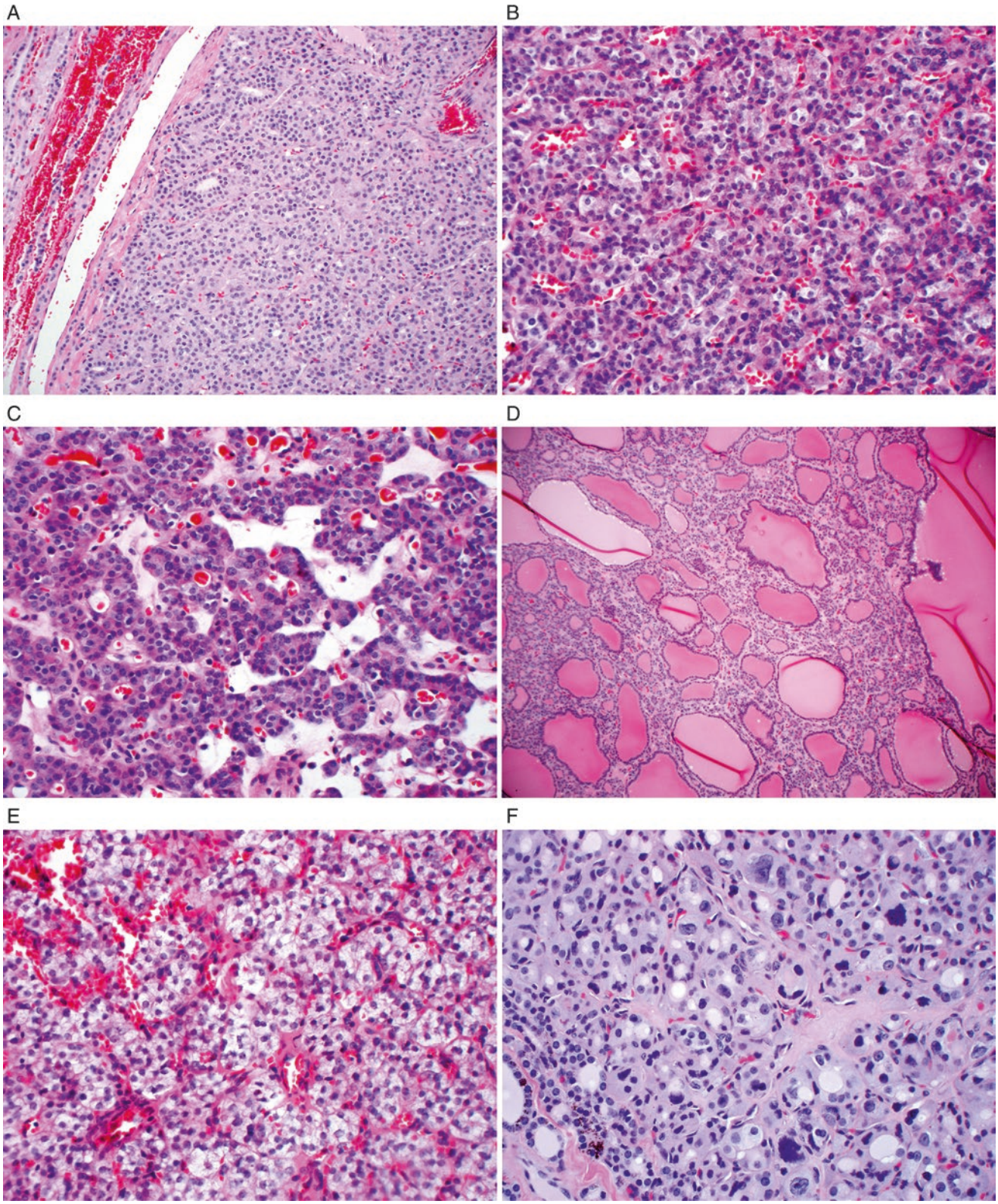

Fig. 3.25 Histologic sections of follicular adenoma with thin fibrous capsule (**a**), microfollicular and solid pattern (**b**), trabecular pattern (**c**), macrofollicular (**d**), clear cell changes (**e**), and bizarre nuclei (**f**)

Histologic Features

- A follicular nodule enclosed by a thick fibrous capsule showing definite capsular and/or vascular invasion.
- Lack of diagnostic nuclear features of PTC.
- Can have variable architectural patterns and cytological features.
- Classically, it can be divided into two categories: (1) minimally invasive follicular carcinoma with limited capsular invasive and vascular invasion (less than four vessels) and (2) widely invasive follicular carcinoma with widespread capsular and vascular invasion (greater than four vessels).

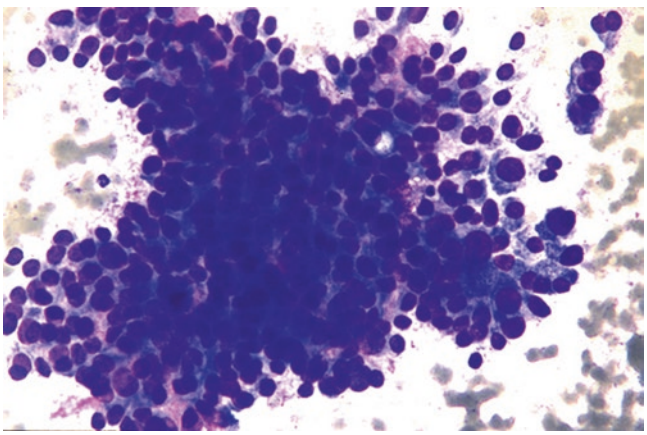

Fig. 3.26 Nuclear enlargement, crowding, and pleomorphism, suggestive of follicular carcinoma

- Fig. 3.29a–g shows some examples of capsular and vascular invasion.
- Oncocytic variant and clear cell variant have been described.

Immunohistochemistry

- Similar to follicular adenoma
- Can be positive for HBME-1 and galectin-3; usually negative for CK19 and TROP2

Differential Diagnosis

- Follicular adenoma
- Follicular variant of papillary carcinoma

Hurthle Cell Neoplasm (Figs. 3.30, 3.31, 3.32, and 3.33a–c)

- May be considered a subtype of follicular neoplasm
- Uniform population of Hurthle cells in small clusters and single cells
- Little or no colloid
- Prominent or small nucleoli
- Three-dimensional or crowded structures
- Features suggestive for Hurthle cell carcinoma, including nuclear pleomorphism, multiple and prominent nucleoli, high nuclear-to-cytoplasmic ratio, nuclear crowding, and mitoses

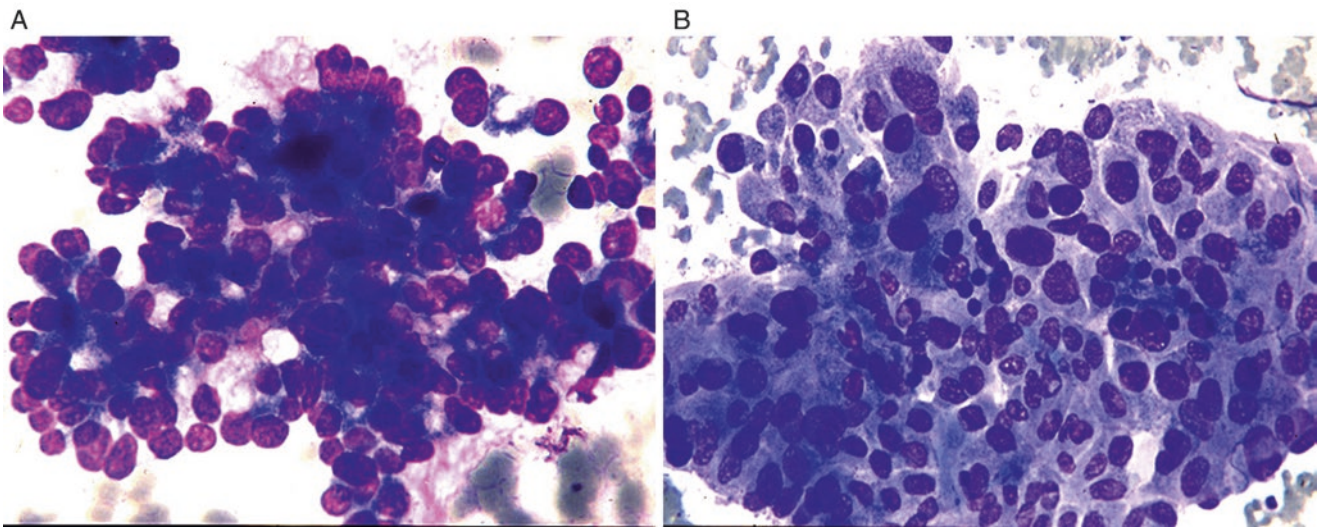

Fig. 3.27 Marked nuclear atypia, suggestive of follicular carcinoma (DQ stain)

Hyalinizing Trabecular Neoplasm

Clinical Features

- A rare tumor of follicular cell origin.
- The nuclear features of the tumor suggest that it may be related to PTC.
- Rearranged during transfection (RET)/PTC rearrangements have been reported in some tumors.
- Much more common in middle-aged women.

Cytological Features (Fig. 3.34a–d)

- Similar cytological features to papillary carcinoma.
- Hyalinizing material may be present between tumor cells.
- Tumor cells may be more elongated or even spindle.
- Nuclear grooves and intranuclear inclusions are frequent findings.
- Psammoma bodies can be seen.

Histologic Features

- A solid neoplasm with or without thin fibrous capsule.
- Trabecular or alveolar growth pattern.

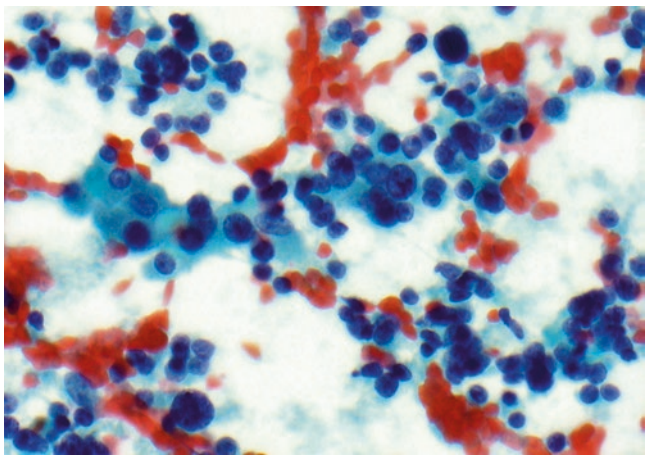

Fig. 3.28 Follicular carcinoma on Pap stain

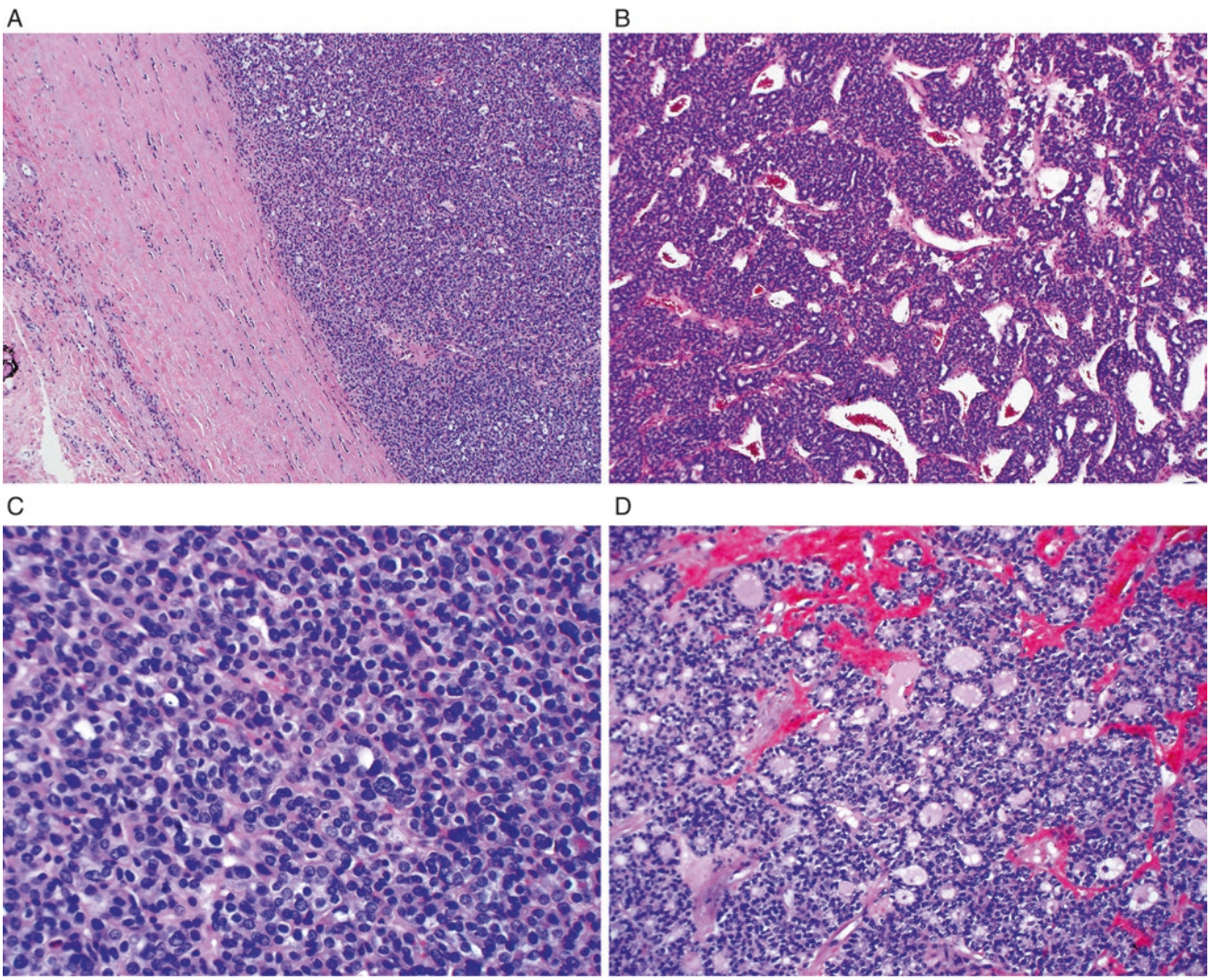

Fig. 3.29 Histology section of follicular carcinoma with capsular invasion (**e**) and vascular invasion (**f**, **g**)

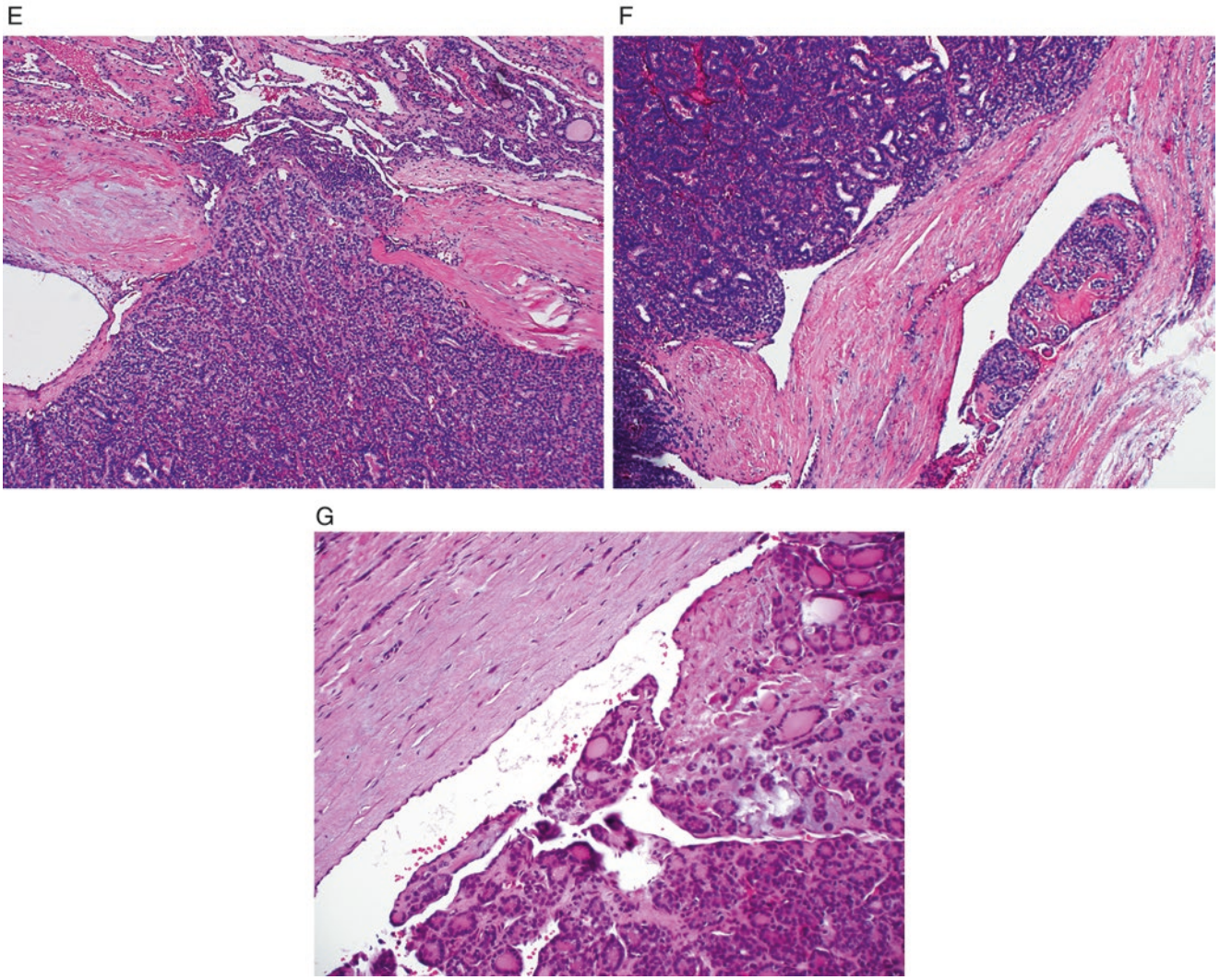

Fig. 3.29 (continued)

- Polygonal or spindle tumor cells, with granular to clear cytoplasm, with a prominent hyaline stroma between nests or trabeculae of tumors.
- Elongated nuclei, centrally located, with nuclear grooves and intranuclear pseudoinclusion (Fig. 3.35a, b).
- Mitotic figures are rarely seen; psammoma bodies may be present.
- Usually absence of colloid.

Immunohistochemistry

- MIB-1 (a specific clone for Ki-67) staining showing distinctive membranous staining pattern in the majority of cases (Fig. 3.35c)
- Frequently positive for galectin-3; can be positive for CK19
- Positive for TTF1 and PAX8 and negative for calcitonin and neuroendocrine markers

Differential Diagnosis

- Papillary carcinoma
- Medullary carcinoma
- Table 3.2 below summarizes useful markers for the distinction among these three tumors.

PTC (Papillary Thyroid Carcinoma)

Clinical Features

- Accounts for about 70% of malignant thyroid neoplasms.
- More common in young females, with female-to-male ratio of 4:1, especially under age 40.
- Slow growing; patient may survive for many years even after local lymph node metastasis.

- Papillary microcarcinoma is defined as a tumor 1 cm or less in diameter.
- Tall cell variant, columnar cell variant, diffuse sclerosing variant, and solid variant tend to show a more aggressive clinical behavior than a conventional PTC.

Cytological Features of Conventional PTC (Figs. 3.36, 3.37, 3.38, 3.39, 3.40, 3.41, 3.42, 3.43, 3.44, 3.45, 3.46, 3.47, and 3.48)

- Hypercellular specimen with three-dimensional or two-dimensional papillary structures
- Nuclear enlargement, overlapping, open nuclear chromatin, small and marginated nucleoli, nuclear grooves, and intranuclear cytoplasmic inclusions

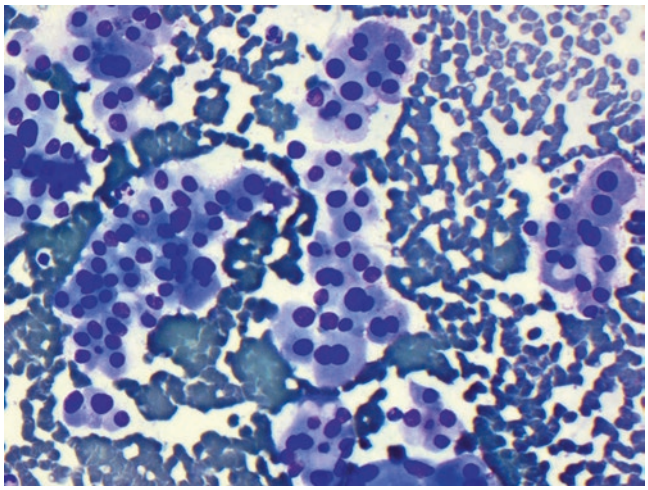

Fig. 3.30 Hurthle cell neoplasm with groups of Hurthle cells and absence of colloid in the background (DQ)

- Squamoid cytoplasm, oncocytic cytoplasm, or cytoplasm with small vacuoles
- Thick colloid or gummy colloid
- Multinucleated giant cells
- Psammoma bodies

Cytologic Features for Variants of PTC

Follicular Variant
- Resembles an FNA smear of follicular neoplasm.
- Tumor cells mostly arranged in microfollicles with absence or near absence of papillary structures.
- Nuclear features for PTC tend to be subtle when comparing to a classical PTC.
- Less intranuclear pseudoinclusions.
- Multinucleated giant cells, psammoma bodies, and cystic changes are usually absent.
- Follicular neoplasm and parathyroid neoplasm are included in the diagnostic consideration.

Tall Cell Variant
- Resembles a classic PTC.
- The tumor cells have an elongated shape, with a height-to-width ratio of 3:1 or greater (Fig. 3.49a, b).
- Classic nuclear features are needed to render a definitive diagnosis.

Columnar Cell Variant
- The neoplastic cells are arranged in papillae, groups, and sheets.
- The nuclei are elongated and stratified.
- The nuclear chromatin tends to be more hyperchromatic than open chromatin.
- The intranuclear inclusions are less prominent.
- Definitive nuclear changes for PTC are required to render a diagnosis.

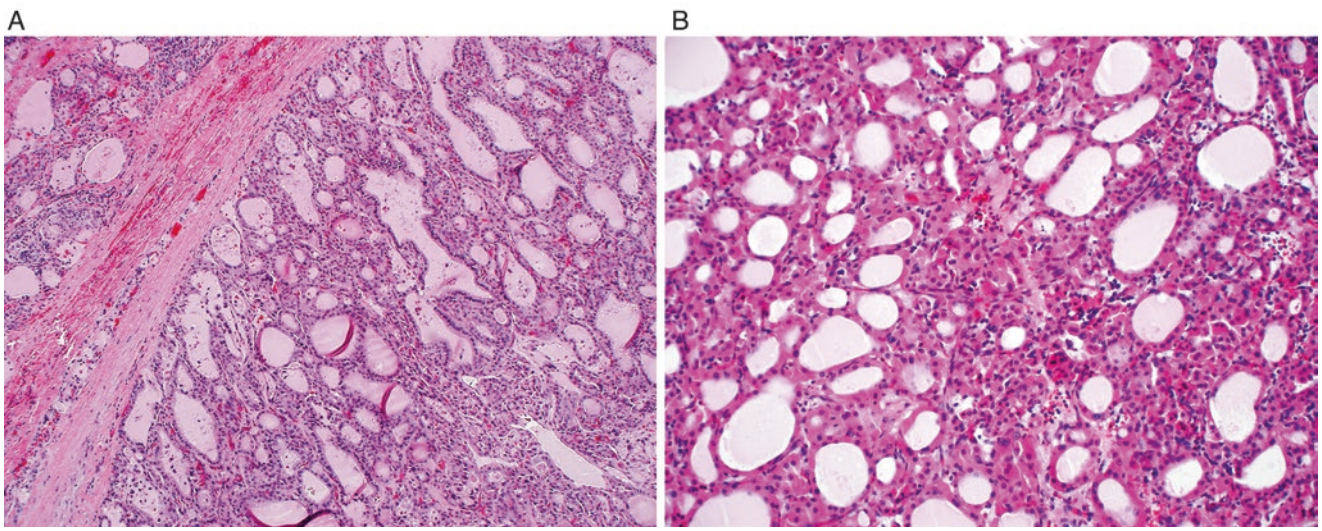

Fig. 3.31 Histology section of Hurthle cell adenoma

Macrofollicular Variant

- Resembles a benign colloid nodule on a low-power view with a mixture of sheets of follicular cells, some with microfollicular patterns, and abundant colloid.

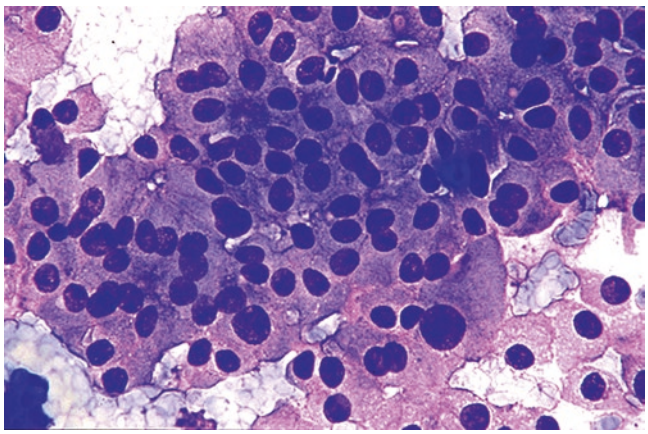

Fig. 3.32 Hurthle cell carcinoma on FNA smear (DQ)

- Diagnosis is based on the observation of nuclear changes for PTC at higher magnification. In general, these tend to be subtle.

Oncocytic Variant

- Resembles Hurthle cell proliferation, including Hurthle cell neoplasm.
- The majority of tumor cells contain abundant oncocytic cytoplasm and are isolated or arranged in sheets or papillae.
- Classic nuclear changes for PTC, including intranuclear inclusions.
- Absence of lymphoid cells.
- Nucleoli tend to be more conspicuous than in a conventional PTC; however, prominent nucleoli, frequently seen in a Hurthle cell neoplasm, are not typical features for an oncocytic variant of PTC.

Cystic Variant

- Resembles a colloid cyst with very low cellularity or mainly hemosiderin-laden histiocytes and clear background.

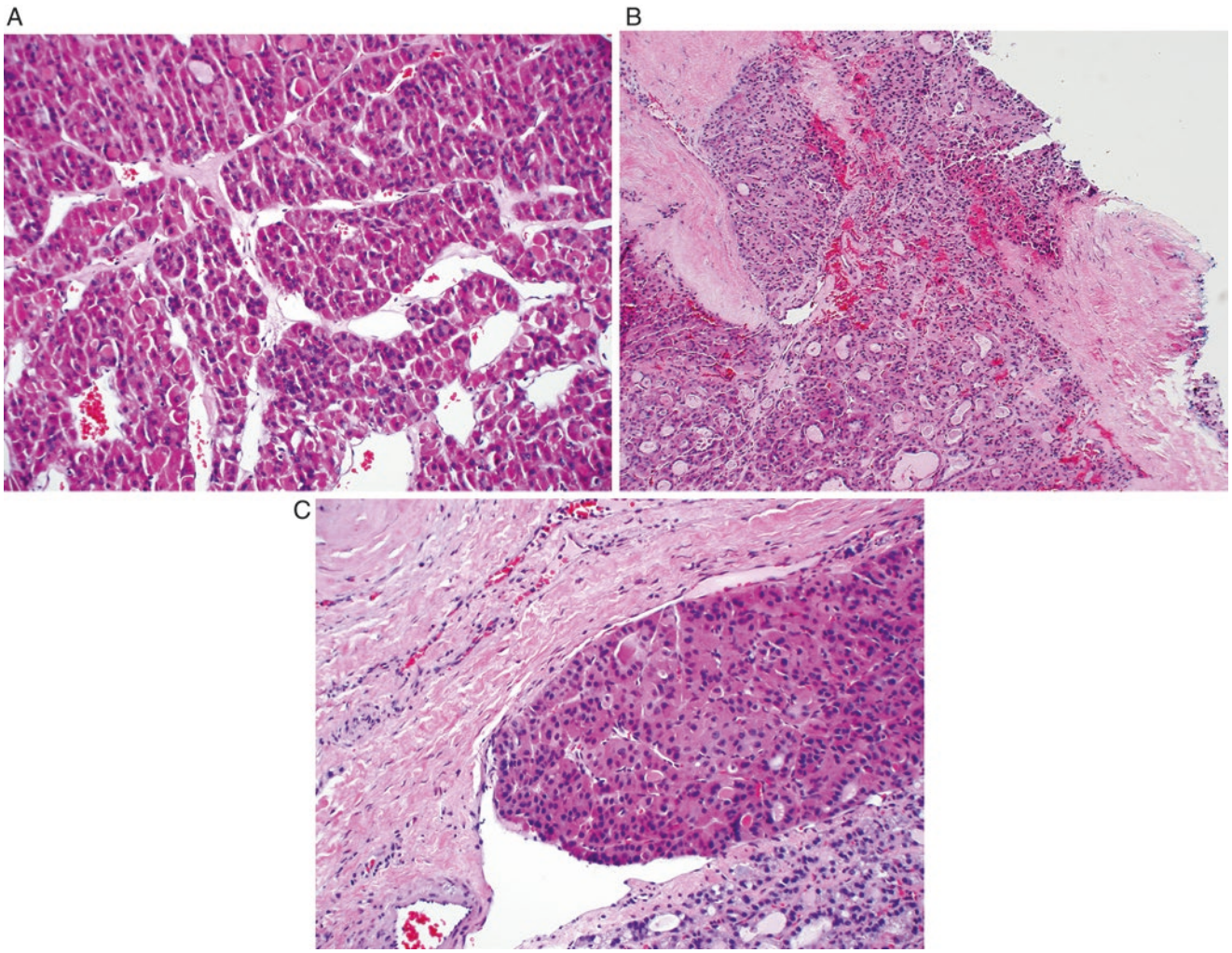

Fig. 3.33 Histologic sections of Hurthle cell carcinoma (a) with capsular (b) and vascular invasion (c)

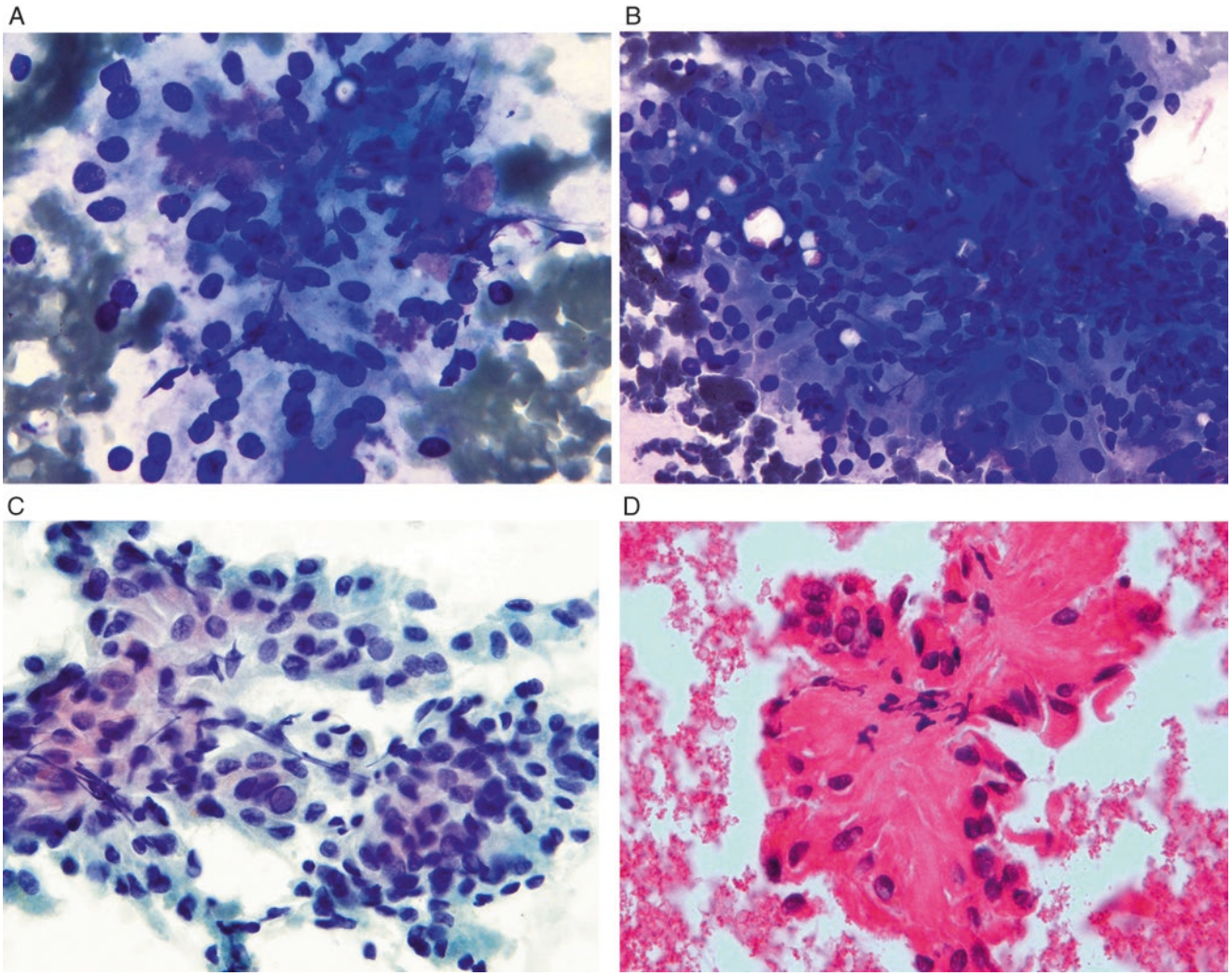

Fig. 3.34 Hyalinizing trabecular adenoma with many cytological features of PTC, including intranuclear inclusion. Note that eosinophilic hyalinizing material between cells (**a**, DQ) and cellblock (**d**)

- Only a few groups of neoplastic follicular cells are present, and they are usually arranged in a small groups, sheets, papillae, or follicles (Fig. 3.49c).
- The tumor cells may show "histiocytoid" features with cytoplasmic vacuoles.
- Identification of diagnostic nuclear features for PTC, including intranuclear inclusions, is required to render a diagnosis.

Warthin-Like Variant

- Resembles Hashimoto's thyroiditis.
- Oncocytic tumor cells arranged in sheets, groups, and papillary and follicular structures.
- Lymphoplasmacytic background with lymphoid cells and plasma cells intimately associated with tumor cells (Fig. 3.49d).
- Classic nuclear features for PTC are required to render a diagnosis.

Histologic Features

- The characteristic nuclear features mentioned above are the key to making a diagnosis.
- Complex papillary architectures with branching and squamous metaplasia are commonly seen.
- The papillae may have markedly edematous changes.
- Cystic changes are frequent.
- Psammoma is frequently present.
- Many histologic variants are present: (1) follicular variant (Fig. 3.50a), (2) oncocytic variant, (3) tall cell variant (Fig. 3.50b, c), (4) columnar cell variant, (5) diffuse sclerosing variant, (6) clear cell variant, (7) solid variant, (8) cystic variant (Fig. 3.50d, e), (9) cribriform variant (Fig. 3.50f, g), (10) macrofollicular variant, and (11) Warthin-like variant (Fig. 3.50h).

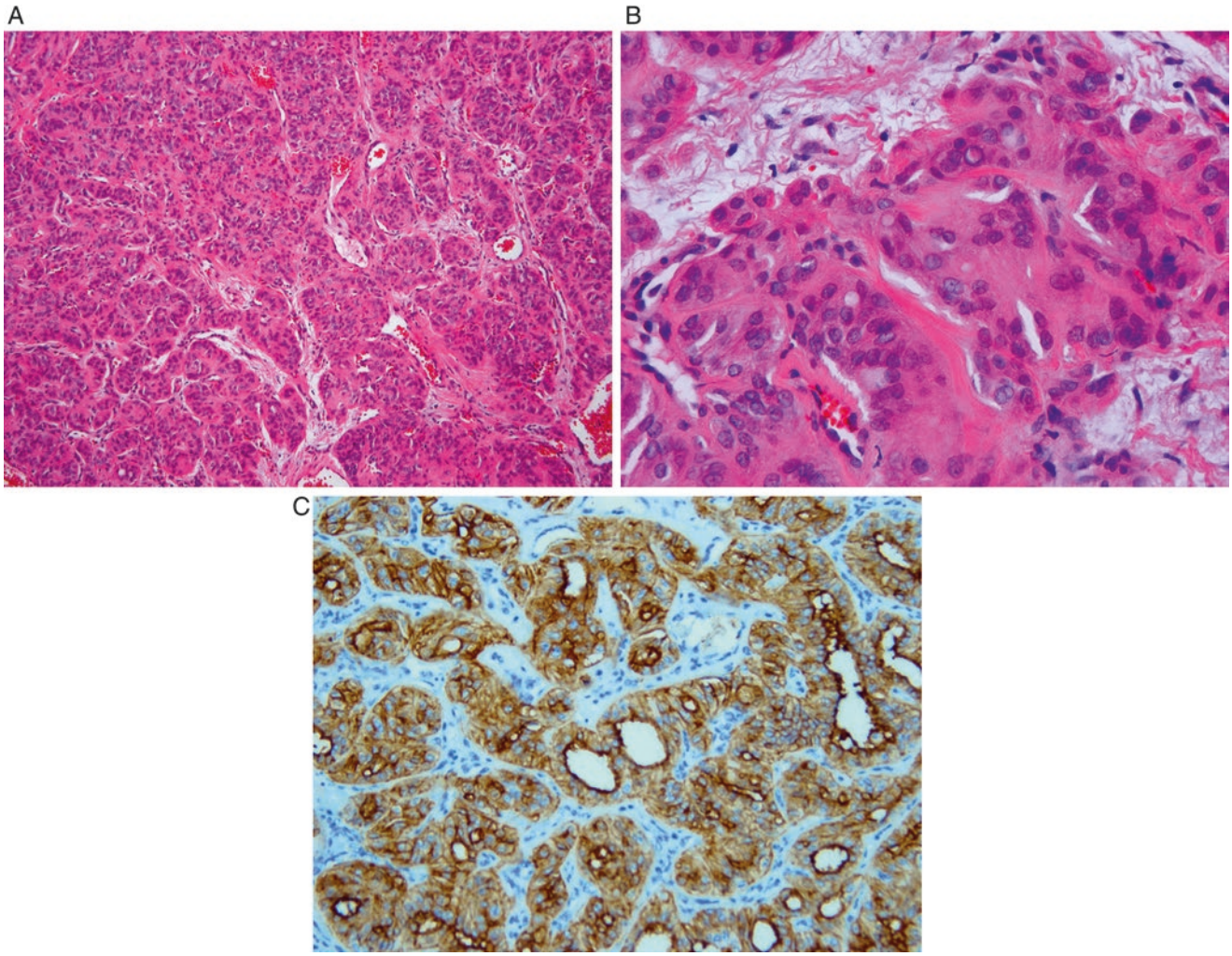

Fig. 3.35 Hyalinizing trabecular adenoma. Histologic sections showing elongated nuclei, centrally located with nuclear grooves and intranuclear pseudoinclusion (**a**, **b**). Note that MIB-1 (Ki-67) immunostain on histology section showing distinct membranous staining pattern (**c**)

Table 3.2 Differentiation of hyalinizing trabecular neoplasm, papillary carcinoma, and medullary carcinoma by immunostains

Marker	Hyalinizing trabecular neoplasm	Papillary carcinoma	Medullary carcinoma
Thyroglobulin	+	+	–
Calcitonin	–	–	+
MIB-1 (Ki-67)	Membranous	Nuclear	Nuclear

- A small proportion of papillary carcinomas may show a combination of histologic variants, with focus/foci of (1) insular carcinoma, (2) squamous cell carcinoma, (3) mucoepidermoid carcinoma, (4) spindle cell and giant cell carcinoma, (5) and medullary carcinoma.

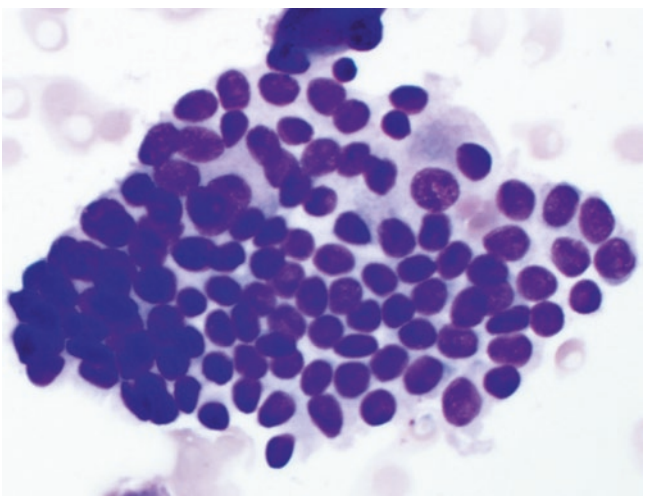

Fig. 3.36 Papillary carcinoma with two-dimensional papillary structure (DQ stain)

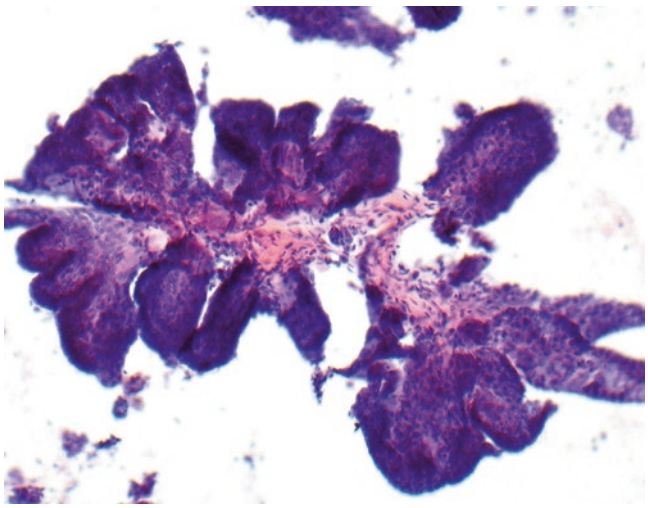

Fig. 3.37 Papillary carcinoma with three-dimensional papillary fronds (DQ stain)

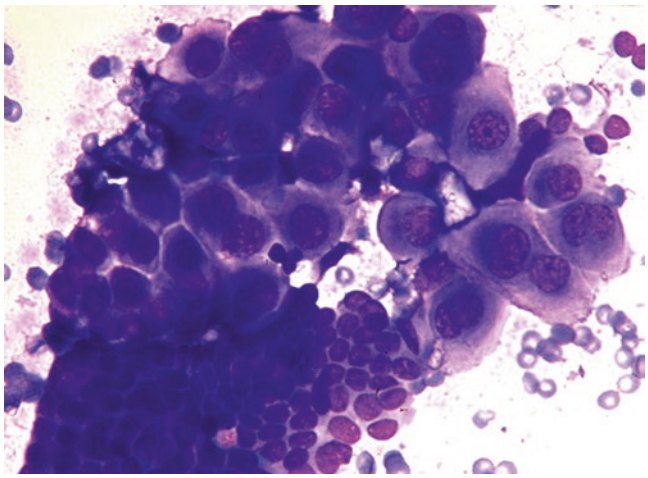

Fig. 3.38 Papillary carcinoma with nuclear enlargement and squamoid cytoplasm (DQ stain)

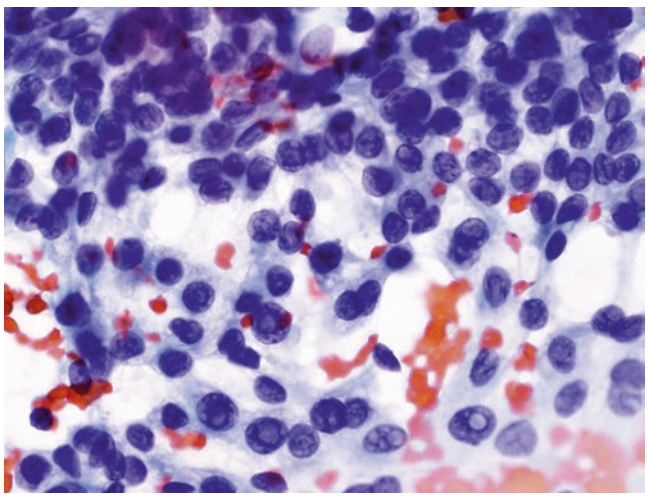

Fig. 3.39 Papillary carcinoma with nuclear enlargement, overlapping, nuclear grooves, and intranuclear inclusions (Pap stain)

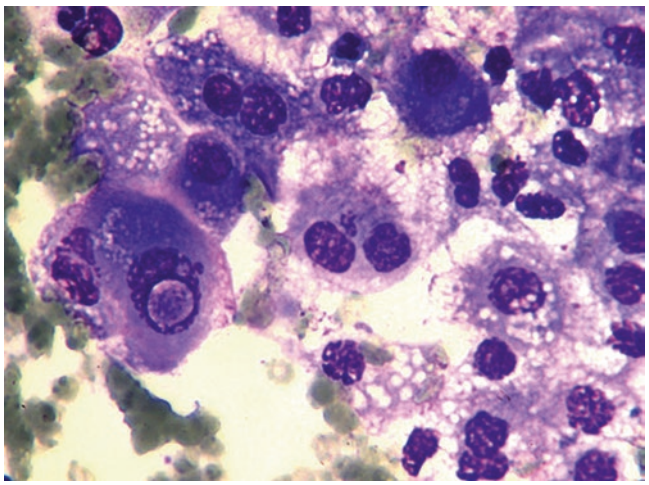

Fig. 3.40 Papillary carcinoma with squamoid cytoplasm and septated cytoplasmic vacuoles and intranuclear cytoplasmic inclusion (DQ stain)

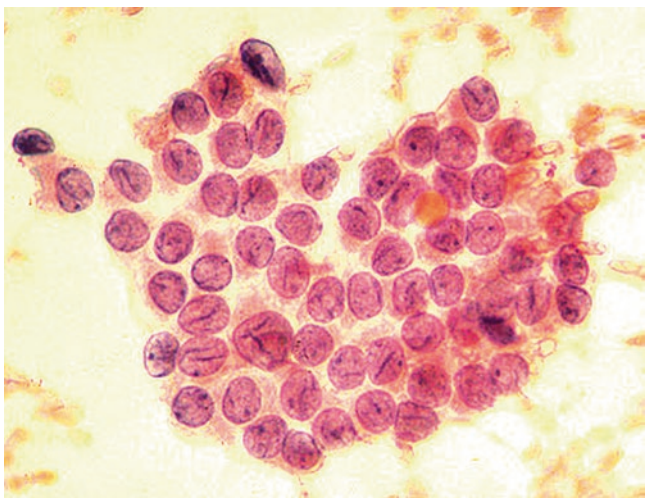

Fig. 3.41 Papillary carcinoma with open nuclear chromatin, grooves, and intranuclear cytoplasmic inclusions (Pap stain)

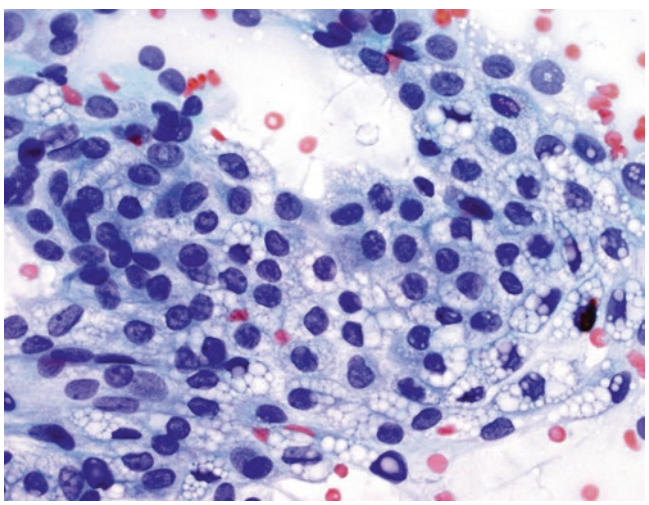

Fig. 3.42 Papillary carcinoma. Cytoplasmic vacuoles (Pap stain)

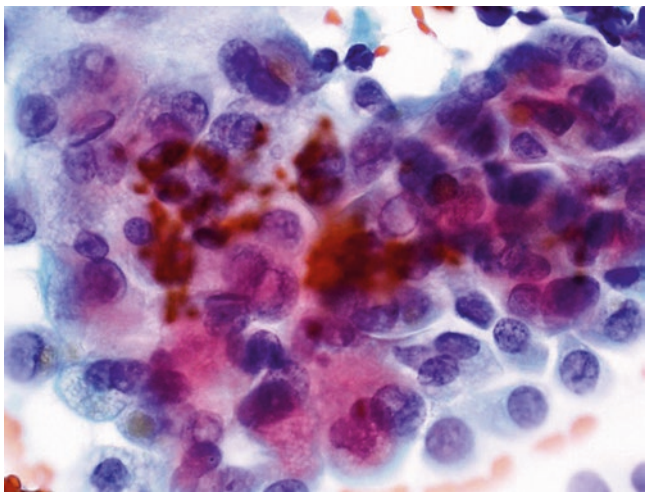

Fig. 3.43 Papillary carcinoma. Squamoid cytoplasm (Pap stain)

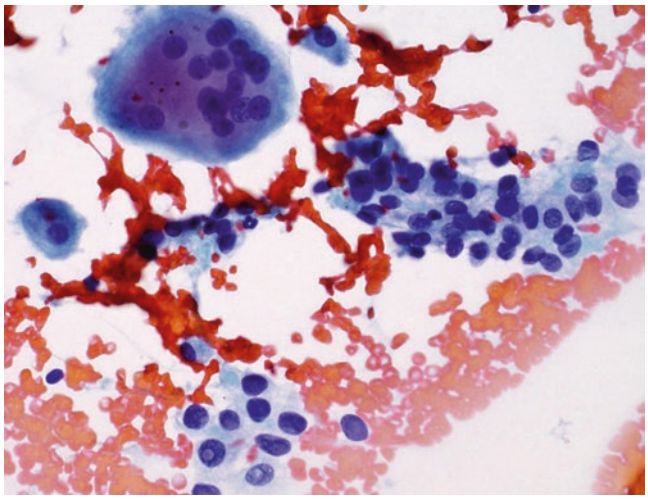

Fig. 3.44 Papillary carcinoma. Multinucleated giant cells (Pap stain)

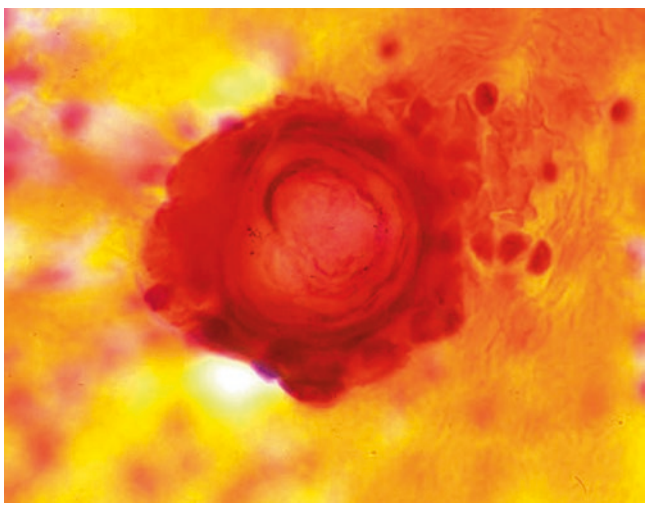

Fig. 3.45 Papillary carcinoma. Psammoma body (Pap stain)

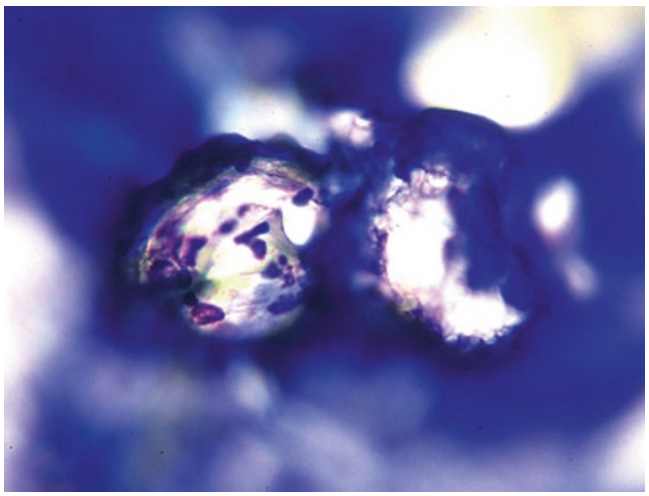

Fig. 3.46 Papillary carcinoma. Psammoma body (DQ stain)

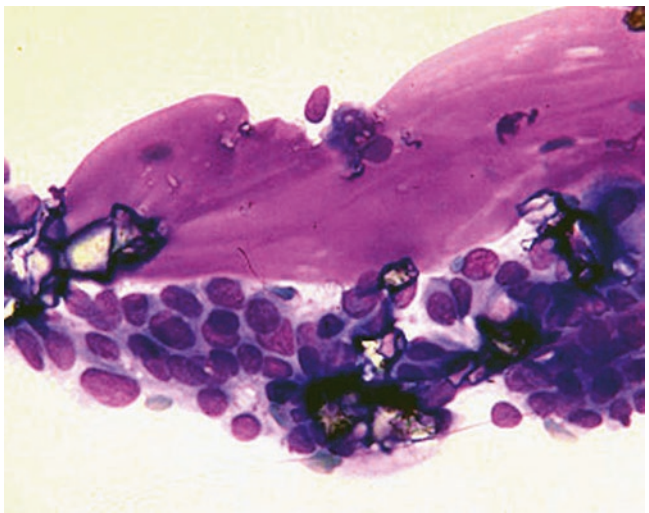

Fig. 3.47 Papillary carcinoma. Gummy/sticky colloid (DQ stain)

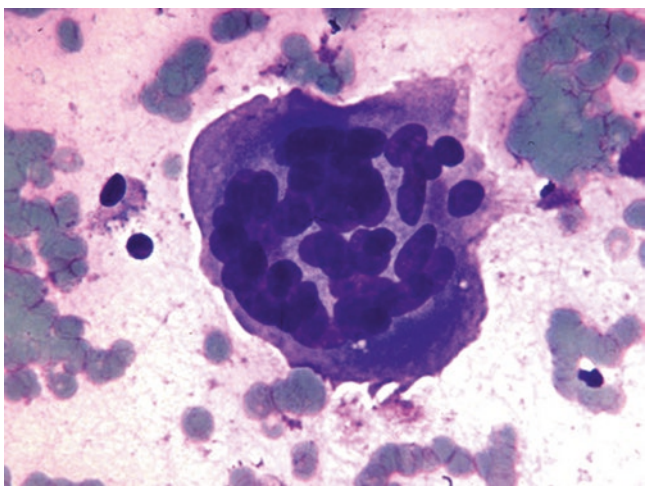

Fig. 3.48 Papillary carcinoma. Multinucleated giant cells (DQ stain)

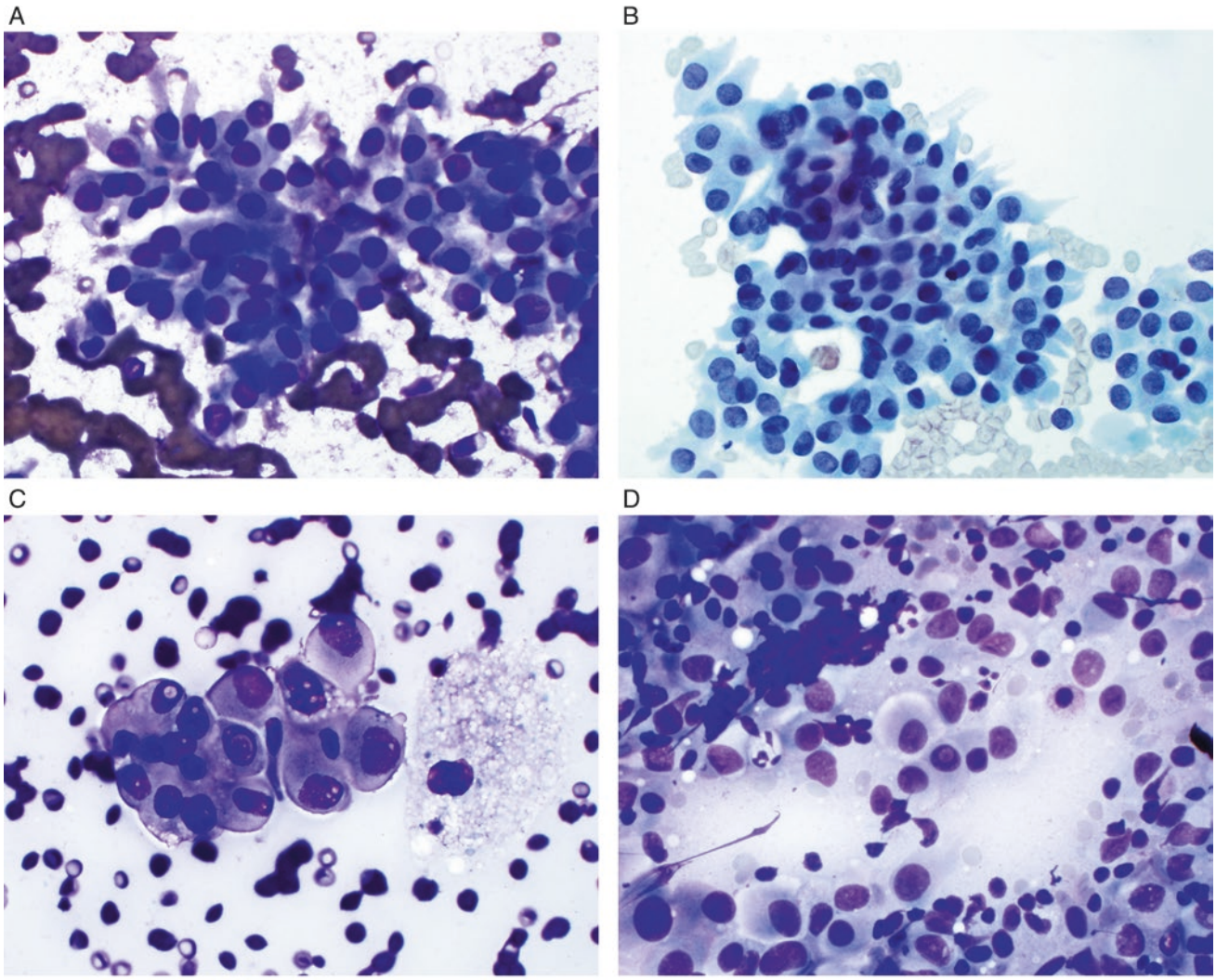

Fig. 3.49 Cytologic features of some variants, tall cell variant (**a**, **b**), cystic variant (**c**), and Warthin-like variant (**d**)

Immunohistochemistry

- Positive for thyroglobulin, TTF1, vimentin, and PAX8; negative for neuroendocrine markers and calcitonin.
- Calectin-3, CK19, HBME-1, and TROP2 are a useful panel of markers for the diagnosis of papillary carcinoma as summarized in Table 3.3. However, no single marker in this panel is entirely sensitive or specific for papillary carcinoma.
- Antibodies to RET/PTC rearrangement and BRAF mutation can be useful as well.
- An example of micropapillary PTC on FNA smear, CB, and positive for CK19, HBME-1, and TROP2 was shown in Fig. 3.51a–e. The histologic section was shown in Fig. 3.51f, g.

Molecular Alterations of Thyroid Tumors of Follicular Cell Origin

Table 3.4 summarizes the common genetic alterations reported in thyroid tumors of follicular cell origin.

Differential Diagnosis

- Atypical follicular cells in nodular goiter or Hashimoto's thyroiditis
- Hyalinizing trabecular neoplasm
- Medullary carcinoma
- Follicular carcinoma

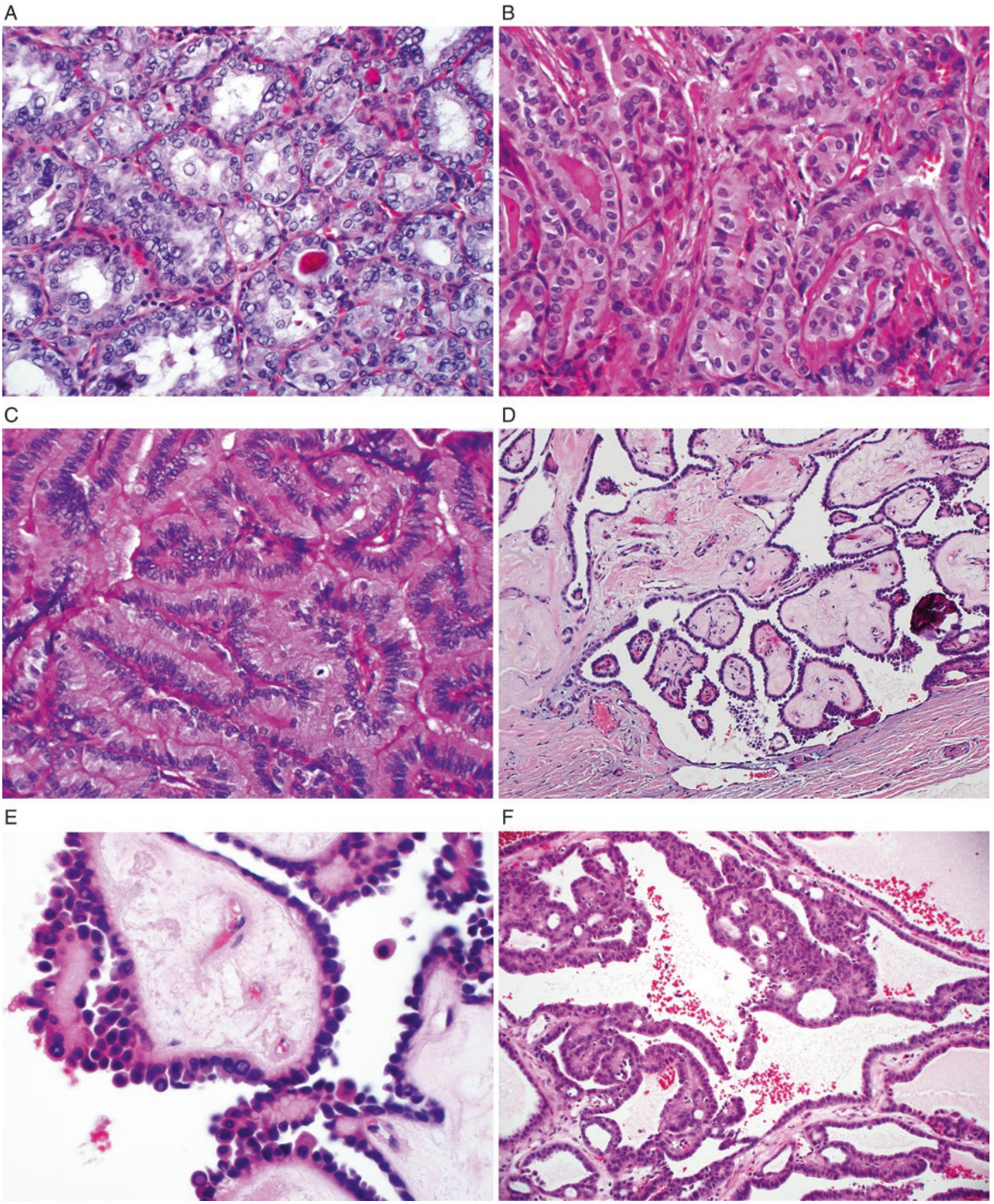

Fig. 3.50 Histologic sections of follicular variant (**a**), tall cell variant (**b**, **c**), cystic variant (**d**, **e**), cribriform variant (**f**, **g**), and Warthin-like variant (**h**)

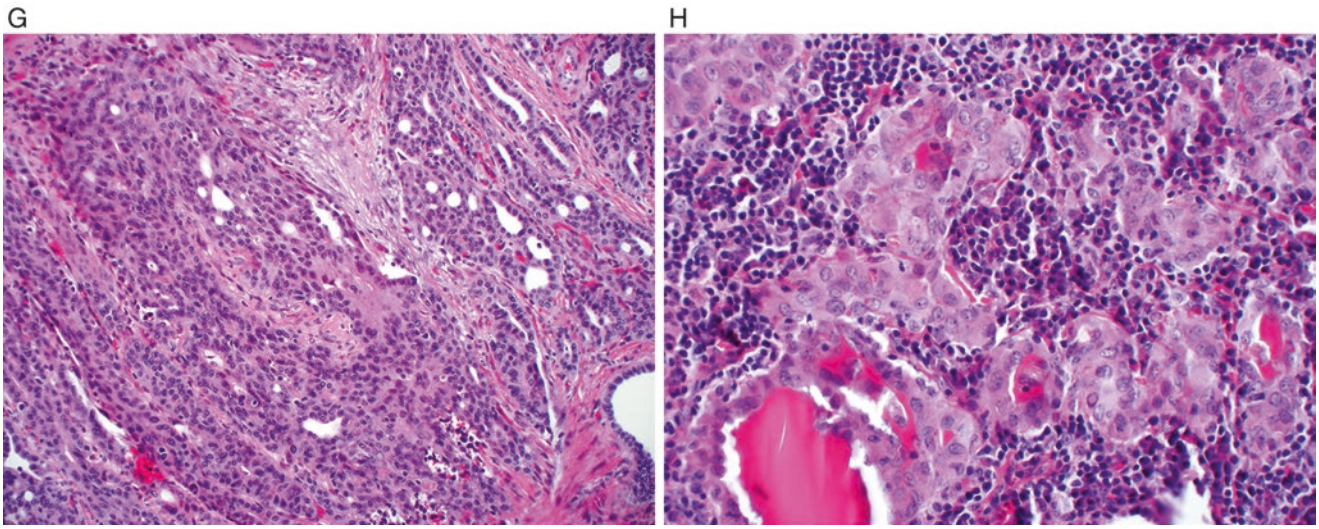

Fig. 3.50 (continued)

Table 3.3 Differentiation of PTC, follicular variant PTC, follicular adenoma, and reactive atypia by immunostains

Marker	PTC	Follicular variant PTC	Follicular adenoma	Reactive atypia
Galectin-3	+	+	−/+	−/+
CK19	+	+/−	−	−
HBME-1	+	+	−/+	−
TROP2	+	+/−	−	−

Medullary Carcinoma

Clinical Features

- Accounts for 5–10% of malignant thyroid neoplasms.
- More common in ages 40–60, male-to-female ratio is 2:3.
- Most cases are associated with RET oncogene in chromosome 10 q11.2.
- Associated with autosomal dominant trait in some patients.
- Over 90% of tumors secrete calcitonin.
- Painless thyroid mass.
- C-cell hyperplasia is the precursor of heritable medullary carcinoma.

Cytological Features (Fig. 3.52a–i)

- Mixed population of epithelioid and spindle neoplastic cells.
- The tumor cells can be predominately single or in clusters, including sheets, follicles, microfollicles, rosettes, cords, or papillae.
- Plasmacytoid cells with binucleation or multinucleation or bizarre cells.
- Small to inconspicuous nucleoli.
- Salt-and-pepper nuclear chromatin.
- Intranuclear cytoplasmic inclusions.
- Intracytoplasmic inclusions can be seen.
- Amyloid in the background.

Histologic Features (Fig. 3.53a–d)

- Variable histologic growth patterns and architectures, including sheets, nests, trabeculae, pseudopapillary, follicular, and solid.
- Polygonal, epithelioid, oncocytic, clear, spindle, melanotic, and small tumor cells or a mixture of different types of cells.
- Salt-and-pepper chromatin, granular cytoplasm, and small nucleoli are common.
- Prominent nucleoli are observed in oncocytic variant.
- Intranuclear inclusions are frequently seen.
- Intracytoplasmic lumen and mucin production have been reported.
- Amyloid stroma has been reported in 80% of cases; giant cell reaction and calcification may be present.
- Tumor necrosis and hemorrhage are uncommon.
- Focal nuclear pleomorphism may be present but does not indicate a more clinical aggressiveness.

Immunohistochemistry

- 95% of cases positive for calcitonin.
- Over 95% of cases positive for carcinoembryonic antigen (CEA).

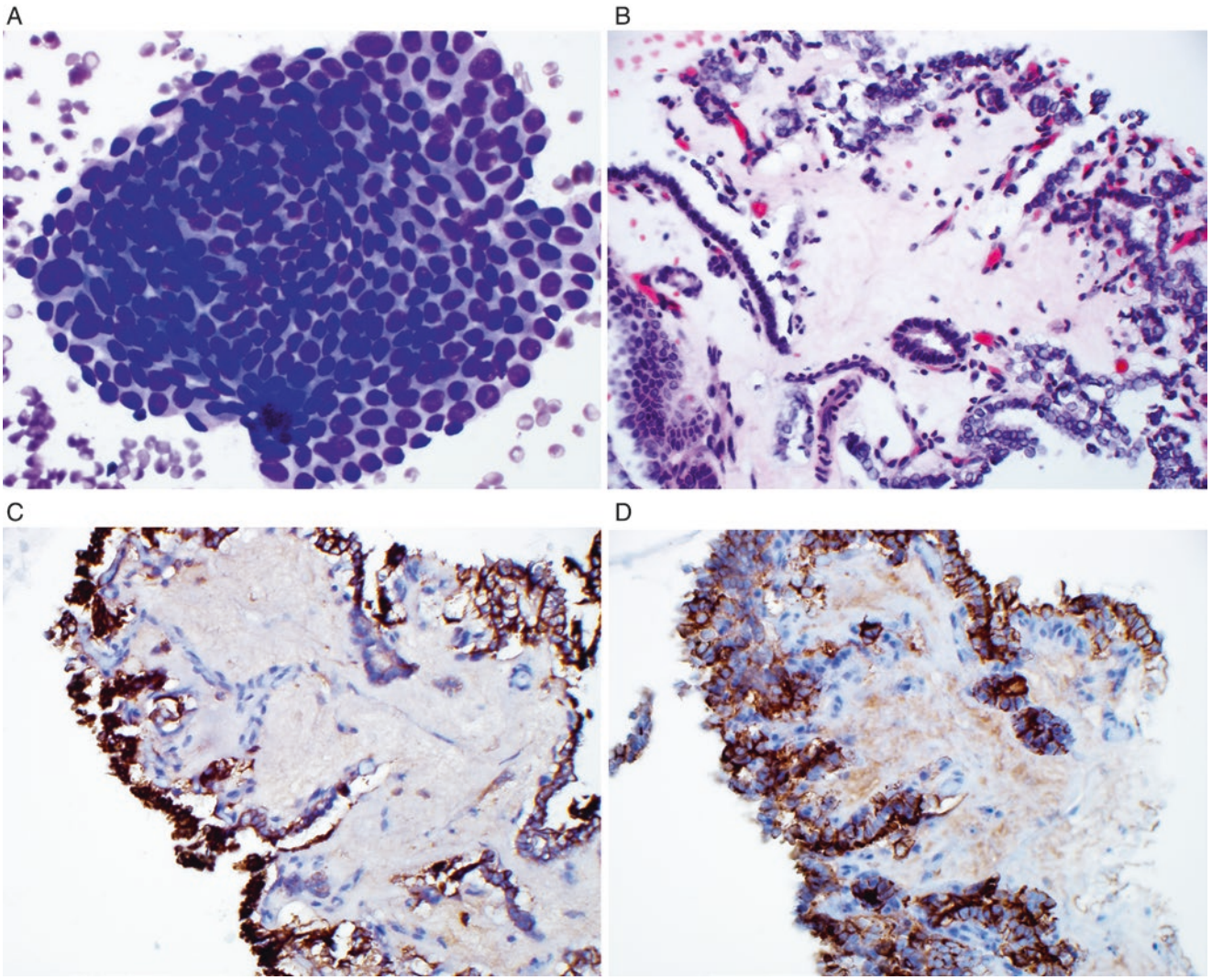

Fig. 3.51 Example of micropapillary carcinoma on FNA smear (**a**), cellblock (**b**), positive for CK19 (**c**), HBME-1 (**d**), and TROP2 (**e**), and the histologic section (**f**, **g**)

- Usually weakly positive for TTF1.
- Positive for chromogranin and synaptophysin.
- Negative for thyroglobulin and PAX8.
- An example of IHC is shown in Fig. 3.54a–c.

Differential Diagnosis

- Insular carcinoma/poorly differentiated carcinoma of the thyroid
- Anaplastic carcinoma of the thyroid
- Hyalinizing trabecular neoplasm
- Metastasis

Poorly Differentiated (Insular) Carcinoma

Clinical Features

- More common in elderly patients
- Prognosis better than anaplastic carcinoma but worse than papillary and follicular carcinoma

Cytological Features (Fig. 3.55a–c)

- Relatively uniform population of neoplastic cells.
- Single or small clusters of neoplastic cells.

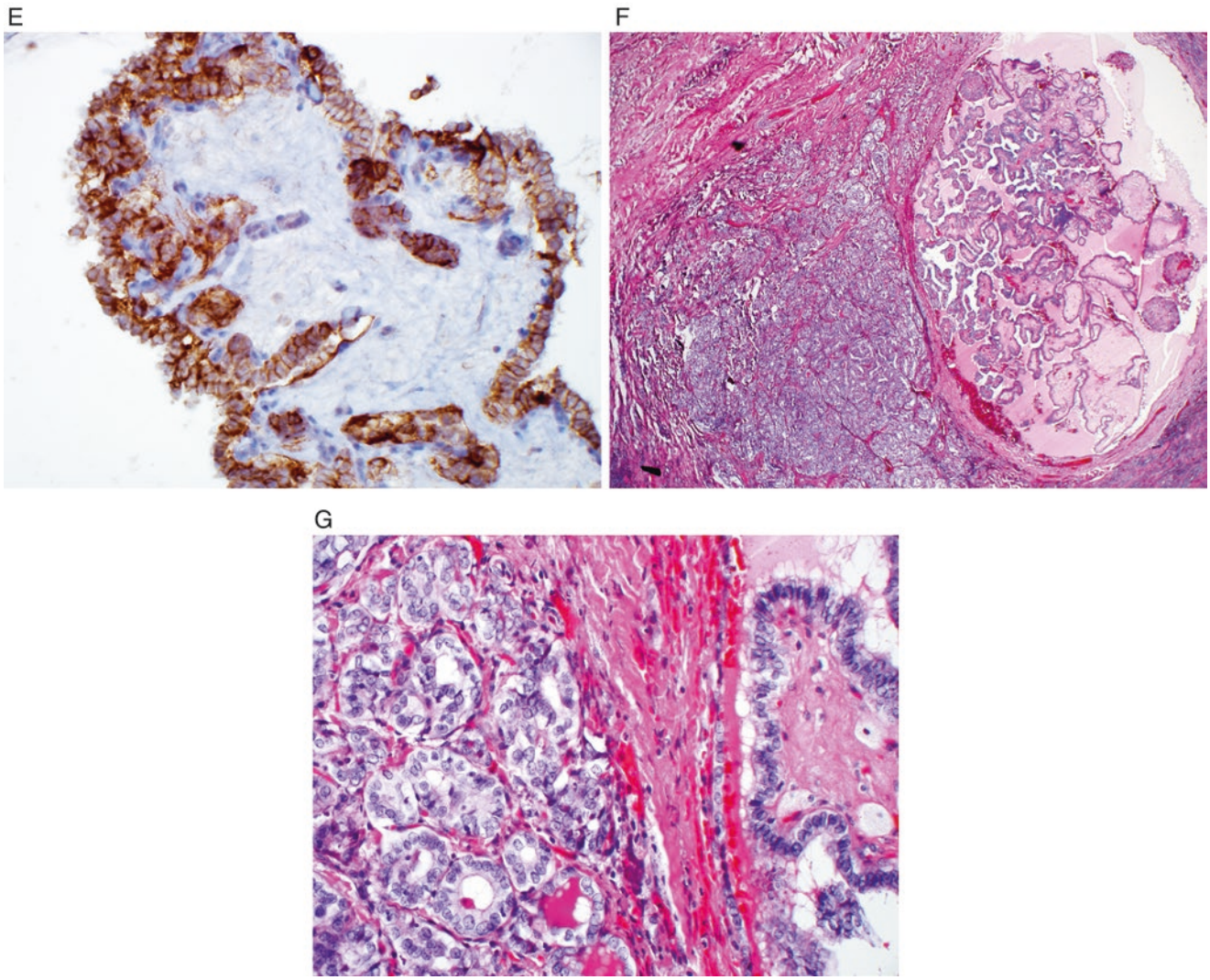

Fig. 3.51 (continued)

Table 3.4 Common molecular alterations in thyroid tumors of follicular cells

Diagnosis	Molecular alterations							
	BRAF	RET/PTC	RAS	PAX8-PARr	PIK3CA	B-catenin (CTNNB1)	TP53	PTEN
Papillary carcinoma	30–70%	20%	10%	–	–	–	–	–
Papillary carcinoma-encapsulated follicular variant	5–10%	5–10%	25–45%	0–30%	–	–	–	–
Follicular adenoma	–	–	20–40%	5–20%	–	–	–	–
Follicular carcinoma	–	–	45%	35%	<10%	–	–	<10%
Poorly differentiated (insular) carcinoma	5–15%	–	35%	–	–	20%	20%	–
Undifferentiated (anaplastic) carcinoma	25%	–	55%	–	5–25%	65%	70%	5–20%

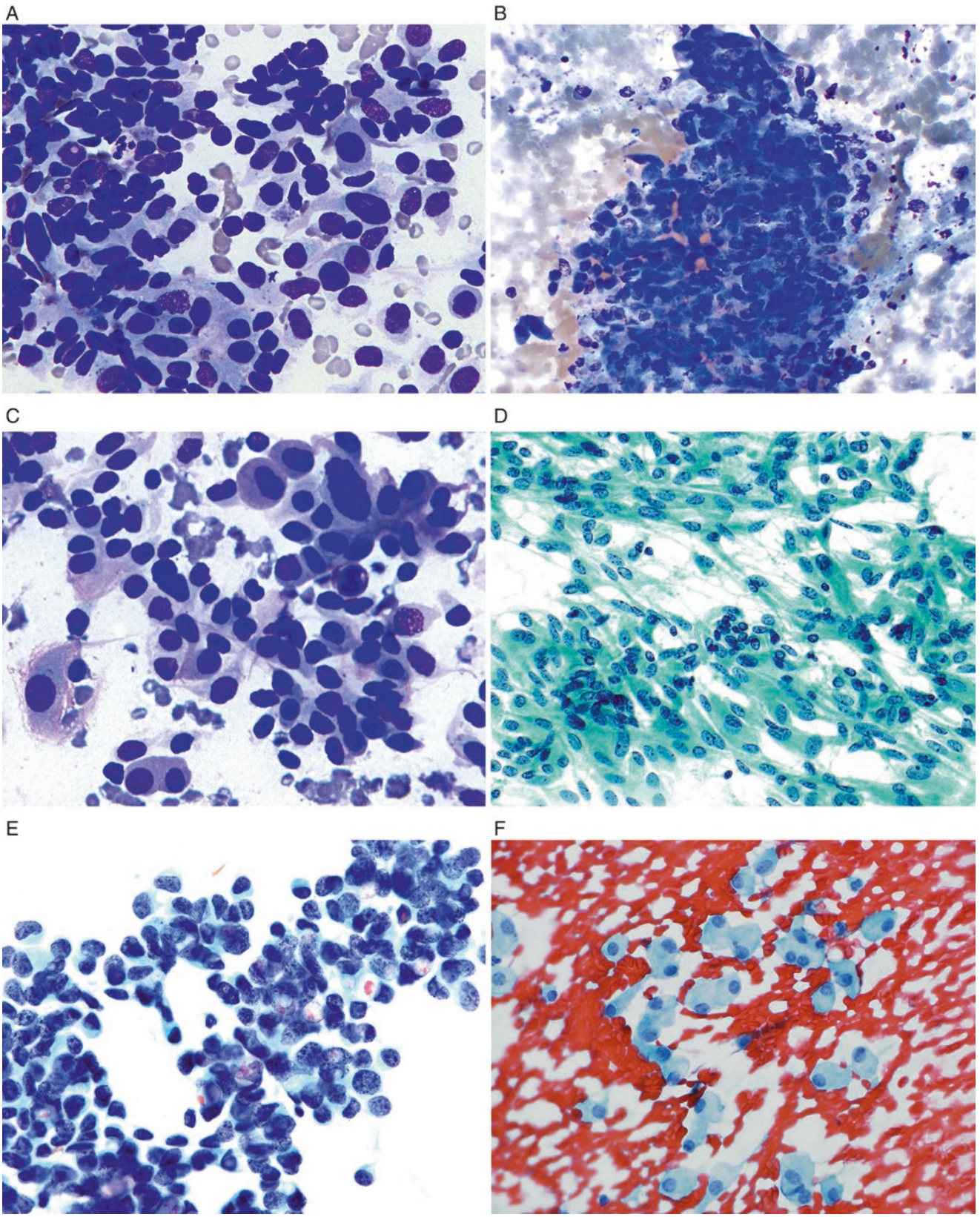

Fig. 3.52 Cytologic features of medullary carcinoma with epithelioid and spindle cells (**a**, **b**), plasmacytoid cells and binucleation (**c**), spindle cells (**d**), intracytoplasmic inclusion (**e**), foamy cytoplasm (**f**), amyloid stroma (**g**), amyloid on Congo-red stain (**h**), and positive for calcitonin on cellblock (**i**)

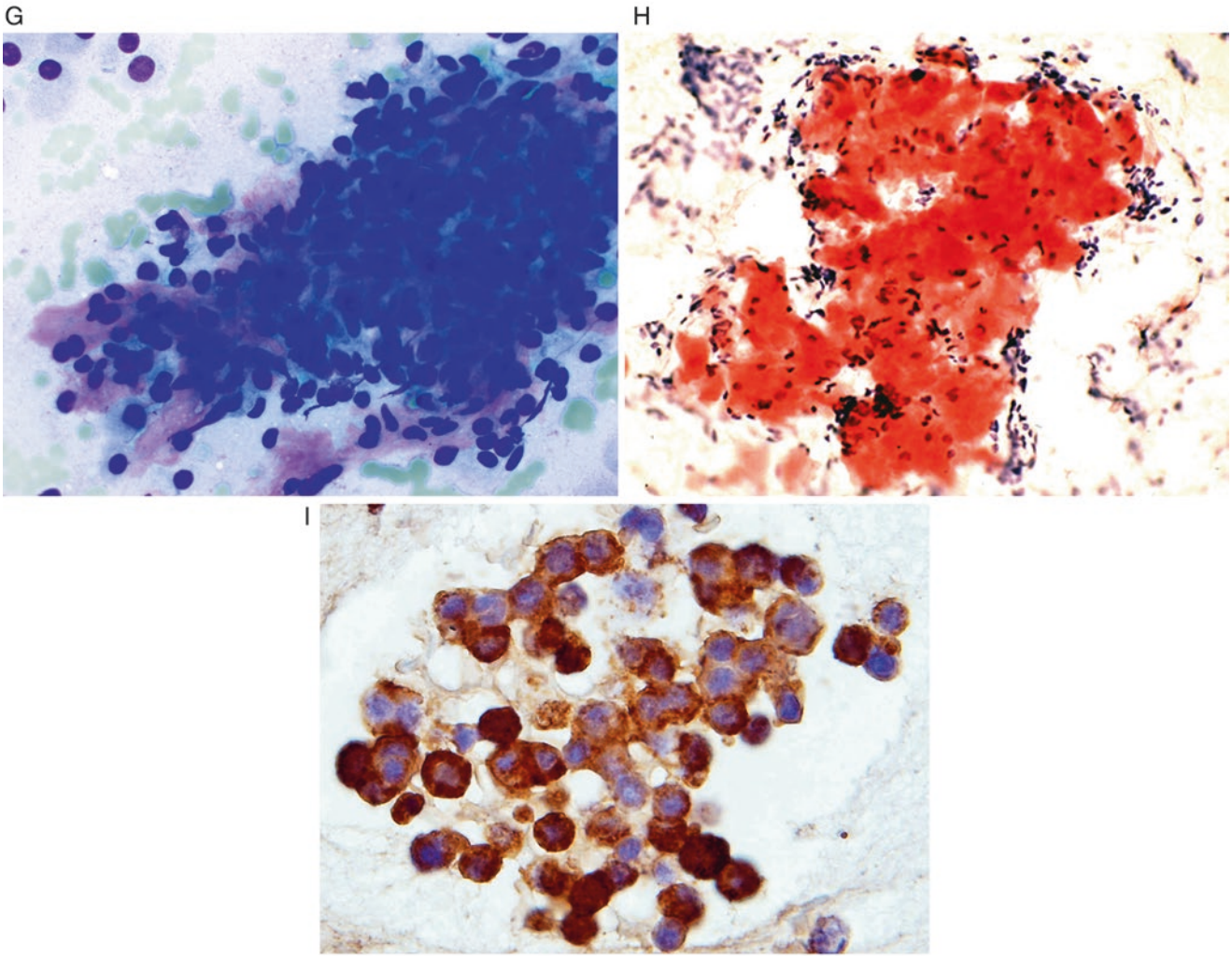

Fig. 3.52 (continued)

- Round to oval nuclei with hyperchromatic chromatin and high nuclear cytoplasmic ratio.
- Little or absence of colloid.
- Tumor necrosis can be seen.

Histologic Features

- Variable histologic growth patterns and insular, trabecular, solid, peritheliomatous, and infiltrating growth (Fig. 3.56a–c).
- Small uniform tumor cells with round, hyperchromatic to vesicular nuclear chromatin and small nucleoli.
- Mitotic figures, vascular invasion, and tumor necrosis are common.
- A small proportion of papillary carcinoma or follicular carcinoma may be present.
- Regardless of the percentage, the presence of undifferentiated carcinoma component should be reported.

Immunohistochemistry

- Positive for TTF1, PAX8, and thyroglobulin
- Focal p53 positivity
- Increased MIB-1 proliferative index
- Negative for calcitonin and neuroendocrine markers

Differential Diagnosis

- Medullary carcinoma
- Follicular carcinoma
- Metastasis

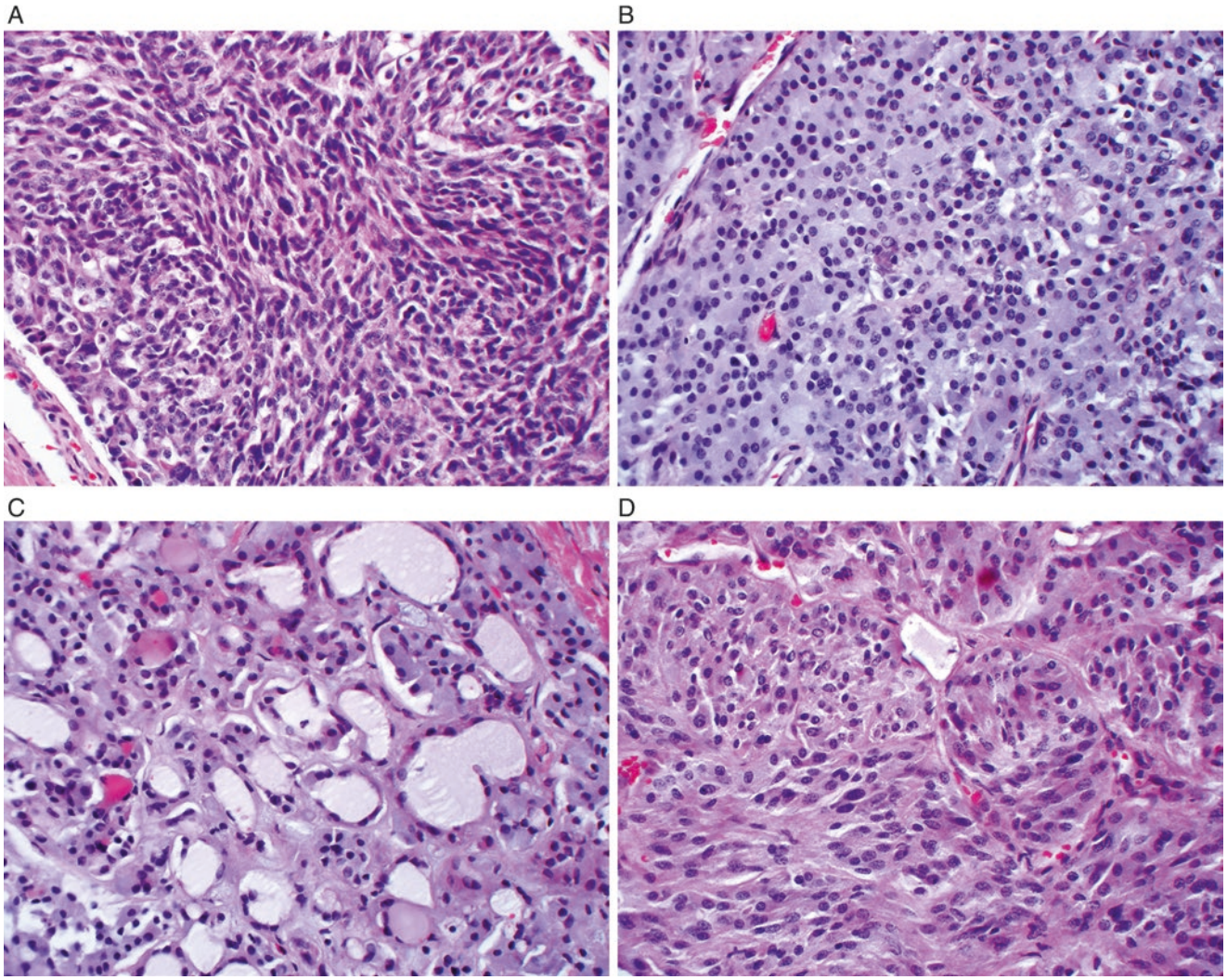

Fig. 3.53 Histologic pattern of medullary carcinoma

Undifferentiated (Anaplastic) Carcinoma

Clinical Features

- Rare, accounting for 5% of malignant thyroid neoplasms
- Usually occur after age 50, more common in women
- Rapid growth in months
- Diffuse enlargement of the thyroid with firm nodules and masses
- Can be a painful or painless mass

Cytological Features (Fig. 3.57a–d)

- Epithelioid, spindle, or giant neoplastic cells, singly or in small clusters
- Marked nuclear pleomorphism, bizarre nuclei, with single or multiple prominent nucleoli
- Frequent mitotic figures with abnormal mitoses
- Extensive tumor necrosis and acute inflammatory cells in the background

Histologic Features

- Admixture of spindle cells, pleomorphic giant cells, and epithelioid cells (Fig. 3.58a–d).
- Tumor may show predominately or exclusively spindle cells with a sarcomatoid appearance.
- Squamoid changes are common.
- Prominent neutrophilic infiltrate can be seen.
- Vascular invasion may be present.
- Several histologic variants have been described: osteoclastic variant, paucicellular variant, and lymphoepithelioma-like variant.

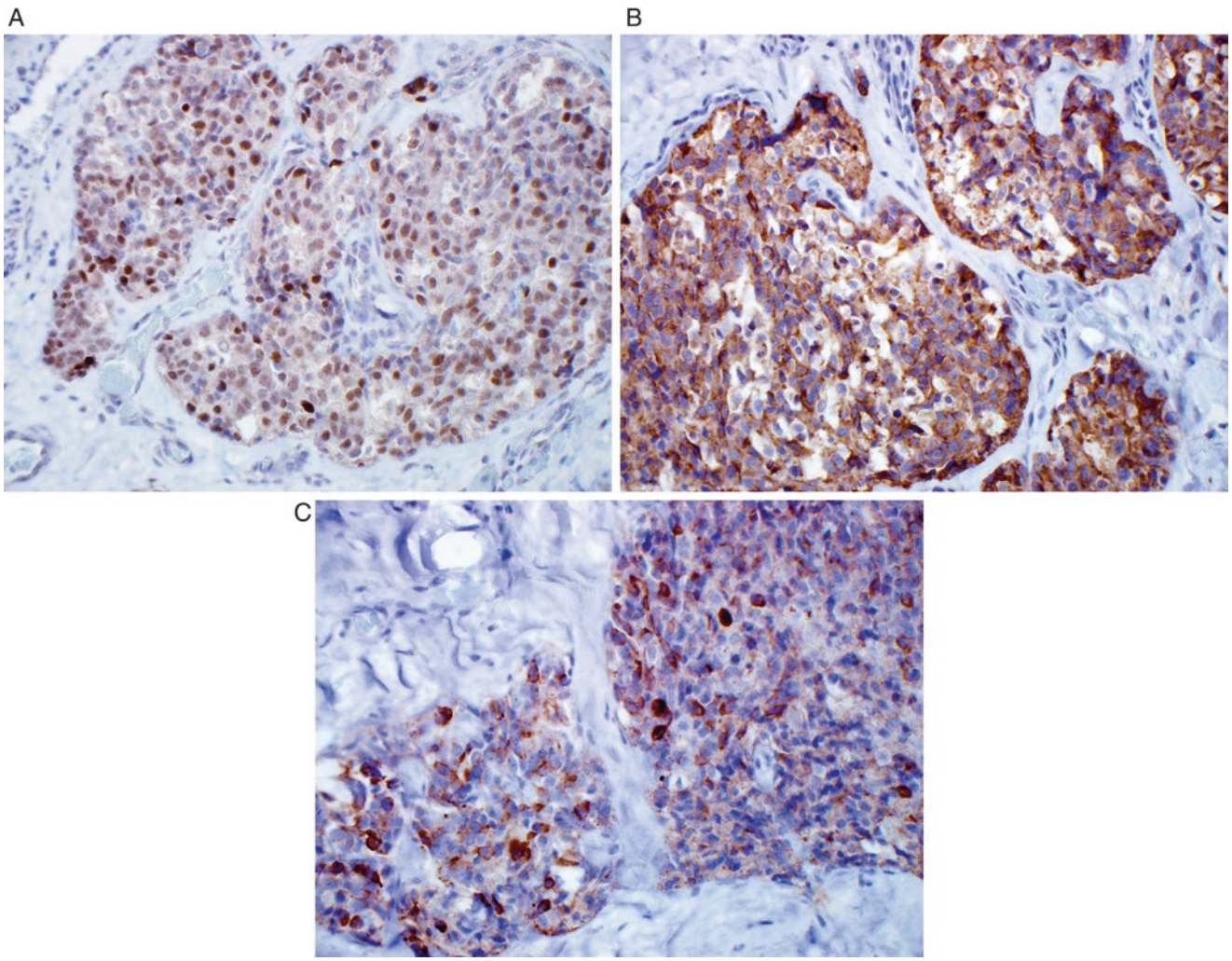

Fig. 3.54 Example of medullary carcinoma weakly positive for TTF1 (**a**) and positive for calcitonin (**b**) and chromogranin (**c**)

- A focus of well-differentiated or poorly differentiated thyroid carcinoma may be identified following an extensive sampling.

Immunohistochemistry

- Most cases are negative for TTF1 and thyroglobulin.
- About 50% of cases are positive for PAX8 (Fig. 3.59d) as shown in a needle core biopsy case (Fig. 3.59a–d).
- Strong p53 positivity is common.
- Over 80% of cases are positive for one of the cytokeratins (AE1/3, CAM5.2, CK5/6, and 34betaE12).
- Epithelial membrane antigen (EMA) is positive in less than 50% cases.

Differential Diagnosis

- Medullary carcinoma
- Soft tissue sarcomas
- Metastasis, especially from the lung and pancreas

Uncommon and Rare Thyroid Lesions

Lymphoma and Plasmacytoma

- Most cases are non-Hodgkin's lymphoma with secondary involvement of the thyroid (Fig. 3.60a, b).
- Approximately 15–20% of lymphomas may involve the thyroid.

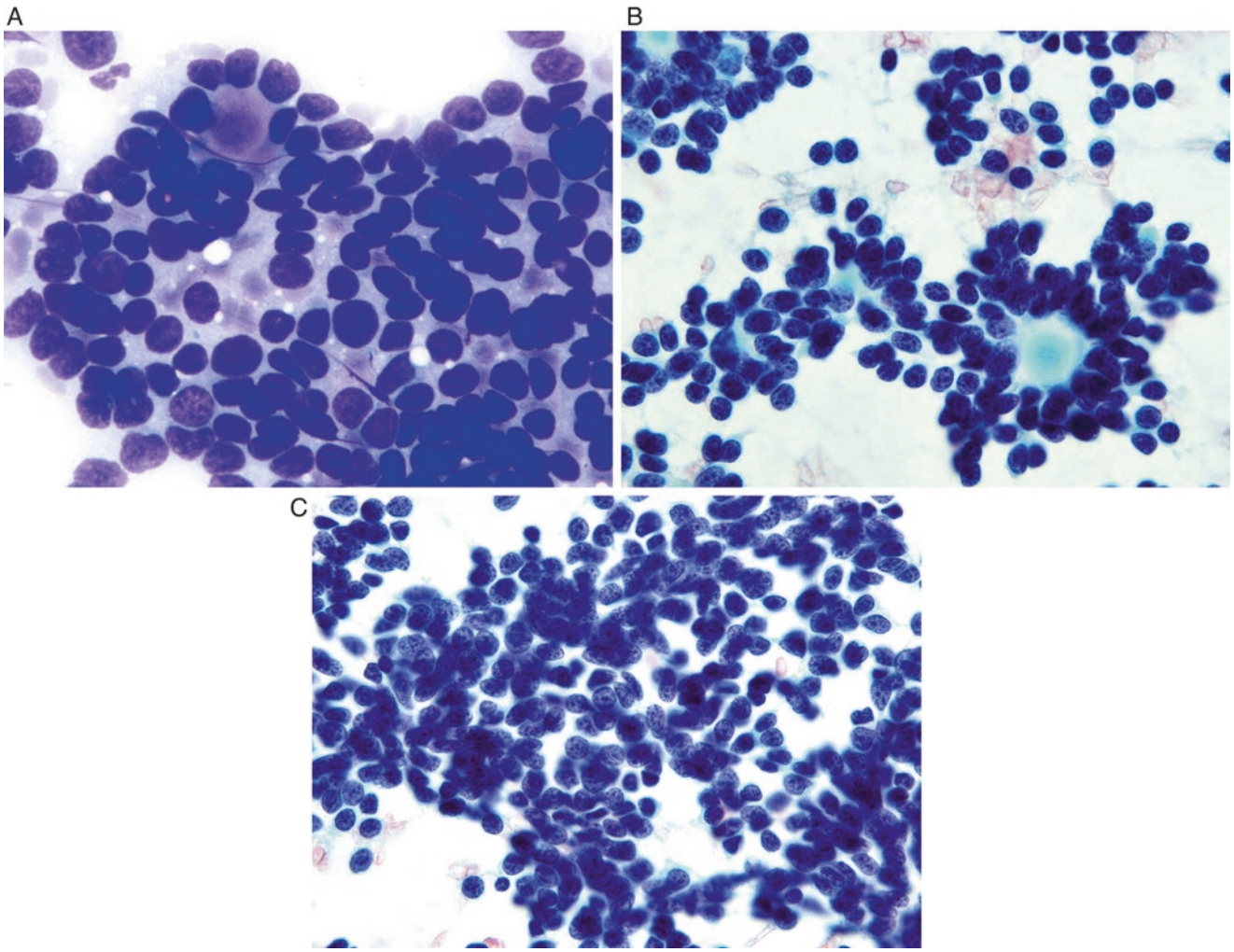

Fig. 3.55 Poorly differentiated (insular) carcinoma showing relatively uniform population of neoplastic cells with round to oval nuclei with hyperchromatic chromatin and high nuclear cytoplasmic ratio (**a**, DQ stain) and (**b**, **c**, Pap stain)

- Account for 1–3% of all malignant neoplasms of the thyroid
- Plasmacytoma/multiple myeloma as a primary presentation in the thyroid (Fig. 3.61a, b).

Squamous Cell Carcinoma

- Primary squamous cell carcinoma of the thyroid accounts for less than 1% of the malignant neoplasms of the thyroid. A metastasis especially from the head and neck, lung, and esophagus should be excluded.

Many other rare primary thyroid neoplasms have been recognized and reported in the literature. Table 3.5 summarizes the clinical, cytologic, and histologic features of these neoplasms and any ancillary tests which are potentially useful in making a diagnosis.

Metastases

- The most common metastases are from the kidney, skin (melanoma), lung, breast, stomach, and head and neck. Lymphomas and leukemias account for 15% of the cases.
- Can be a solitary mass or multiple nodules; 80% of cases involve a single lobe.
- Table 3.6 summarizes the useful IHC markers for the most common differential diagnosis.

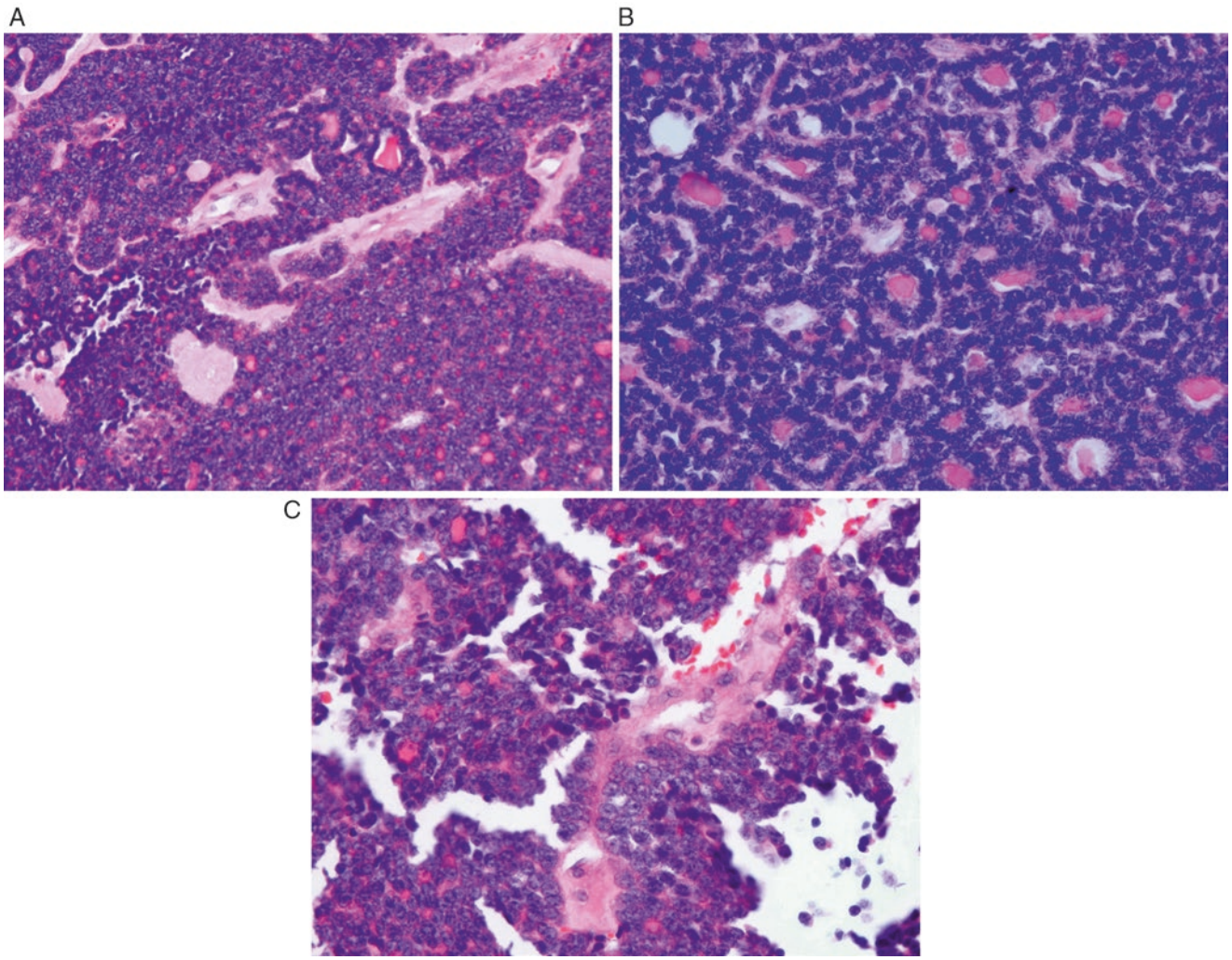

Fig. 3.56 Histologic sections showing insular and trabecular growth and follicular patterns

- Several examples of secondary tumors including metastatic renal cell carcinoma (Fig. 3.62a), breast carcinoma (Fig. 3.62b), and lung squamous cell carcinoma (Fig. 3.62c) are shown.

Parathyroid Adenoma/Neoplasm and Carcinoma

Parathyroid Adenoma/ Neoplasm

Clinical Features

- Clinical hypercalcemia is very helpful.
- Usually involve a single parathyroid gland.
- More common in patients 50–60 years of age.
- Female-to-male ratio of approximately 3:1.

Cytologic Features (Fig. 3.63a–g)

- Hypercellular specimen with similar features to follicular neoplasm.
- Neoplastic cells tend to be smaller than follicular cells.
- Numerous naked nuclei in the background.
- Vascular-rich stroma.
- Neuroendocrine nuclear chromatin.
- Fine cytoplasmic vacuoles.
- Oncocytic cytoplasm resembling Hurthle cell neoplasm.
- Clear cell change is a frequent finding.
- Focal marked nuclear pleomorphism may be present.

Histologic Feature (Fig. 3.64a–g)

- With or without a well-defined fibrous capsule.
- Proliferation of chief cells, oncocytic cells, or a mixture of different cell types.

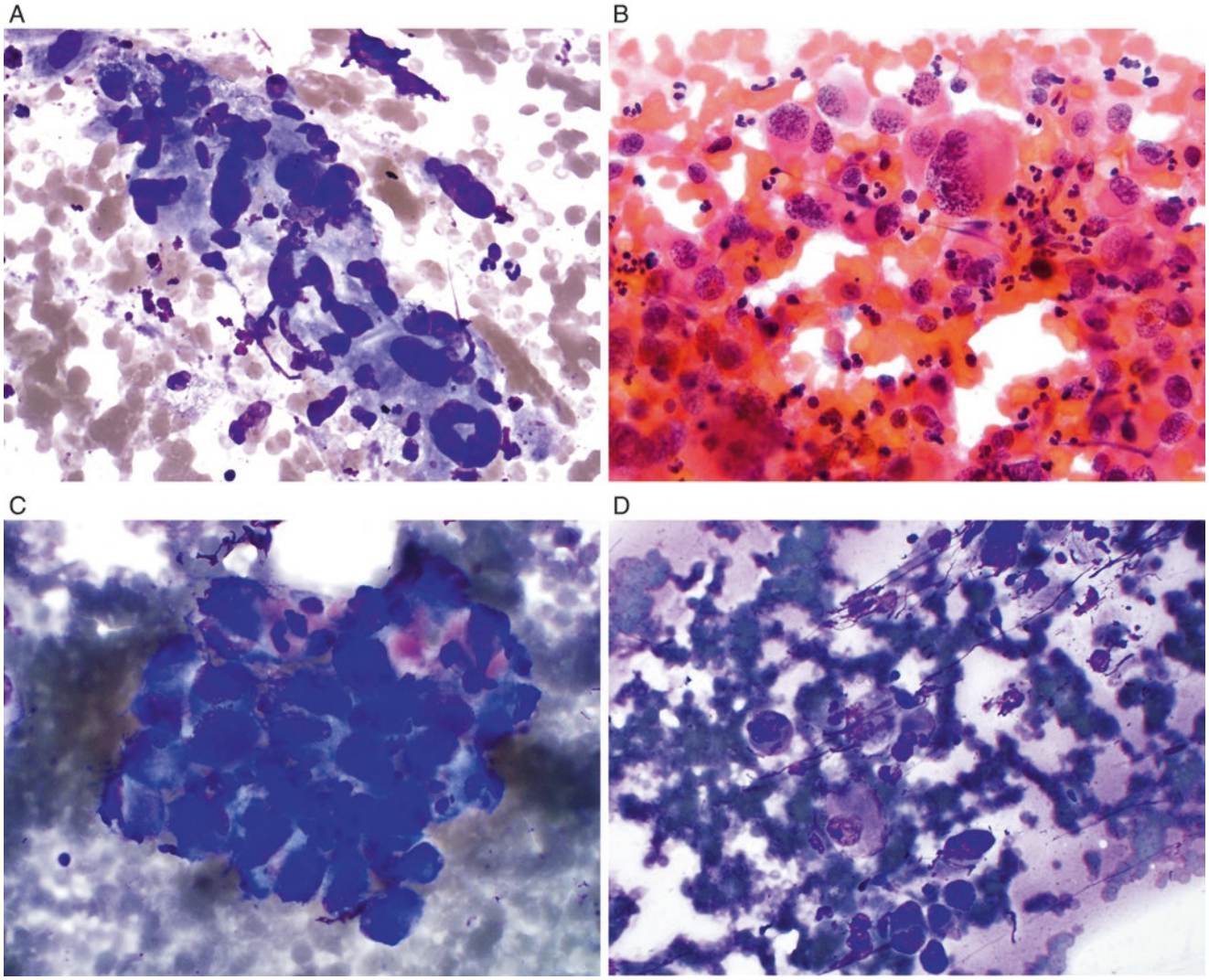

Fig. 3.57 Cytologic features of undifferentiated (anaplastic) carcinoma with a mixture of epithelioid, spindle, or giant neoplastic cells (**a**), numerous acute inflammatory cells (**b**, **c**), and abnormal mitosis (**d**)

- Many growth patterns such as solid sheets, nodular, trabecular, follicular, and acinar patterns; a mixture of growth patterns is common.
- Cystic degeneration may be present.
- Richly vascular stroma with limited fibrotic areas or fibrous bands.
- Calcification or even ossification can occur.
- The neoplastic chief cells show round nuclei, neuroendocrine chromatin, and small nucleoli.
- Focal nuclear pleomorphism with giant hyperchromatic and multilobar nuclei may be seen.
- A thin rim of normal parathyroid tissue at the periphery.
- Mitotic figures are generally absent.
- Massive infarction following an FNA can occur, but tumor necrosis is absent.
- Three histologic variants have been described: oncocytic adenoma, water-clear cell adenoma, and lipoadenoma.
- Absence or marked reduction of intracellular and extracellular neutral lipid by oil red O stain.
- Atypical parathyroid adenoma has been used to describe an adenoma with broad fibrous bands and lack of other malignant features, such as vascular invasion, capsular invasion, increased mitoses, and tumor necrosis.

Immunohistochemistry

- Table 3.7 summarizes a panel of useful IHC markers in the differential diagnosis.

Differential Diagnosis

- Follicular neoplasm
- Hurthle cell neoplasm
- Medullary carcinoma
- Papillary carcinoma

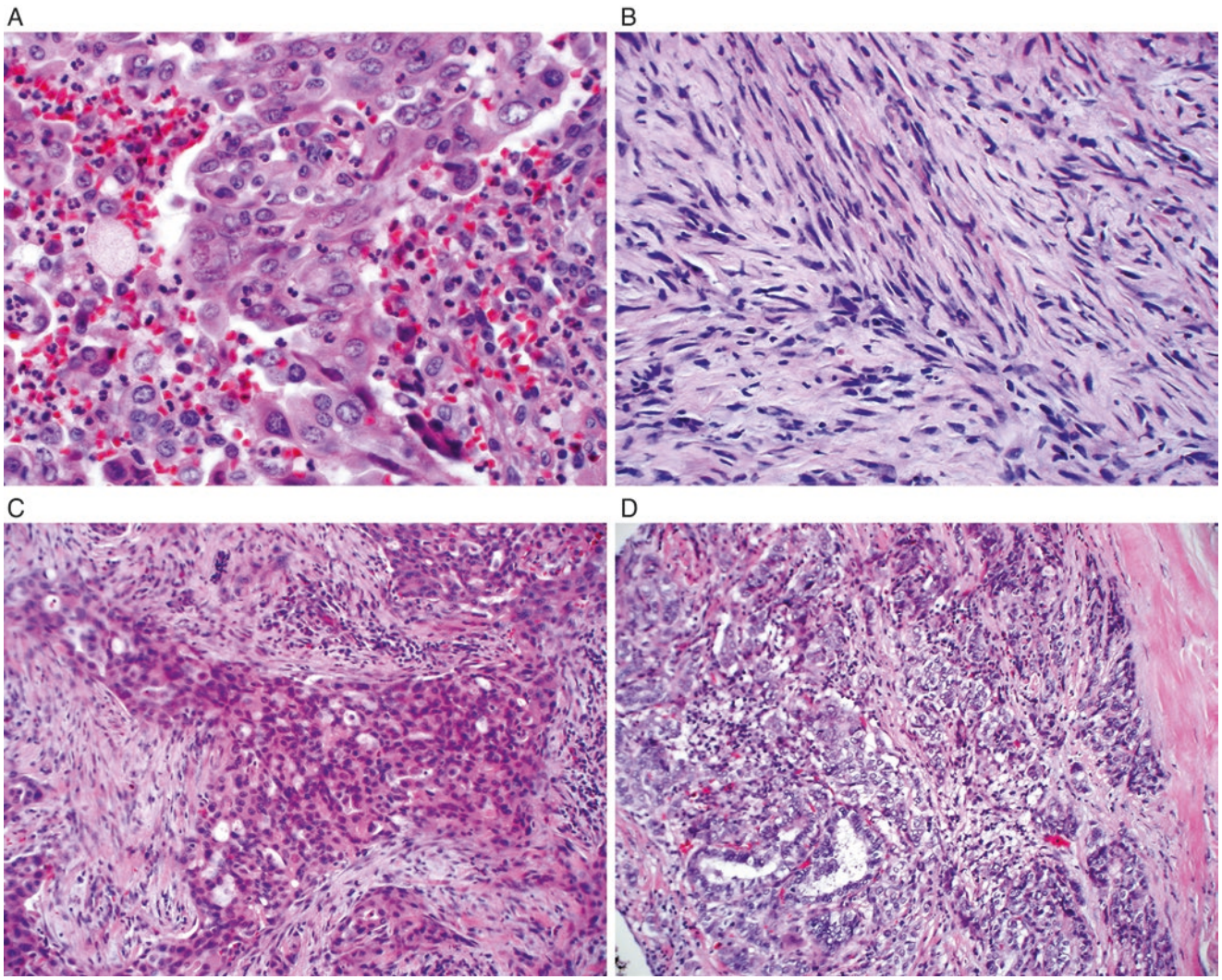

Fig. 3.58 Undifferentiated (anaplastic) carcinoma showing histologic sections with pleomorphic giant cells, and epithelioid cells (**a**), exclusively spindle cells (**b**), squamoid changes (**c**), and transformation from PTC (**d**)

Parathyroid Carcinoma

Clinical Features

- Rare; accounting for less than 1% of patients with primary hyperparathyroidism
- Male-to-female ratio of approximately 1:1
- High serum PTH and hypercalcemia

Cytologic Features

- Tumor cells with large nuclei and prominent nucleoli, diffuse nuclear atypia, tumor necrosis, and increased mitoses are suggestive of malignancy.

Histologic Features (Fig. 3.65a–c)

- Usually solid sheets, trabecular, follicular, rosette-like, and spindle cell growth patterns.
- Can be chief cells, oncocytic cells, clear cells, or a mixture.
- Broad fibrous bands and focal coagulative necrosis are commonly seen.
- Enlarged nuclei with prominent nucleoli may be present.
- Mitotic activity is extremely variable but often more than 5 per 50 high-power fields.
- For a definitive malignancy, one of these features must be seen: (1) vascular invasion in the fibrous capsule or the surrounding soft tissue, (2) capsular penetration with invasion into the adjacent tissues, or (3) metastasis.

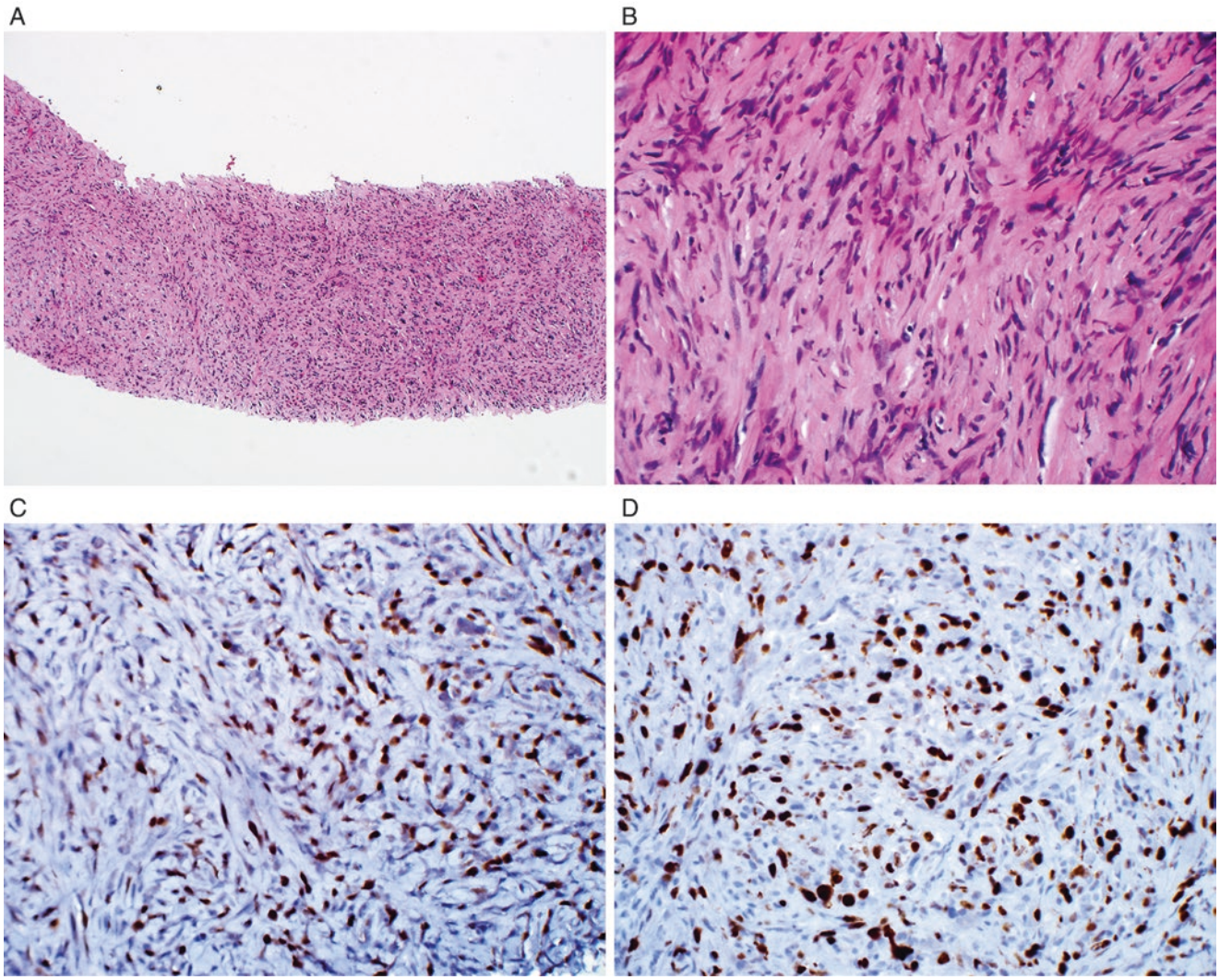

Fig. 3.59 An example of anaplastic carcinoma with spindle cell morphology on needle core biopsy specimen (**a** and **b**). Note tumor cell is positive for PAX8 (**c**) and high MIB1 proliferative index (**d**)

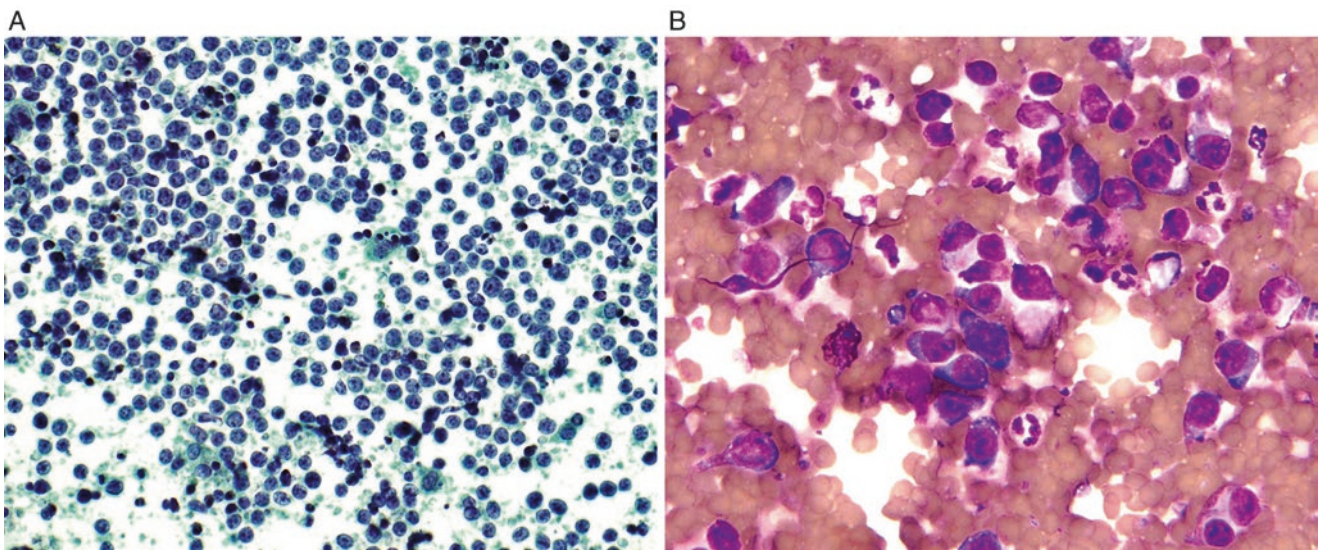

Fig. 3.60 A diffuse large B-cell lymphoma on FNA smear

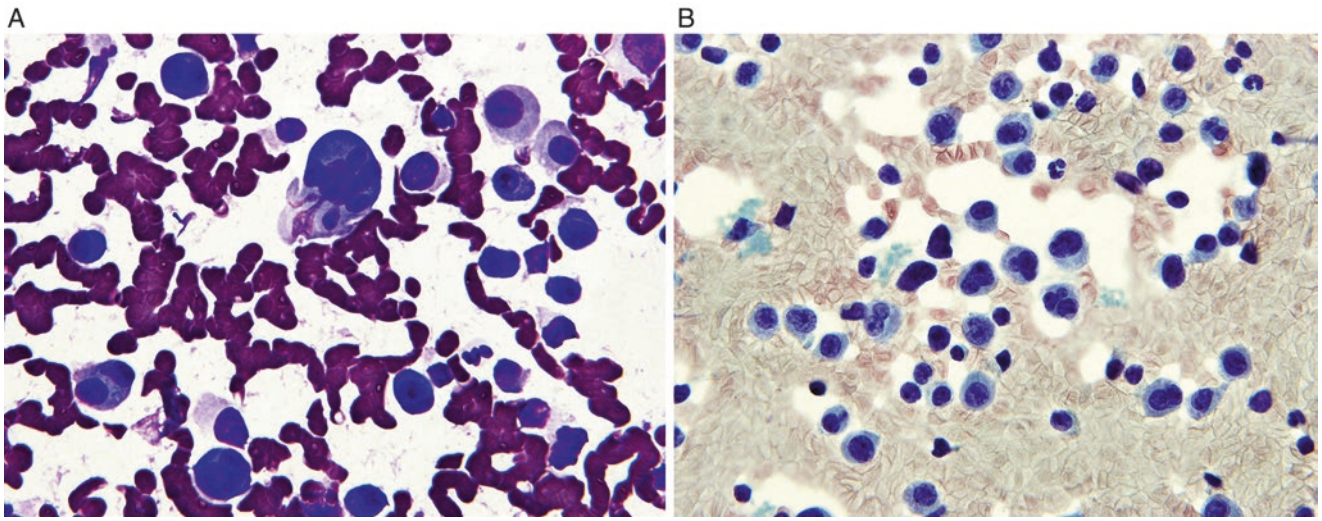

Fig. 3.61 A plasmacytoma involving the thyroid as a primary presentation

Table 3.5 Summary of uncommon and rare thyroid neoplasms/lesions

Diagnosis	Clinical features	Cytologic features	Histologic features	Ancillary tests
Mucoepidermoid carcinoma	Rare, more common in female adults	Epidermoid cells and mucin-containing cells in the background of mucin	Similar histologic features of the salivary gland	Mucicarmine stain for intracellular mucin positive, focally positive for TTF1 and thyroglobulin,
SMECE	Rare, nearly always in adult women	Bland-looking epithelial cells and mucin-containing cells	Sclerotic stroma with infiltrating epithelial tumor cells, mucin-containing cells, and numerous eosinophils and plasma cells, squamous metaplasia commonly seen	May be focally positive for TTF1 and CEA, usually negative for thyroglobulin
Mucinous carcinoma	Very rare	Groups of epithelial cells in a background of mucin	Clusters of tumor cells in pools of mucin	Focally positive for TTF1, thyroglobulin, and MUC2
SETTLE	Adolescents or young adults, male-to-female ratio about 1.5:1		Lobulated tumor growth in fibrous stroma, usually biphasic with both spindle cells and glandular or tubulopapillary structures, similar to synovial sarcoma	Both spindle cells and glands are positive for cytokeratin, spindle cells can be positive for myoepithelial markers, negative for calcitonin, CEA, S100, CD5, and S100
CASTLE	Very rare, middle-aged adults	Atypical epithelial cells in groups	Anastomosing epithelial tumor islands in a desmoplastic stroma, tumor cells with squamoid or syncytial appearance	IHC profile is similar to thymic carcinoma including positive for CD5, can be positive for PAX8 and p63
Angiosarcoma	Iodine deficiency has been suggested to be a possible etiologic factor, elderly, male-to-female ratio of 1.2:1	Large pleomorphic epithelioid tumor cells with large vesicular nuclei, prominent central nucleoli, and abundant eosinophilic cytoplasm in the background of necrosis	Anastomosing vascular channels lined by atypical endothelial cells, discrete cytoplasmic vacuoles, or sheets of atypical epithelioid cells	Positive for ERG, CD31, and CD34, focal or diffusely positive for cytokeratin, can be seen in epithelioid angiosarcoma, a metastasis must be excluded.

(continued)

Table 3.5 (continued)

Diagnosis	Clinical features	Cytologic features	Histologic features	Ancillary tests
PNST	Very rare	Spindle cells	Spindle cells with variable degree of atypia	Focal and weak positive for S100 in MPNST, diffusely and strongly positive for S100 in Schwannoma
SFT	Adults	Bland-looking spindles	Alternating hypercellular and hypocellular areas, with haphazardly distributed bland spindle or stellate cells in fibrous stroma of thick collagen fibers	Positive for STAT6, CD99, CD34, and Bcl2, negative for cytokeratin and S100
SMT	Very rare, more often malignant	Spindle cells with variable degree of atypia	Fascicles of mitotically active atypical spindle cells, with necrosis, hemorrhage, and invasive growth pattern in a leiomyosarcoma	Positive for SMA and desmin
FDCT	Rare, may be associated with Epstein-Barr virus	Spindle to epithelioid cells with vesicular chromatin, distinct nucleoli, and moderate amount of eosinophilic cytoplasm	Sheets of spindle to epithelioid cells with vesicular chromatin, distinct nucleoli, and moderate amount of eosinophilic cytoplasm, small lymphocytes are present, mitotic rate is variable from 0 to 10 per high-power field	Positive for vimentin, CD21, CD23, and CD35, may be focally positive for S100, CD68, CD45, and CD20
LCH	Rare, most patients are younger than 20	Histiocyte-like cells with prominent nuclear grooves, mixed with abundant eosinophils and lymphocytes in a hemorrhagic background	Sheets of large histiocyte-like cells with vesicular chromatin, prominent nuclear folds ("coffee-bean"), and small nucleoli, multinucleated cells may be present, abundant eosinophils and lymphocytes	Positive for CD1a and S100, can be positive or CD68, negative for cytokeratin, CD21, and CD35
RDD	Rare, reported in adult women	Large histiocytes with foamy cytoplasm containing intact lymphocytes	Nodules of histiocyte-like cells with emperipolesis and lymphoid cells in the background	Positive for S100 and CD68
Paraganglioma	Rare, female predilection, 40–60 years	Single cells or loose clusters of large cells with ovoid nuclei and focally discrete nucleoli	Lobules of ovoid cells with finely granular cytoplasm in the vascular-rich networks, scattered tumor cell nuclei can be enlarged, hyperchromatic, or bizarre	Positive for synaptophysin and chromogranin, S100 highlighting sustentacular cells
Ectopic thymoma	Very rare, most common in middle-aged women	Spindle cells, epithelioid cells, and lymphoid cells in a various proportions depending on the histologic type	Similar to the histologic types of mediastinal thymoma	Positive for PAX8 and p63
Teratoma	Very rare, about 75% in the neonates and infants and 25% in children and adults, >90% of the tumors are benign in the neonatal group, >50% of the tumors are malignant in the adult group	Various cellular components from a mixture of benign elements to small round cells from the immature elements	A wide range of tissue types and growth patterns as seen in other teratomas, the maturation of the neural-type tissue determines the grade, immature teratomas with prominent primitive neuroectodermal tissues (grade 3 or malignant)	Some IHC markers such as S100, myogenin, NSE, and GFAP are useful to further determine the immature components

Bcl2 B-cell CLL/lymphoma 2, *CASTLE* carcinoma showing thymus-like differentiation, *CD5* cluster of differentiation 5, *ERG* ETS-related gene, *FDCT* follicular dendritic cell tumor, *GFAP* glial fibrillary acidic protein, *IHC* immunohistochemical, *LCH* Langerhans cell histiocytosis, *MPNST* malignant peripheral nerve sheath tumor, *MUC2* mucin 2, *NSE* neuron-specific enolase, *PNST* peripheral nerve sheath tumor, *RDD* Rosai-Dorfman disease, *SETTLE* spindle epithelial tumor with thymus-like differentiation, *SFT* solitary fibrous tumor, *SMA* smooth muscle actin, *SMECE* sclerosing mucoepidermoid carcinoma with eosinophils, *SMT* smooth muscle tumor, *STAT6* signal transducer and activator of transcription 6

Table 3.6 Summary of useful IHC markers for the common differential diagnoses

Diagnosis/markers	Thyroid	CRCC	Lung	Breast	Stomach	SCC
CK7	+	−	+	+	+	−/+
CK20	−	−	−	−	−/+	−
Vimentin	+	+	−	−	−	−
TTF1	+	−	+	−	−	−
PAX8	+	+	−	−	−	−
Thyroglobulin	+	−	−	−	−	−
pVHL	−	+	−	−	−	−
RCCma	−	+/−	−	−	−	−
CD10	−	+	−/+	−	−	−
GATA3	−	−	−	+	−	−/+
ER	−/+	−	−	+	−	−
CDX2	−	−	−	−	+/−	−
p40	−	−	−	−	−	+

Breast breast carcinoma, *CDX2* caudal type homeobox 2, *CRCC* clear cell renal cell carcinoma, *GATA3* GATA-binding protein 3, *Lung* lung adenocarcinoma, *stomach* gastric and upper gastrointestinal adenocarcinoma, *pVHL* von Hippel-Lindau tumor suppressor gene protein, *RCCma* renal cell carcinoma marker, *SCC* squamous cell carcinoma, *Thyroid* thyroid carcinoma of follicular cell origin

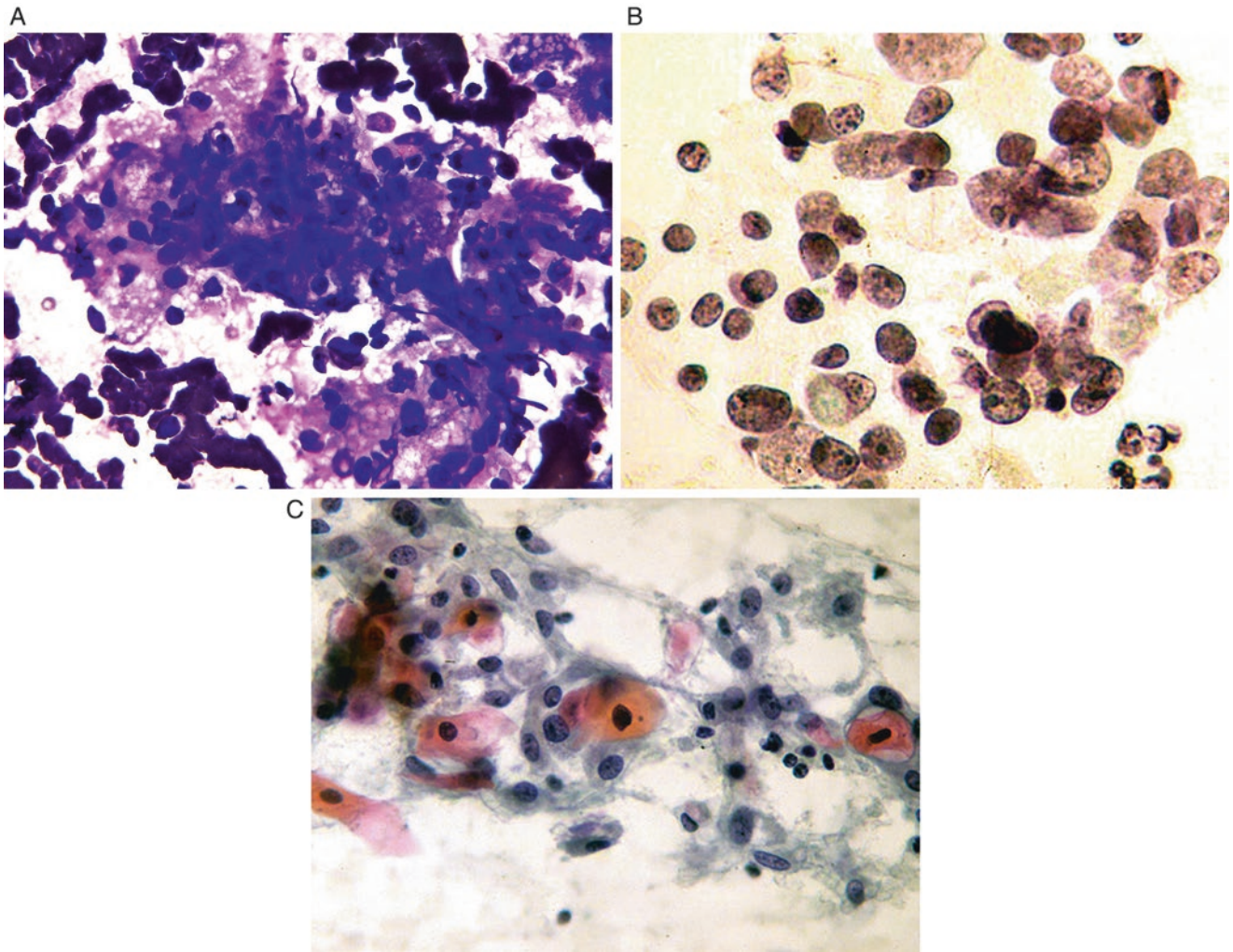

Fig. 3.62 Examples of secondary tumors with metastatic renal cell carcinoma (**a**), breast carcinoma (**b**), and squamous cell carcinoma (**c**)

Immunohistochemistry

- Positive for PTH, chromogranin, and GATA3.
- Negative for calcitonin, TTF1, PAX8, and thyroglobulin.
- Table 3.8 summarizes a panel of useful IHC markers in distinction of parathyroid carcinoma from parathyroid adenoma.

Differential Diagnosis

- Thyroid carcinoma
- Medullary carcinoma
- Metastasis

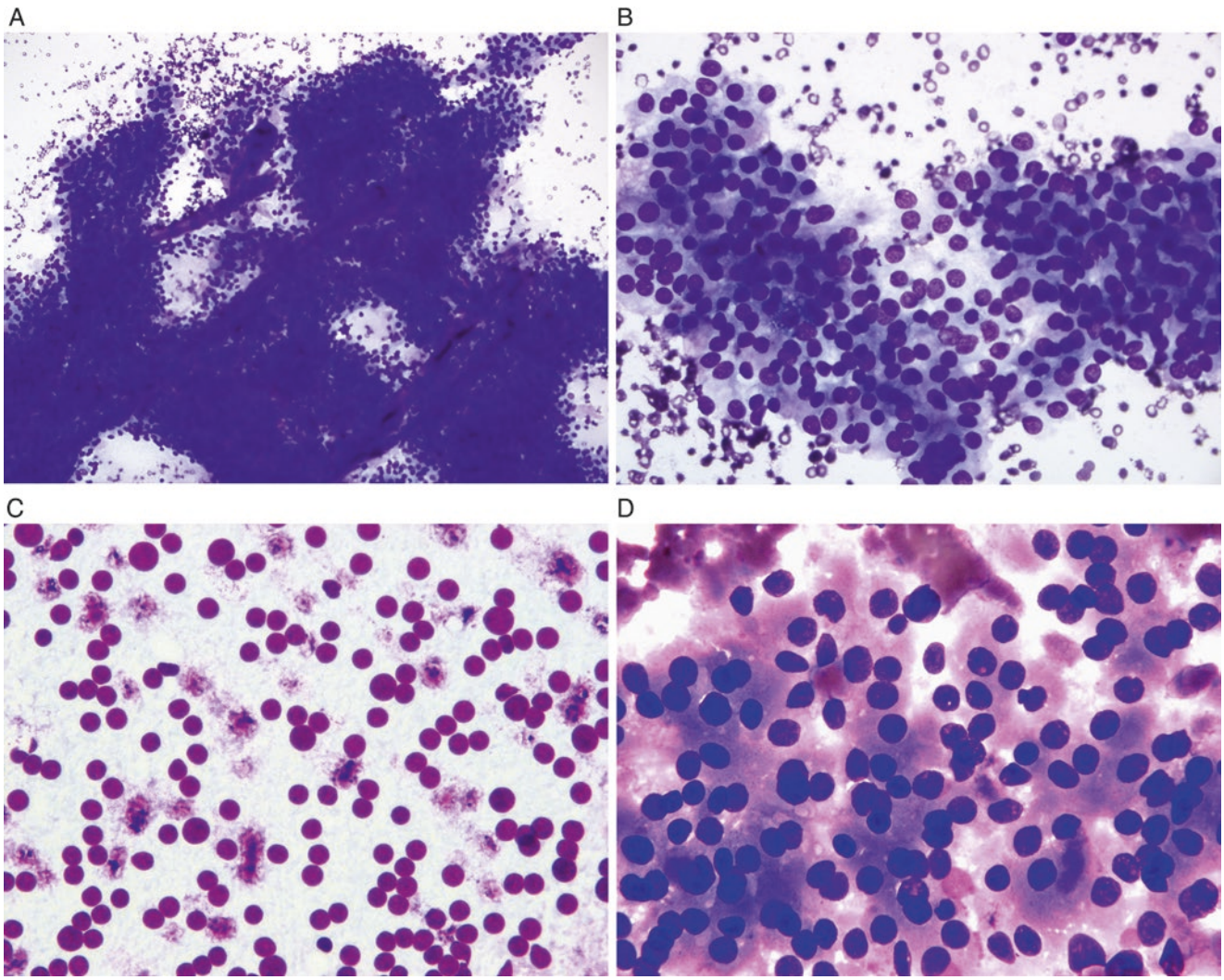

Fig. 3.63 Cytologic features of parathyroid neoplasm are similar to follicular neoplasm with neoplastic cells smaller than follicular cells, numerous naked nuclei in the background, vascular-rich stroma, and oncocytic changes (**a**–**e**). Note the cellblock section (**f**) and positive for PTH (**g**)

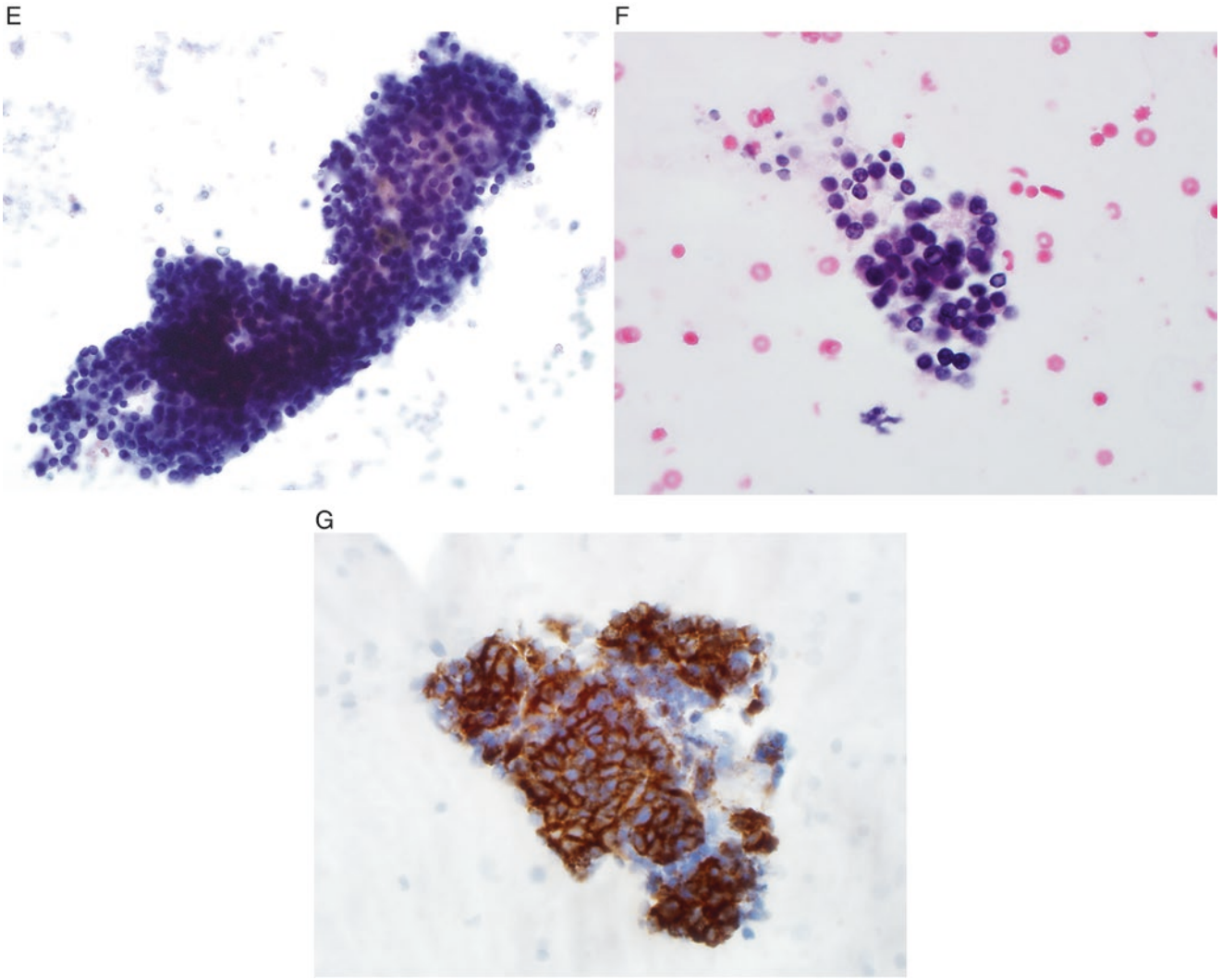

Fig. 3.63 (continued)

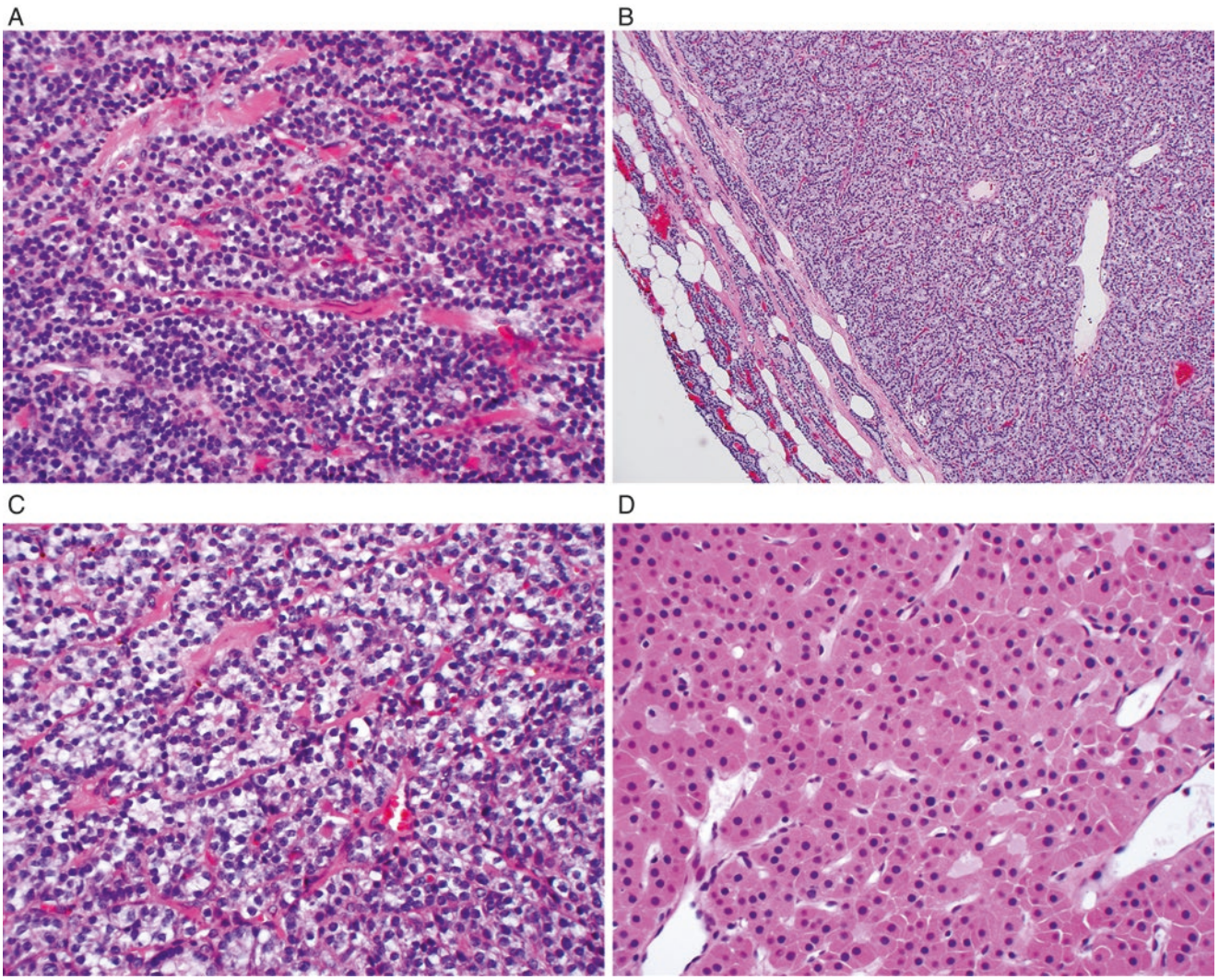

Fig. 3.64 Histologic sections of parathyroid adenoma with different growth patterns and cell changes. Note that a rim of normal parathyroid tissue (**b**), clear cell changes (**c**), oncocytic changes (**d**), cystic changes (**e**), follicular-like structures (**f**), and positive for PTH (**g**)

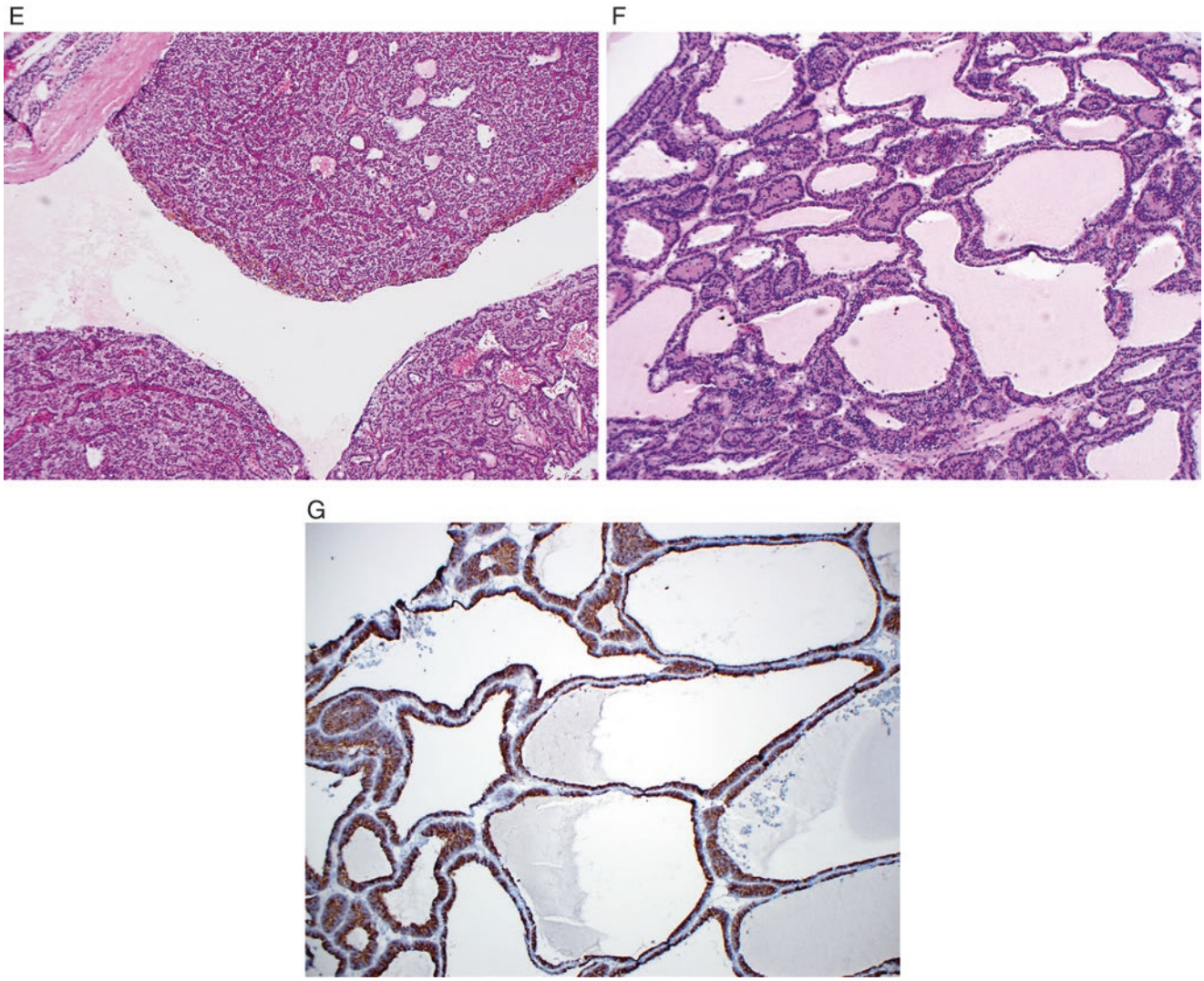

Fig. 3.64 (continued)

Table 3.7 Summary of useful IHC markers for differential diagnosis of follicular neoplasm/Hurthle cell neoplasm, parathyroid adenoma, and medullary carcinoma

Marker	Follicular neoplasm/ Hurthle cell neoplasm	Parathyroid adenoma	Medullary carcinoma
TTF1	+	–	Weak +
Thyroglobulin	+	–	–
PAX8	+	–	–
PTH	–	+	–
GATA3	–	+	–
Calcitonin	–	–	+

PTH parathyroid hormone

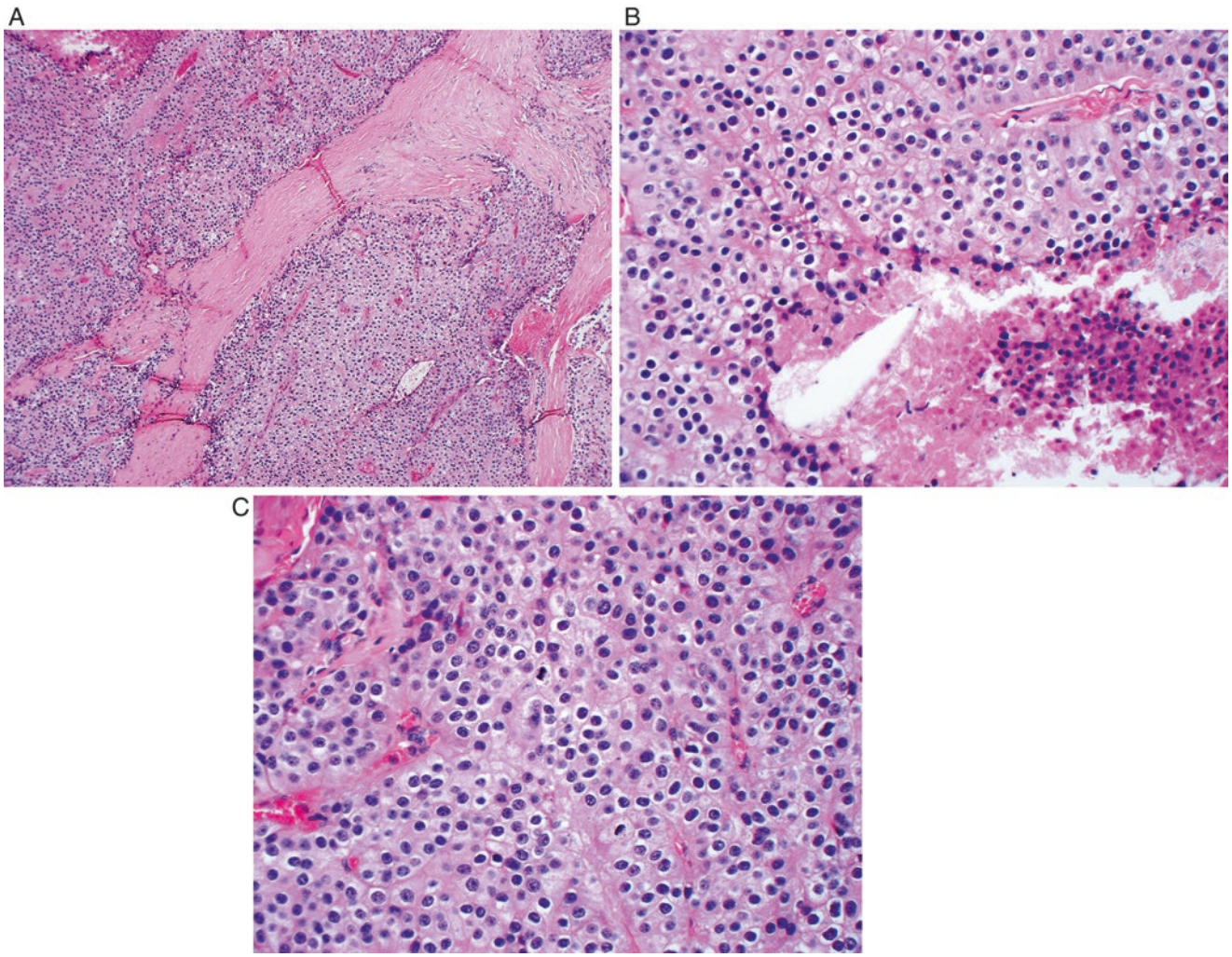

Fig. 3.65 Histologic sections of parathyroid carcinoma with thick fibrous bands (**a**), trabecular growth pattern, nuclear atypia, tumor necrosis (**b**), and many mitoses (**c**)

Table 3.8 Summary of IHC markers in distinction between parathyroid carcinoma from adenoma

Markers	Parathyroid carcinoma	Parathyroid adenoma
Parafibromin (HRPT2)	−/weak	+
Galectin-3	±	−
MIB-1 (Ki-67)	High or mildly increased	Low
PTH	+	+
GATA3	+	+

Case Presentations

Diagnosis of a common thyroid lesion such as nodular goiter, lymphocytic thyroiditis, papillary carcinoma, and follicular/Hurthle cell neoplasm in an adequately cellular FNA specimen is usually straightforward. There are three challenging scenarios sometimes encountered when evaluating an FNA biopsy of a mass lesion of the thyroid with or without a cellblock preparation. Case scenario 1 is how to identify a medullary carcinoma and its variants; case scenarios 2 and 3 are how to make a diagnosis of variants of papillary carcinoma; case scenario 4 is how to deal with an overt malignancy or neoplastic process in which an undifferentiated carcinoma, a rare primary tumor, and a secondary tumor are included in the diagnostic consideration.

Case Scenario 1

Learning Objectives

1. Reiterate the diagnostic criteria for medullary carcinoma of the thyroid.
2. Review the most effective panel of immunomarkers for diagnosis of medullary carcinoma and its mimics.

Case

A 22-year-old woman presented with a 1.0 × 0.8 cm nodule at the left lobe of the thyroid. She has no known history of a prior malignancy and no significant family history for cancer. An ultrasound-guided FNA was performed. The FNA smear showed a cellular specimen with cytologically bland histiocyte-like cells singly, in small groups, or follicular or acinar patterns. No colloid was seen. The cellular components showed small- to medium-sized nuclei with fine nuclear chromatin and abundant fine granular to foamy cytoplasm as shown in Fig. 3.66a–c. Occasional binucleation was noted. Significant nuclear atypia, nuclear grooves, intranuclear inclusions, or diagnostic nuclear features for papillary carcinoma were not observed. Spindle cells and inflammatory cells were not seen. The cellblock preparation was nearly acellular with occasional histiocyte-like cells as shown in Fig. 3.66d.

Based on the cytologic features, the diagnostic consideration included (1) medullary carcinoma, (2) follicular/Hurthle cell neoplasm, (3) histiocytic lesion, and (4) a secondary tumor. The presence of a mixture of cytologically bland small groups and single cells without colloid in the background was highly suspicious for medullary carcinoma. Follicular neoplasm can have clear cell changes, but it is unusual to have many single cells with intact cytoplasm. In addition, extensive microfollicular patterns were not seen. The presence of small cohesive clusters and binucleated cells made them less likely to be histiocytes. Lack of nuclear grooves and inflammatory cells, including eosinophils, excluded Langerhans cell histiocytosis. The absence of a vascular pattern, in addition to the patient's age and no known history of renal cell carcinoma, largely excluded a metastatic renal cell carcinoma.

As mentioned earlier, rare single cells were noted in the cellblock preparation. A small panel of IHC including calcitonin and CEA was attempted on the cellblock sections; the results showed that rare single cells were strongly positive for calcitonin and CEA (Fig. 3.66e, f), supporting the diagnosis of medullary carcinoma of the thyroid. A typical medullary carcinoma of the thyroid usually demonstrates a strong immunoreactivity for CEA, calcitonin, chromogranin, and other neuroendocrine markers, is weakly positive for TTF1, and is negative for PAX8, thyroglobulin, PTH, and GATA3. A thyroid tumor of follicular cell origin tends to be strongly positive for TTF1, PAX8, and thyroglobulin. In contrast, parathyroid neoplasm is positive for PTH, neuroendocrine markers, and GATA3 and negative for calcitonin, TTF1, and thyroglobulin. Thyroglobulin tends to show some background staining or a low staining sensitivity. Therefore, it is not a very useful marker in a daily practice.

Subsequently, a total thyroidectomy was performed. The histologic features of the tumor were similar to the cytologic findings, with predominately histiocyte-like tumor cells (Fig. 3.66g) and small foci of the tumor with spindle cell morphology as shown in Fig. 3.66h. Foci of C-cell hyperplasia were present. An incidental papillary thyroid microcarcinoma (3.0 mm) with a classic papillary growth pattern and typical nuclear features was also found.

Final Diagnosis on FNA Specimen

Medullary carcinoma of the thyroid

Final Diagnoses on Surgical Specimen

Medullary carcinoma of the thyroid
- C-cell hyperplasia
- Papillary microcarcinoma (3.0 mm)

What Are the Learning Points from This Case?

1. Regardless of the degree of cytologic atypia, a diagnosis of medullary carcinoma should be considered when many single cells with intact cytoplasm and absence of colloid were seen.

(continued)

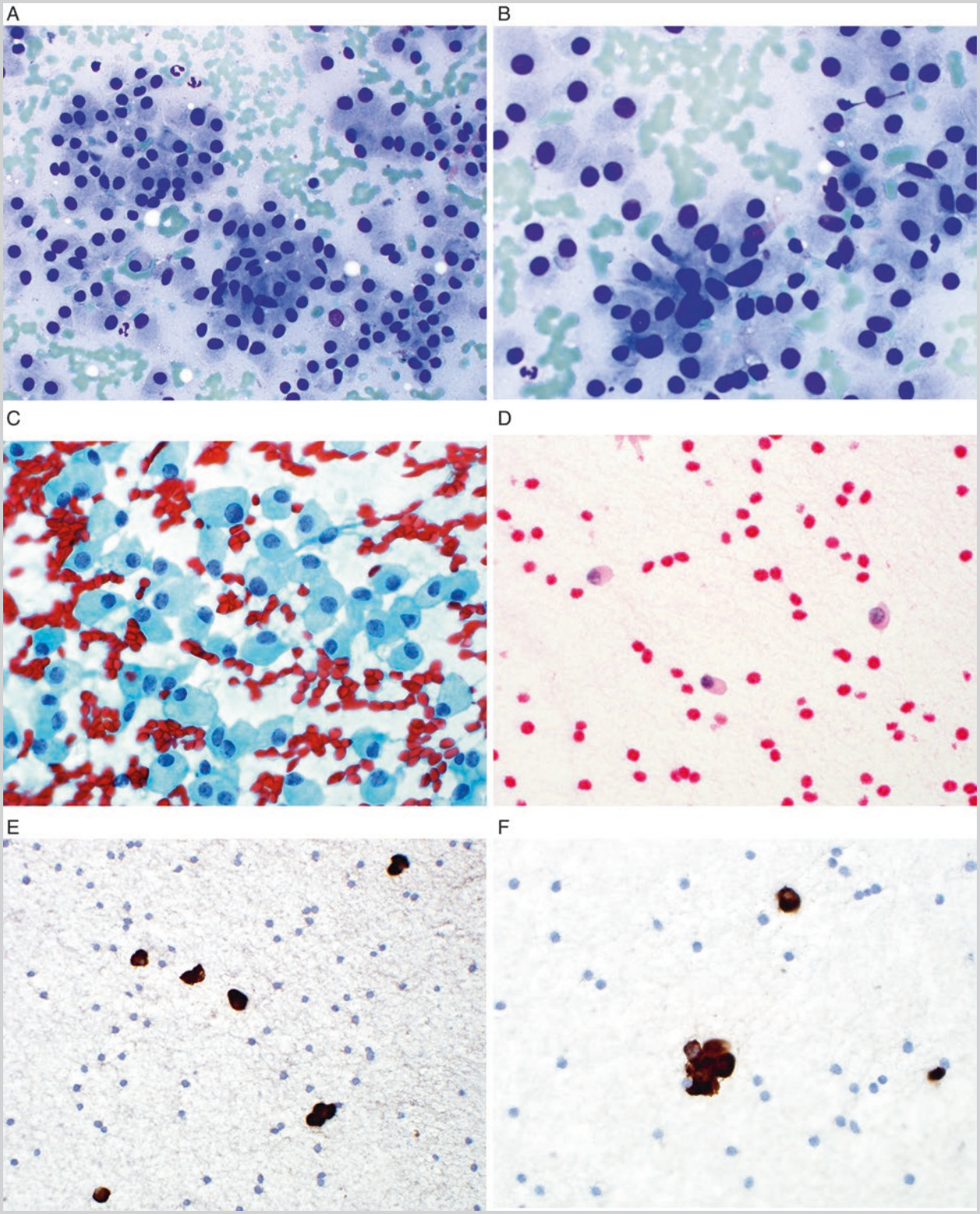

Fig. 3.66 A case of medullary carcinoma. Note that histiocyte-like cells, singly, in small groups, or follicular or acinar patterns (**a**–**c**). Cellblock (**d**), positive for CEA (**e**) and calcitonin (**f**), histologic sections (**g**, **h**)

(continued)

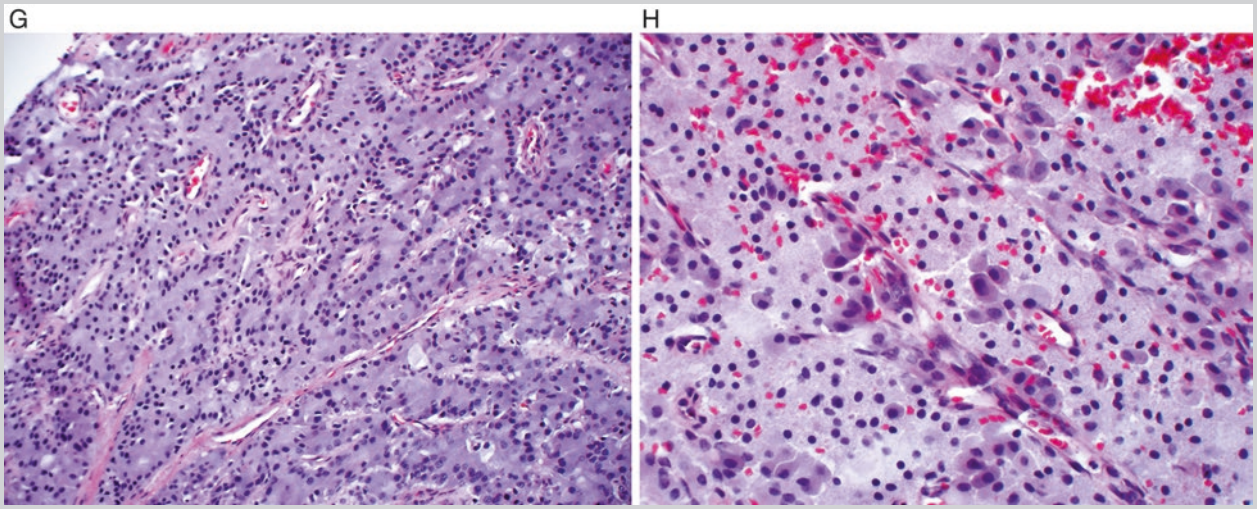

Fig. 3.66 (continued)

2. If a medullary carcinoma was suspected at time of an immediate assessment, additional passes of FNA for a cellblock should be obtained.
3. A small panel of immunostains including calcitonin and CEA should be attempted even if a cellblock preparation was essentially acellular on the hematoxylin and eosin (H&E)-stained slide as shown in the case.

Case Scenario 2

Learning Objectives

1. Reiterate the diagnostic criteria for this variant of PTC.
2. Review the differential diagnosis.

Case

A 23-year-old woman presented with a 0.9-cm-hypoechoic nodule with an irregular margin at the left lobe of the thyroid by ultrasound examination. An FNA was performed. The FNA smears were hypercellular with numerous oncocytic epithelial cells, singly or loosely in groups and small clusters, in the background of lymphoid cells. The epithelial cells contained moderate to abundant granular cytoplasm with round to ovoid nuclei, small to inconspicuous nucleoli, and scattered intranuclear pseudoinclusions as shown in Fig. 3.67a–c. Scattered spindle cells and atypical follicular cells with larger nuclei and small nucleoli were also noted. No colloid was seen. Neither distinct papillary structures nor a microfollicular pattern was observed. A cellblock preparation was obtained with essentially no cells identified.

Based on the cytologic findings above, the diagnostic consideration included (1) oncocytic variant of papillary carcinoma in the background of lymphocytic/Hashimoto's thyroiditis, (2) oncocytic variant of medullary carcinoma, (3) Hurthle cell neoplasm and lymphocytic thyroiditis, (4) Hashimoto's thyroiditis with atypia, (5) metastatic PTC in a lymph node adjacent to the thyroid, and (6) less likely, hyalinizing trabecular neoplasm. A small panel of IHC including CEA and calcitonin was attempted on the cellblock sections. The results were negative for both markers in the rare cellular components. A diagnosis of suspicious for PTC was issued.

Subsequently, a left lobectomy was performed. The histologic sections showed an oncocytic tumor with diagnostic nuclear changes for papillary carcinoma and the presence of a dense lymphoplasmacytic infiltration as shown in Fig. 3.67d–f. The adjacent nonneoplastic thyroid tissue showed lymphocytic/Hashimoto's thyroiditis. A final diagnosis of Warthin-like variant of PTC was rendered.

Final Diagnosis on the FNA Specimen

Suspicious for papillary thyroid carcinoma

Final Diagnoses on the Surgical Specimen

Papillary thyroid carcinoma, Warthin-like variant
Lymphocytic thyroiditis

(continued)

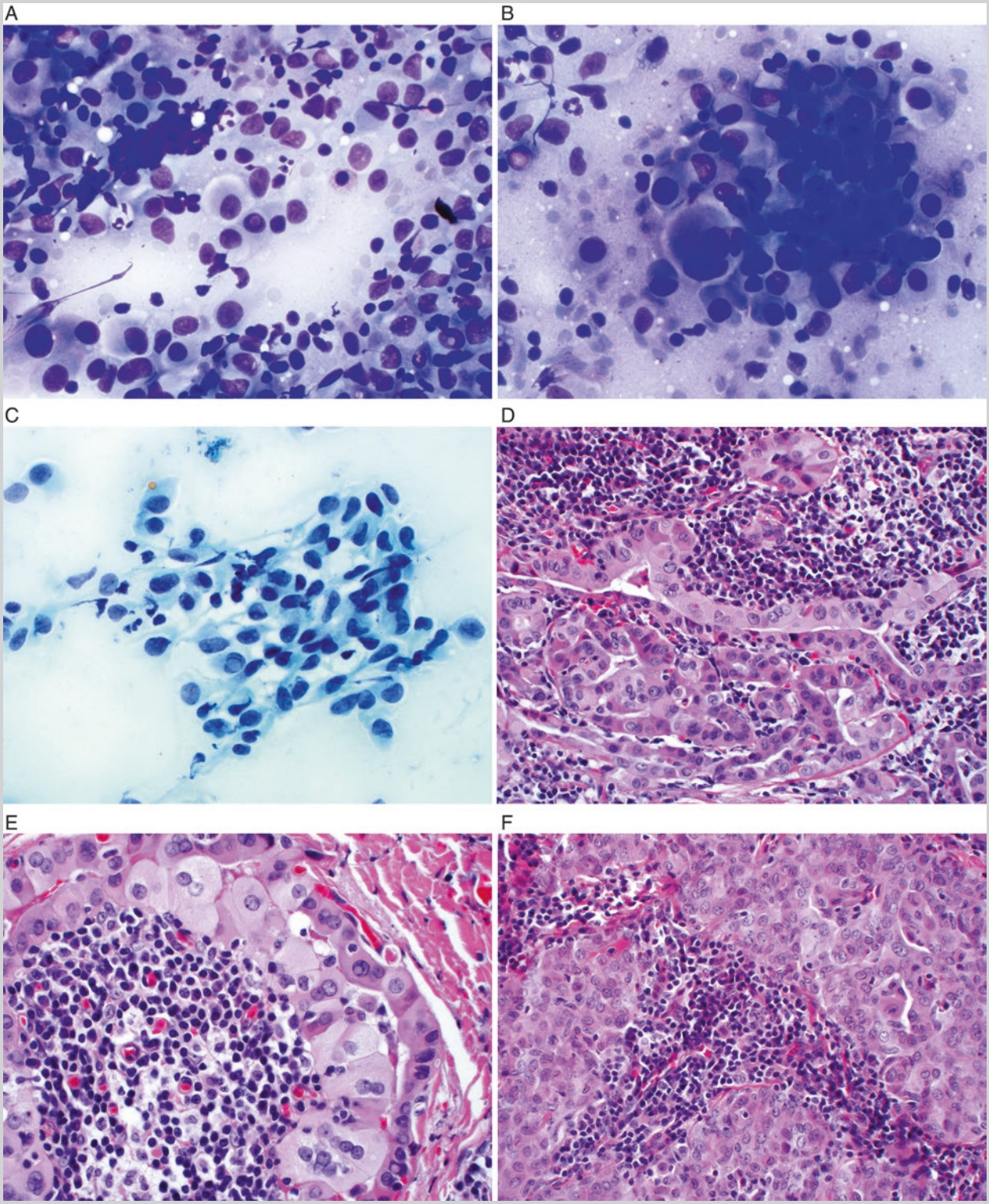

Fig. 3.67 A case of Warthin-like variant of PTC. Note that oncocytic follicular cells with nuclear changes of PTC (**a–c**) and histologic sections (**d–f**)

(continued)

What Are the Learning Points from This Case?

1. When an FNA sample demonstrates an oncocytic lesion with nuclear changes suspicious for PTC in the background of lymphoid cells, a Warthin-like variant PTC needs to be included in the differential diagnosis.
2. A Warthin-like PTC often coexists with a lymphocytic thyroiditis.
3. A small IHC panel including CEA and calcitonin can be useful in excluding a medullary carcinoma, even in a hypocellular cellblock preparation.

Case Scenario 3

Learning Objectives

1. Reiterate the diagnostic criteria for this variant of papillary carcinoma and its mimics.
2. Review the most effective panel of immunomarkers for diagnosis of this specific variant.

Case

A 60-year-old woman presented with a 3.0 cm mass at the right thyroid. Her previous medical history was significant for adenomatous colon polyps and nodular goiter which was confirmed by FNA 20 years ago. An ultrasound-guided FNA of the right lobe mass was performed. The FNA smears were hypercellular with numerous sheets and groups of atypical follicular cells with nuclear changes such as nuclear overlapping, grooves, and intranuclear inclusions for papillary carcinoma as shown in Fig. 3.68a, b. In addition to the characteristic nuclear features for a PTC, many epithelial groups/sheets showed (1) punched-out spaces resembling ductal carcinoma in situ of the breast (Fig. 3.68c), (2) large blunt papillary configuration without fibrovascular cores (Fig. 3.68d), (3) follicular cells highly cohesive and extremely overcrowded, and (4) foci of spindle cell morphology suggestive of squamous differentiation. Microfollicular pattern, colloid, and psammoma bodies were absent.

Based on the classic nuclear changes for PTC, the FNA diagnosis of PTC was issued.

Subsequently, a total thyroidectomy was performed. Histologic sections demonstrated a mixture of growth patterns, including cribriform, tubular/follicular, solid areas with spindled cells and squamoid changes, and large papillary fronds without distinct fibrovascular cores (Fig. 3.68e–h). Tumor cells exhibited definitive nuclear features for PTC and a moderate amount of granular cytoplasm. No colloid was seen throughout the tumor sections. The histologic findings raised a concern for cribriform variant of PTC. A panel of IHC including beta-catenin, CK19, HBME-1, p53, and galectin-3 was performed. The tumor cells demonstrated diffuse and strong nuclear and cytoplasmic positivity for beta-catenin and were positive for CK19, p53, and galectin-3, but negative for HBME-1 as shown in Fig. 3.68i–l. This immunostaining profile supported the morphologic impression of cribriform variant of PTC. Some investigators preferred to consider this as a distinct entity. It has been well documented that this tumor typically occurs in young patients with familial adenomatous polyposis (FAP) or Gardner syndrome. In this setting, the tumor tends to be multiple foci. A solitary sporadic tumor also has been reported as well. This particular patient most likely fit into a sporadic category since she was 60 at the time of this diagnosis and did not have a documented history of FAP.

Final Diagnosis on FNA Specimen

Papillary thyroid carcinoma

Final Diagnosis on Surgical Specimen

Papillary thyroid carcinoma, cribriform variant

What Are the Learning Points from This Case?

1. On an FNA smear, a cribriform variant of PTC should be excluded if one sees the following cytologic features: punched-out spaces resembling ductal carcinoma in situ of the breast, large blunt papillary configuration without fibrovascular cores, and foci of spindle cell morphology suggestive of squamous differentiation.
2. When this entity is suspected, additional sample should be requested for a cellblock preparation, and immunostains for beta-catenin and other useful diagnostic markers as mentioned earlier should be performed.
3. In a patient with this diagnosis, additional studies to exclude FAP in the patient and the family members are warranted.

Case Scenario 4

Learning Objectives

1. Review the differential diagnosis for an undifferentiated thyroid neoplasm.
2. Reiterate the diagnostic clues for an angiosarcoma.
3. Review the most effective panel of immunomarkers for diagnosis of this specific entity.

(continued)

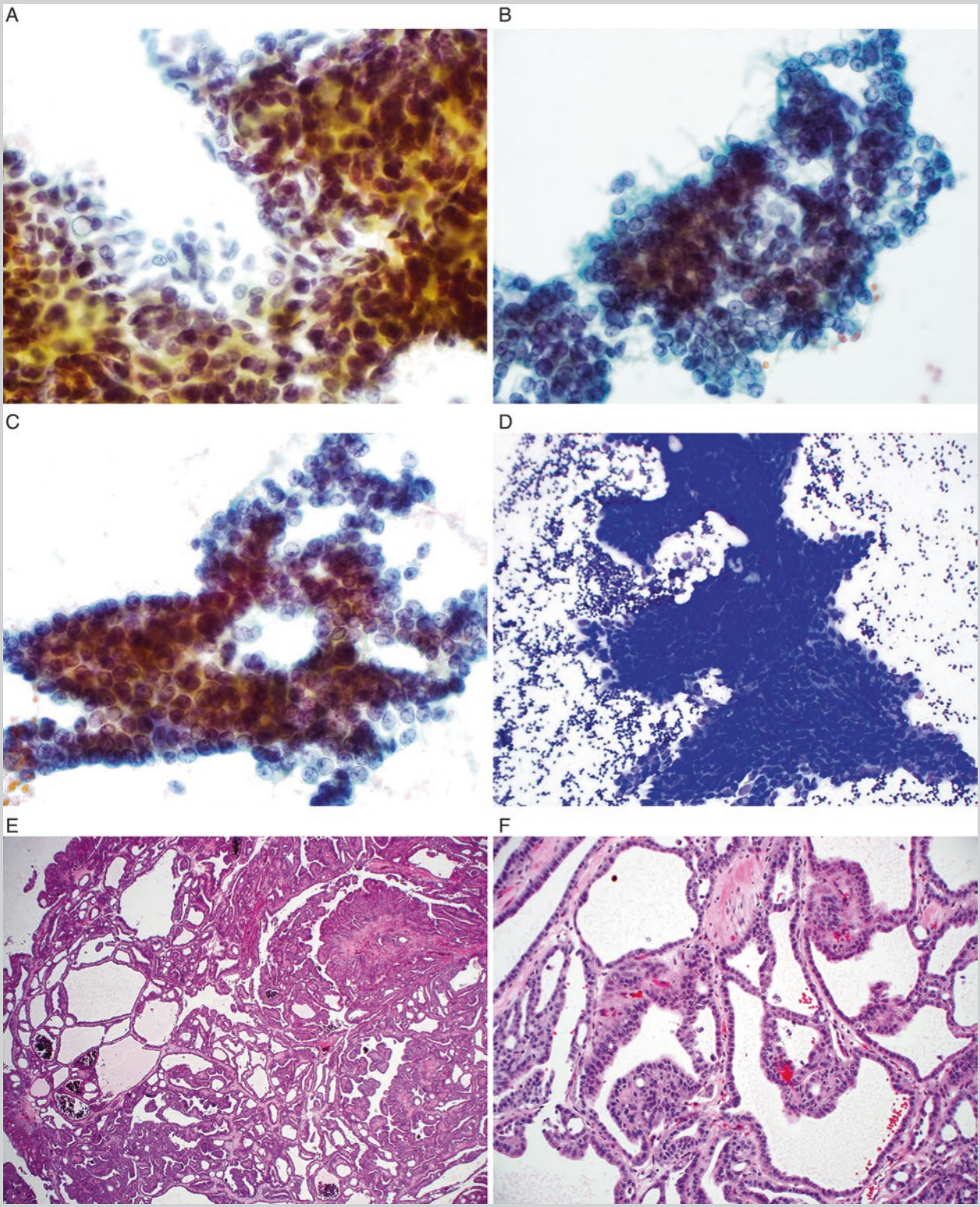

Fig. 3.68 A case of cribriform variant of PTC. Note that atypical follicular cells with nuclear changes such as nuclear overlapping, grooves, and intranuclear inclusions for papillary carcinoma (**a**, **b**), punched-out spaces resembling ductal carcinoma in situ of the breast (**c**), large blunt papillary configuration without fibrovascular cores (**d**), histologic sections (**e**–**h**), and positive stain for beta-catenin (both nuclear and cytoplasmic staining) (**i**), CK19 (**j**), and p53 (**k**) and negative for HBNE1 (**l**)

(continued)

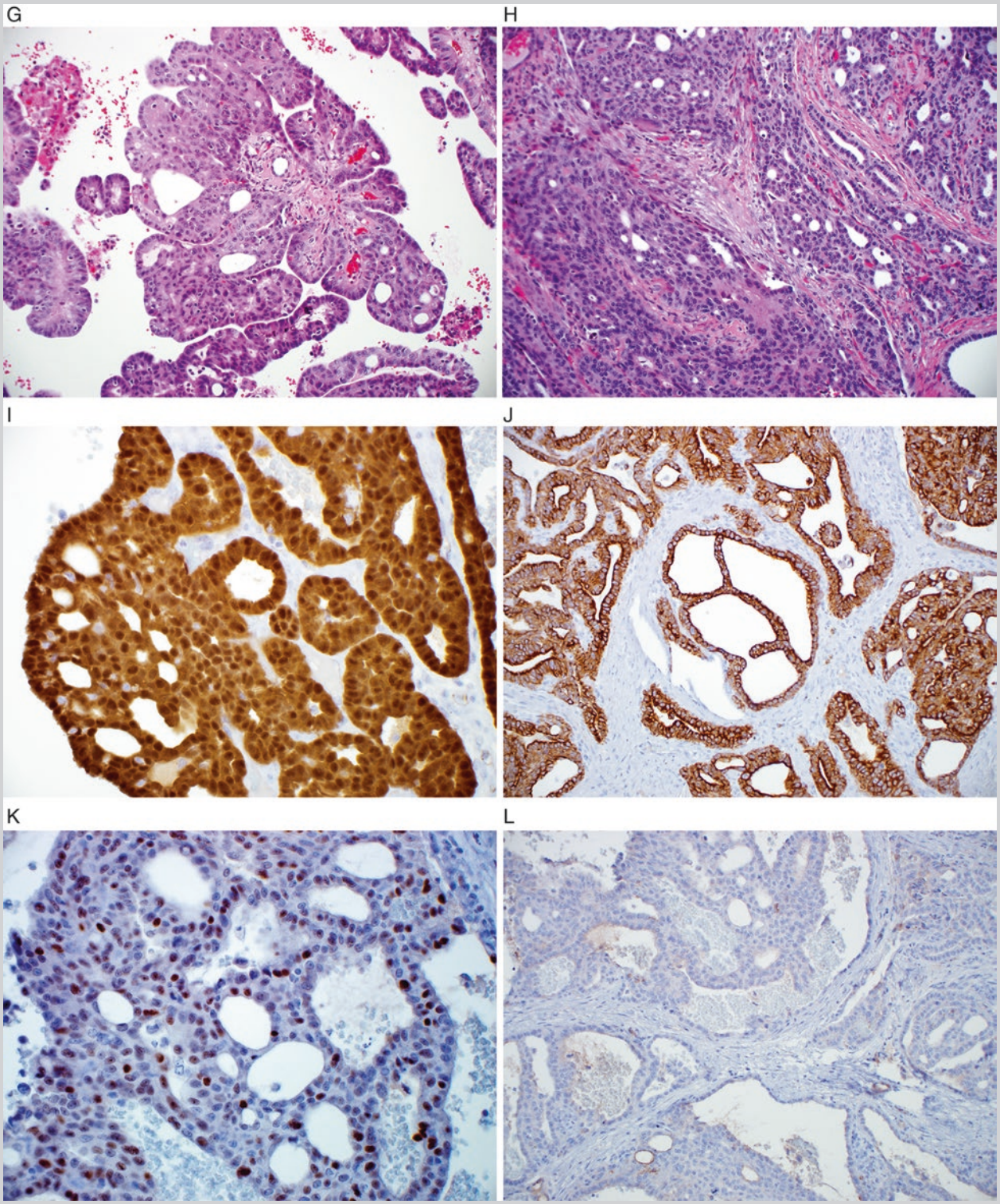

Fig. 3.68 (continued)

(continued)

Case

A 70-year-old man with a history of high-grade prostatic adenocarcinoma presented with a 4.0 cm mass at the left lobe of the thyroid. An ultrasound-guided FNA was performed. The FNA smears demonstrated low cellularity with large discohesive cells with enlarged nuclei, prominent nucleoli, some with a plasmacytoid appearance, and some with clear cytoplasm and cytoplasmic vacuoles containing red blood cells as shown in Fig. 3.69a–c. Necrosis and/or fibrin-like material were present in a bloody background. Fibrin and fibromuscular-like tissue were noted in the cellblock preparation as shown in Fig. 3.69d. Based on the cytologic features seen above, a diagnosis of positive for malignant cells, which favors poorly differentiated carcinoma, was rendered. It was recommended to obtain additional tissue for immunostains to further classify this malignant tumor.

Subsequently, a hemithyroidectomy was performed. Multiple sections contained a hemorrhagic and necrotic mass within the parenchyma of the thyroid gland. The mass expanded the thyroid lobe and infiltrated into the benign thyroid tissue. The tumor was composed of anastomosing vascular channels lined by pleomorphic, malignant endothelial cells with pleomorphic nuclei and prominent nucleoli as shown in Fig. 3.69e–g. Mitoses were frequent. Many of the vascular channels were necrotic and thrombosed. A panel of immunostains revealed that the atypical lining cells were positive for ERG, CD31, and CD34 as shown in Fig. 3.69h, i, and negative for cytokeratin and TTF1, which confirmed the diagnosis of angiosarcoma of the thyroid.

Final Diagnoses on the FNA Specimen

Positive for malignant cells
Favor poorly differentiated carcinoma
Recommend additional tissue for immunostains

Final Diagnosis on the Surgical Specimen

Angiosarcoma of the thyroid

What Are the Learning Points from This Case?

1. When the cytologic features of the atypical/malignant cells do not resemble a common thyroid tumor, such as papillary carcinoma, follicular/Hurthle cell neoplasm, and medullary carcinoma, an undifferentiated thyroid carcinoma, a rare primary thyroid tumor including angiosarcoma especially in an elderly man, and a secondary tumor should be included in the diagnostic consideration.
2. Atypical epithelioid cells with prominent nucleoli and cytoplasmic vacuoles containing red blood cells in a bloody background and the presence of fibrin-like material can be the clues for a diagnosis of angiosarcoma.
3. If an angiosarcoma is suspected, a panel of IHC markers including ERG and CD31 should be performed, even in a hypocellular cellblock. In the current case, if IHC would have done on the cellblock sections, a definitive diagnosis would have been reached. In retrospect, ERG and CD31 were performed on the cellblock sections, which showed that the "fibromuscular-like tissue" as shown in Fig. 3.69d was fibrin material, and the cellular components were positive for both ERG and CD31.

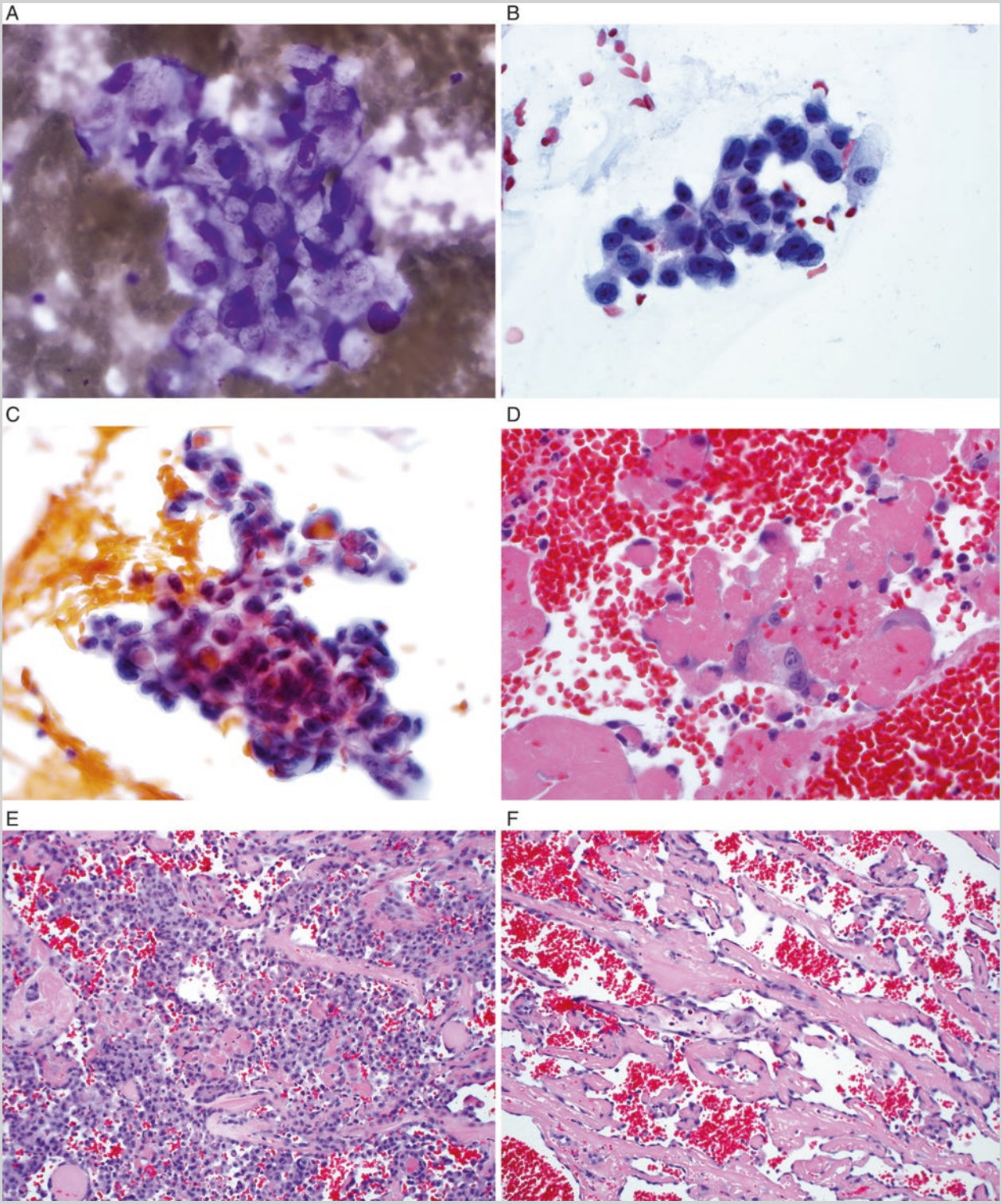

Fig. 3.69 A case of angiosarcoma of the thyroid. Note that large discohesive cells with enlarged nuclei, prominent nucleoli, some with plasmacytoid appearance, some with clear cytoplasm and cytoplasmic vacuoles containing red blood cells (**a**–**c**), cellblock (**d**), histologic sections of anastomosing vascular channels lined by pleomorphic, malignant endothelial cells (**e**–**g**) and positive for ERG (**h**) and CD31 (**i**) and negative or for cytokeratin and TTF1 (not shown)

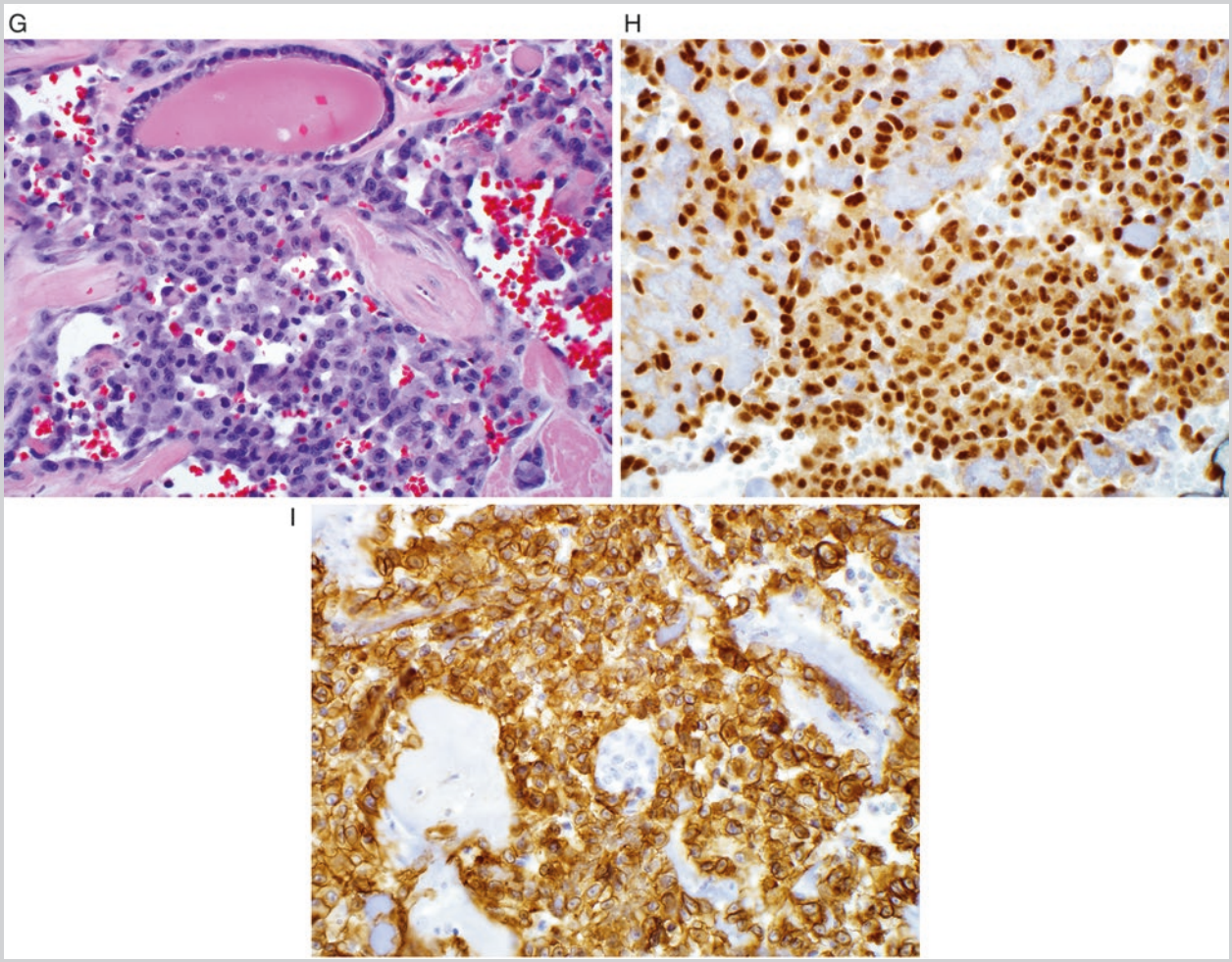

Fig. 3.69 (continued)

Abbreviation List

Abbreviation	Full text
AUS/FLUS	Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance
Bcl2	B-cell CLL/lymphoma 2
CASTLE	Carcinoma showing thymus-like differentiation
CD	Cluster of differentiation
CDX2	Caudal type homeobox 2
CEA	Carcinoembryonic antigen
CK	Cytokeratin
CRCC	Clear cell renal cell carcinoma
DQ	Diff-Quik
EMA	Epithelial membrane antigen
ERG	ETS-related gene
FDCT	Follicular dendritic cell tumor
FNA	Fine-needle aspiration
GATA3	GATA-binding protein 3
GFAP	Glial fibrillary acidic protein
GMS	Grocott's methenamine silver
HBME-1	Hector Battifora mesothelial epitope-1
IHC	Immunohistochemical
LCH	Langerhans cell histiocytosis
MIB-1	Mindbomb E3 ubiquitin protein ligase 1
MPNST	Malignant peripheral nerve sheath tumor
MUC2	Mucin 2
NSE	Neuron-specific enolase
Pap	Papanicolaou
PAX8	Paired box gene 8
PNST	Peripheral nerve sheath tumor

Abbreviation	Full text
PTC	Papillary thyroid carcinoma
PTH	Parathyroid hormone
pVHL	von Hippel-Lindau tumor suppressor gene protein
RCCma	Renal cell carcinoma marker
RDD	Rosai-Dorfman disease
RET	Rearranged during transfection
SCC	Squamous cell carcinoma
SETTLE	Spindle epithelial tumor with thymus-like differentiation
SFT	Solitary fibrous tumor
SMA	Smooth muscle actin
SMECE	Sclerosing mucoepidermoid carcinoma with eosinophils
SMT	Smooth muscle tumor
STAT6	Signal transducer and activator of transcription 6
TROP2	Tumor-associated calcium signal transducer 2
TTF1	Thyroid transcription factor 1
WHO	World Health Organization

Suggested Reading

Cytology/Fine-Needle Aspiration

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