Papillary Thyroid Carcinoma, Subtypes, and Related Tumors

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Background

Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the thyroid gland in both adults and children, accounting for 80–85% of all thyroid cancers in adults and 90% in children [1]. It occurs in all age groups with a peak incidence in the fourth decade, and a M:F ratio of 1:3. Since the introduction of high-resolution imaging techniques (e.g., thyroid ultrasonography) into clinical practice, the incidence of thyroid cancer nearly tripled worldwide from 1975 to 2009, with PTC accounting for most of the surge [1–4]. The mortality rate remained stable during this time, however, suggesting that the more indolent forms of PTC were diagnosed and that overtreatment may occur. This has been referred to as an epidemic of overdiagnosis because of the prevalence of low-risk, non-lethal tumors that are often incidentally detected from a large subclinical reservoir of disease [4]. Recent epidemiological data suggests that the rising incidence and overdiagnosis of thyroid cancer is starting to slow down following several important developments in

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recommendations about the diagnosis, classification, and management of low-risk thyroid cancer in the last decade [4]. The reclassification of the noninvasive follicular variant of PTC (FVPTC) as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) that was proposed in 2016 [5] and endorsed in the 2017 WHO classification may contribute to reduce this trend in overdiagnosis in the future, especially in areas where this tumor is commonly encountered.

Risk factors for PTC include external radiation to the neck during childhood, exposure to ionizing radiation, and genetic susceptibility [1, 2]. PTC usually presents as a thyroid nodule, often discovered incidentally on routine examination, but a minority of patients present with metastatic disease in neck lymph nodes. PTC spreads via lymphatics to the regional lymph nodes and less frequently to the lungs. It generally carries a good prognosis; death secondary to PTC is rare [1].

A malignant thyroid FNA diagnosis accounts for approximately 5% (range 2–16%) of all thyroid FNAs [2, 6], the majority of these are PTCs. When a diagnosis of PTC is made by FNA, 94–96% prove to be PTC on histologic follow-up, taking into consideration the reclassification of some FVPTCs as NIFTP (see also Chaps. 1 and 5) [2, 6–8]. Conventional (classic) PTCs are characterized histologically by numerous papillae lined by cuboidal to low columnar neoplastic follicular cells with distinctive nuclear features. A significant proportion of PTCs exhibit distinct architectural and/or cytologic features from those of conventional PTC, corresponding to different PTC subtypes. Furthermore, some PTC subtypes have different genomic alterations and biological behavior as compared to conventional PTC. An awareness of the cytomorphologic spectrum of PTC subtypes and related tumors helps prevent misdiagnosis, but it is not required to specify the subtype of PTC on an FNA specimen. In the following sections, conventional PTC and other PTC subtypes are described separately to highlight some of the morphologic heterogeneity in this family of tumors. Some uncommon thyroid neoplasms which have been related to PTC in the past, including hyalinizing trabecular tumor (HTT) and cribriform-morular thyroid carcinoma (CMTC), are also discussed in this chapter since they share some cytomorphological features with PTC. In the 5th edition of the WHO Classification of Endocrine and Neuroendocrine Tumors that relate to the thyroid gland, CMTC is no longer classified as a subtype of PTC but as a malignant thyroid tumor of uncertain histogenesis, while NIFTP and HTT are both classified as low-risk follicular cell-derived neoplasms [1].

Given the reclassification of some FVPTC as low-risk neoplasms rather than overt malignancies and the general consensus that FVPTC cannot be reliably distinguished from NIFTP on cytology [9–11], it is desirable to eliminate from the Malignant and Suspicious for Malignancy categories tumors likely to represent a NIFTP, in order to avoid possible overdiagnosis and overtreatment, since the recommended treatment for NIFTP is conservative surgery (e.g., lobectomy) in view of its indolent behavior (see Chap. 5). To accomplish this goal, follicular-patterned aspirates with nuclear changes that raise the possibility of FVPTC or NIFTP (e.g., mild enlargement, contour irregularity, and clearing) are best classified as Follicular

Neoplasm (FN) rather than Malignant or Suspicious for Malignancy, as long as true papillae are absent and intranuclear pseudoinclusions (INPIs) are either absent or very rare (see Chap. 5). In contrast, if the follicular cells show definitive nuclear features of PTC, including frequent INPIs, and there are at least focal elements associated with classical PTC (psammoma bodies and/or true papillae), the specimen should not be interpreted as FN but rather as "Malignant: PTC," or "Suspicious for PTC," depending on the quality and quantity of the cytologic changes. This approach leaves other subtypes of PTC in the Malignant category but minimizes the contribution of FVPTC and NIFTP.

Conventional (Classic) Papillary Thyroid Carcinoma

Definition

Conventional (classic) PTC is a malignant epithelial tumor derived from thyroid follicular epithelium that displays papillary architecture and characteristic nuclear alterations [1].

Criteria

Architecture:
Cells arranged in papillae and/or monolayer sheets and/or 3D groups.
Cellular swirls ("onion-skin" or "cartwheel" patterns) in some cases.

Nuclear features:
Enlarged and crowded nuclei, often molded.
Oval or irregularly shaped nuclei.
Longitudinal nuclear grooves.
Intranuclear pseudoinclusions.
Pale nuclei with powdery chromatin.
Thick nuclear membranes.
Macronucleoli or micronucleoli, central or marginally placed.

Other features:
Psammoma bodies.
Multinucleated giant cells.
Variable amount of colloid; may be stringy, ropy, or "bubble-gum"-like.
"Hobnail" cells.
Oncocytic (Hürthle cell) metaplasia.
Squamoid metaplasia.

"Histiocytoid" cells.

Liquid-Based Preparations

Liquid-based preparations (LBP) have been widely used for managing cytopathological specimens in the last three decades. Relative to conventional smears, LBP provides optimal cell preservation with fewer air-drying artifacts, fewer slides, shorter screening time, easier technical preparation, and a cleaner background because there is decreased obscuring material. In addition, cell block slides prepared from the well-preserved cellular remnants of LBP specimens can be used for further morphological examination, immunohistochemical (IHC) analysis, and molecular testing. There are some minor differences between smears and LBP with regard to the diagnosis of conventional PTC; they vary depending on the LBP methods and their fixatives [12–15]. Awareness of the cytomorphological features observed with the use of the LBP method is helpful because some of the classical features of PTC, such as background and large flat sheets, may not be seen in LBP and may make accurate interpretation more difficult for some cases.

Cytological features more frequent in LBP compared to smears:
Clean background.
High cellularity.
Convoluted nuclei.
Eosinophilic nucleoli.
Perinucleolar halo.
Trabecular and hobnail patterns.
Tall cells.
Collagenous stroma.
Naked capillaries.
Intercellular "window-like" spaces.

Cytological features less frequent or reduced in LBP compared to smears:
Pale/ground-glass nuclei and nuclear crowding/overlapping.
Intranuclear pseudoinclusions are smaller and less obvious in LBP.
Papillary pattern and tissue fragments.

Explanatory Notes

Although several nuclear alterations are characteristic, none are diagnostic of PTC in isolation or low frequency. Only when relatively widespread and in combination are they diagnostic of PTC, whether in direct smears or LBP. The minimum criteria and number of neoplastic cells necessary for an unequivocal diagnosis are uncertain and probably not definable, either cytologically or histopathologically. In other

words, the minimum quantitative threshold (e.g., the number of cells needed with nuclear grooves and/or INPIs) for a diagnosis of PTC in cytological or histologic specimens remains undefined. If, in the judgment of the cytologist, a case has some features of PTC but falls short of an unequivocal diagnosis, it is interpreted as "Suspicious for PTC," "Follicular Neoplasm," or "Atypia of Undetermined Significance (AUS)" (see Chaps. 7, 5, and 4, respectively), depending on the quality and quantity of the changes and the reviewer's degree of suspicion for PTC.

The cells of a conventional PTC are typically arranged in syncytial-like flat sheets or monolayers with crowded and overlapping nuclei (Figs. 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7 and 8.8). The latter feature often leads to conspicuous nuclear molding (Figs. 8.3, 8.4, and 8.5). Nuclear crowding, overlapping, and molding are important diagnostic features that help distinguish the cells of PTC from benign follicular cells. The monolayered sheet is characteristic of conventional PTC and mimics the flat sheet of a macrofollicular fragment typical of benign follicular nodules, such as those commonly seen in nodular hyperplasia (Fig. 8.8). The distinction requires particular attention to the arrangement of the cells in the sheets, evenly spaced vs.

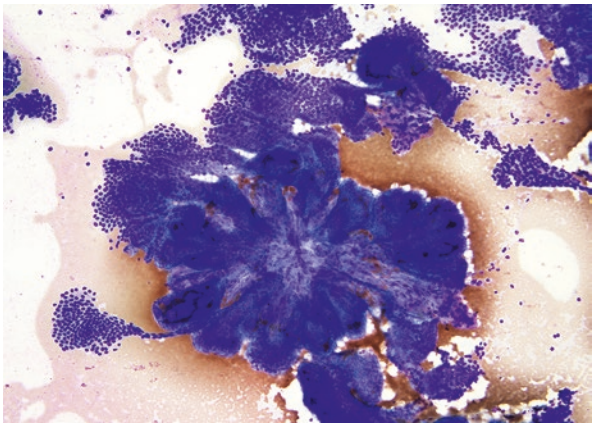

Fig. 8.1 Papillary thyroid carcinoma. Preparations are often highly cellular and composed of numerous monolayer sheets and occasional papillary-like fragments (smear, Diff-Quik stain)

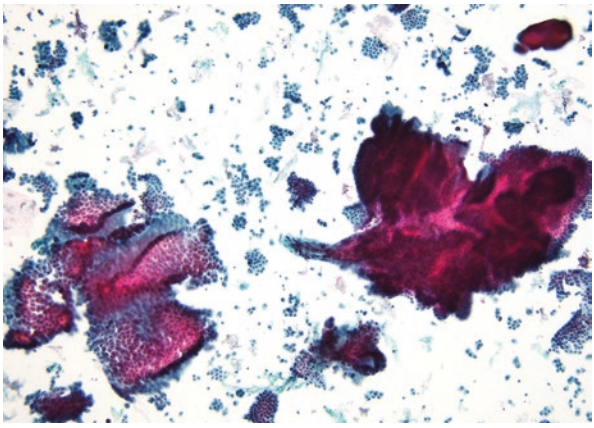

Fig. 8.2 Papillary thyroid carcinoma. Hypercellularity with mostly intact tissue fragments comprising of numerous papillary-like fragments (SurePath, Papanicolaou stain)

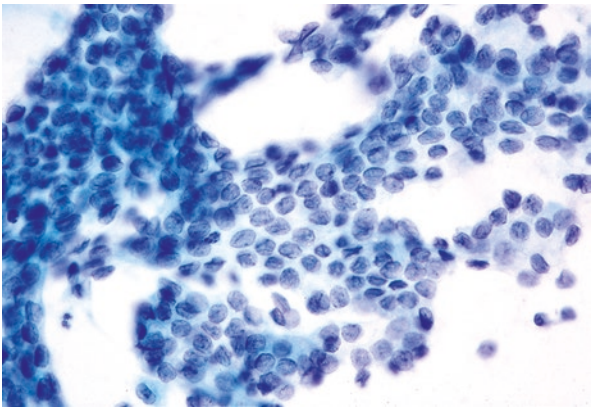

Fig. 8.3 Papillary thyroid carcinoma. Monolayer sheets with a syncytial-like appearance are characteristic of papillary thyroid carcinoma. These flat sheets resemble those of benign follicular nodules; attention to the nuclear features is essential for this distinction (smear, Papanicolaou stain)

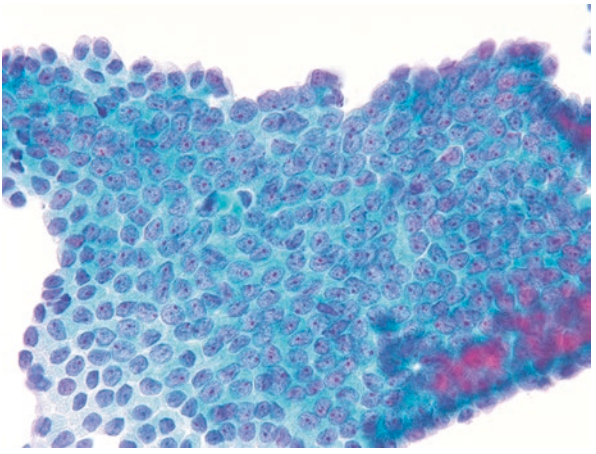

Fig. 8.4 Papillary thyroid carcinoma. This monolayer sheet is comprised of cells with irregular nuclei that show focal molding. Small nucleoli are also visible (ThinPrep, Papanicolaou stain)

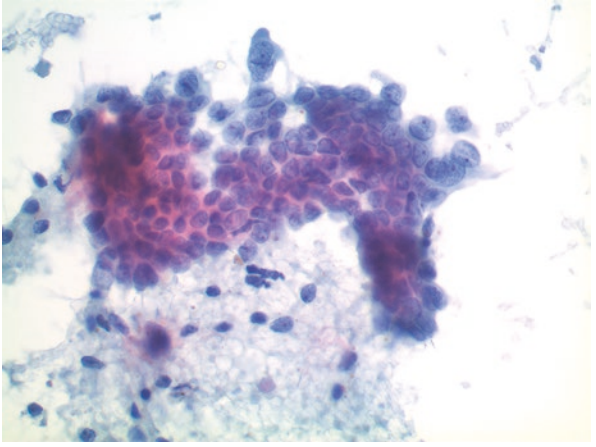

Fig. 8.5 Papillary thyroid carcinoma. This monolayer sheet is comprised of cells with irregular nuclei that show focal molding (Cytospin, Papanicolaou stain)

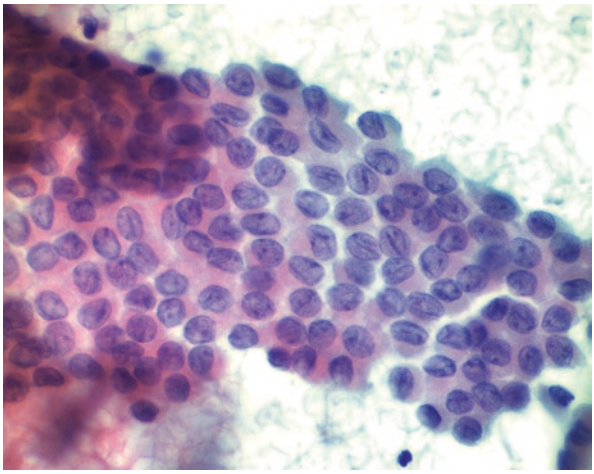

Fig. 8.6 Papillary thyroid carcinoma. This monolayer sheet is comprised of cells with irregular nuclei that show prominent grooving with coffee bean-like nuclei (Cytospin, Papanicolaou stain)

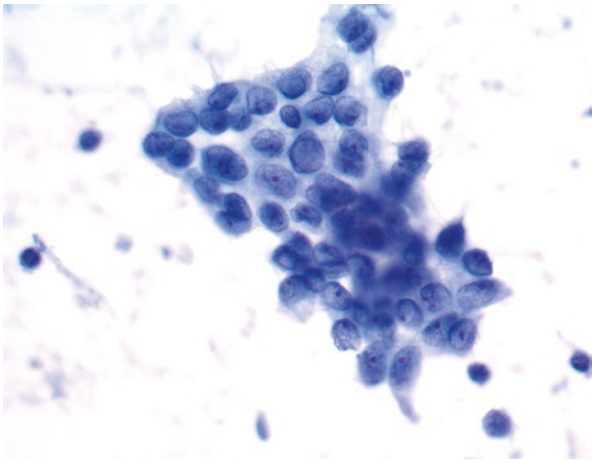

Fig. 8.7 Papillary thyroid carcinoma. This sheet is comprised of cells with irregular nuclei that show prominent nucleoli as well as intranuclear pseudoinclusions (Cytospin, Papanicolaou stain)

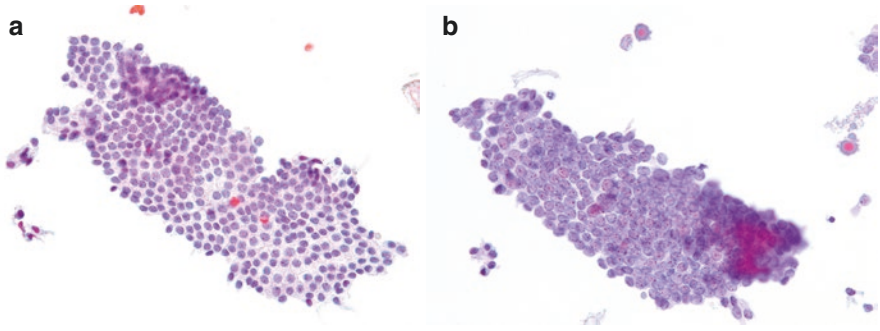

Fig. 8.8 Comparison of benign follicular cells with the cells of papillary thyroid carcinoma. (**a**) Benign follicular cells (nodular goiter). (**b**) Compared with those of the benign follicular cells, the nuclei of papillary carcinoma are larger, paler, more crowded, and more irregular in contour. (**a** and **b**, ThinPrep, Papanicolaou stain)

crowded, and to their nuclear features to avoid a false-negative diagnosis. The architectural pattern varies depending on the subtype of PTC (see below), but FNAs from a conventional PTC often display true papillary fragments with a fibrovascular core (Figs. 8.9 and 8.10), papillary-like fragments which have a rounded shape with smooth edges but lack a fibrovascular core (Fig. 8.11), and cellular swirls. Cellular swirls (Fig. 8.12) are flat, concentrically organized aggregates of about 50–200 tumor cells with a perpendicular arrangement of the most peripherally located ovoid cells relative to the radius of the swirl which is sometimes also called an "onion-skin" pattern [16]. Cellular swirls are a distinctive feature of the conventional PTC, seen in about 17% of cases, both in smears and LBP, and have not been reported in benign thyroid nodules [13, 16]. Although individually dispersed neoplastic cells are seen in PTC, a pattern of predominantly isolated cells is highly unusual, in contrast to the cells of medullary thyroid carcinoma (MTC).

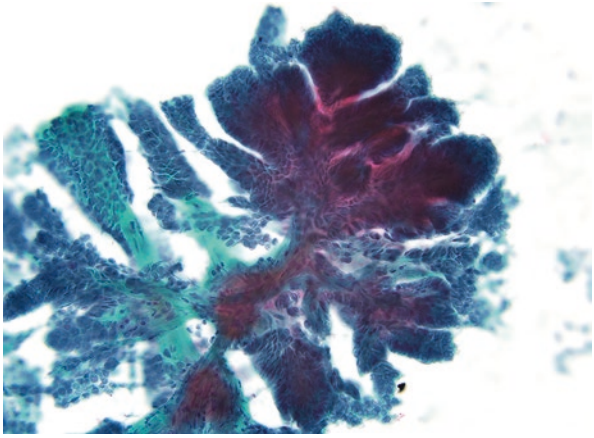

Fig. 8.9 Papillary thyroid carcinoma. True papillary tissue fragments, comprised of fibrovascular cores lined by neoplastic cells, are seen in the conventional type of papillary thyroid carcinoma (smear, Papanicolaou stain)

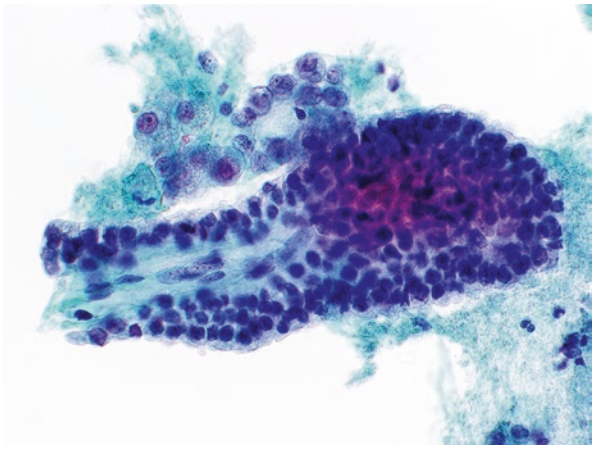

Fig. 8.10 Papillary thyroid carcinoma. The neoplastic cells surround a fibrovascular core (ThinPrep, Papanicolaou stain)

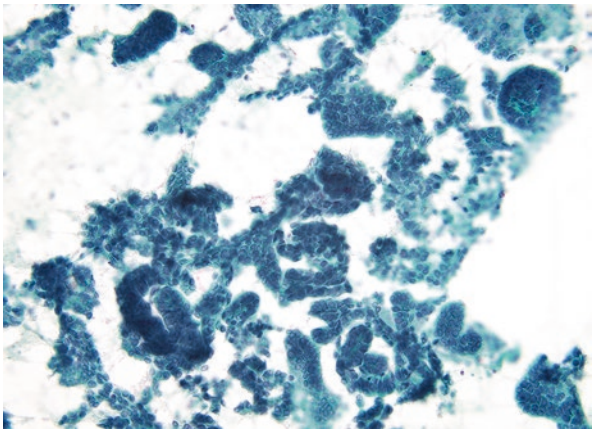

Fig. 8.11 Papillary thyroid carcinoma. There is a mixture of flat sheets and rounded, papillary-like fragments without fibrovascular cores (smear, Papanicolaou stain)

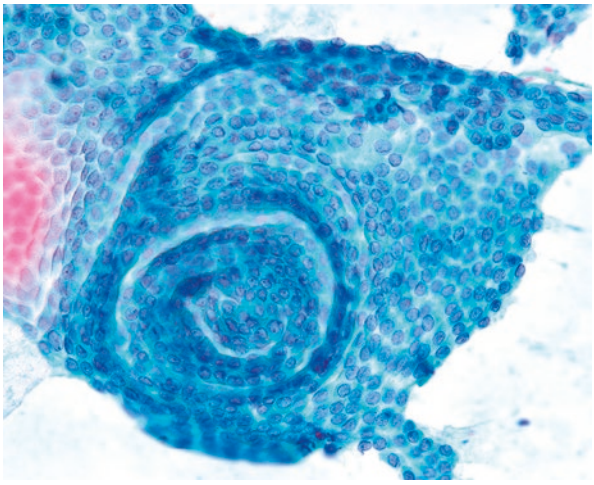

Fig. 8.12 Papillary thyroid carcinoma. Cellular swirls are highly characteristic of the conventional (classic) papillary thyroid carcinoma. They are a concentric aggregate of tumor cells in which many of the peripheral cells have ovoid (rather than round) nuclei and are oriented perpendicular to the radius of the swirl (smear, Papanicolaou stain)

The cells of PTC vary in size (from medium to large) and shape (cuboidal, columnar, polygonal, sometimes spindle-shaped and even histiocytoid). Cell borders are usually well demarcated. The amount and texture of cytoplasm can vary greatly. In some cases, the cells have scant cytoplasm, but abundant oncocytic or granular cytoplasm is common, although usually a focal finding. When extensive, it signals an oncocytic subtype of PTC. A hobnail pattern was suggested as a useful diagnostic criterion, especially on LBP [12, 13], and has been reported in several subtypes of PTC (hobnail, diffuse sclerosing, cystic). "Hobnail pattern" is the term employed to describe cells characterized by a high nuclear/cytoplasmic ratio and apical/eccentric placement of the nuclei that produces a surface bulge like hobnails [14, 17, 18]. Changes resembling squamous metaplasia, such as moderate to abundant dense cytoplasm and cells that fit together like pavement stones, are also seen, usually only as a focal finding in conventional PTC. Hyperkeratinized squamous

cells with orangeophilic cytoplasm on Papanicolaou stain and keratin pearls, however, are rare. Histiocytoid cells are characterized by extensive cytoplasmic vacuolation, like that seen in benign histiocytes, and typically arise in a PTC that has undergone cystic changes (Figs. 7.4 and 8.24).

The defining features of PTC are seen in the nuclei. They are generally slightly enlarged and can be round or oval but are often highly irregular in contour; the nuclear contour irregularity is often one of the first clues to the diagnosis (Figs. 8.6 and 8.8b). Convoluted nuclei, where more than half of the nuclear membrane is wrinkled, are very specific for PTC on LBP (97.3%) [12]. The chromatin of a conventional PTC nucleus is usually pale, finely textured, and evenly distributed (powdery), unlike the dark and coarsely textured benign follicular cell nucleus (Fig. 8.8). This chromatin characteristic is more easily appreciated with alcohol-fixed Papanicolaou-stained smears than air-dried Diff-Quik preparations or LBP, and it may be absent in some PTC subtypes such as columnar cell PTC. This pallor parallels the optically clear appearance of PTC nuclei in formalin-fixed tissue ("Orphan Annie eyes"), which is attributed to a fixation artifact that renders the nucleus practically empty in appearance.

Intranuclear pseudoinclusions are seen in 50–100% of aspirates of PTC, depending on the subtype of PTC (Figs. 8.7, 8.13, and 8.14). For example, INPIs are most frequent and florid in the tall cell PTC, whereas they are often rare or absent in FVPTC. INPIs are not specific for PTC, as they can be seen in aspirates of MTC, anaplastic thyroid carcinoma, HTT, and very rarely NIFTP or benign thyroid nodules (e.g., nodular goiter, follicular adenoma, lymphocytic thyroiditis). INPIs should therefore always be interpreted in light of the other architectural and nuclear features in a given FNA. Ultrastructurally, INPIs are membrane-bound spheroidal masses of cytoplasm that protrude into the nuclei. Thus, a true INPI displays the same color/texture of adjacent cytoplasm, is fully contained within the nucleus, and is sharply bordered by a rim of condensed chromatin like a "wire loop." These features help distinguish INPIs from common mimics: degenerative and artifactual vacuoles, fixation artifacts, and superimposed red blood cells.

Nuclear grooves are another hallmark of PTC [19]. Akin to INPIs, they are best seen with alcohol-fixed, Papanicolaou-stained preparations (Figs. 8.6 and 8.15) and are less conspicuous with air-dried Romanowsky-stained smears (e.g., Diff-Quik). Nuclear grooves and INPIs are manifestations of nuclear membrane increased plasticity which makes them less stiff and much more deformable than normal; a nuclear groove, for example, results from a nucleus folded onto itself [20]. Although a sensitive feature for the cytologic diagnosis of PTC, nuclear grooves are not specific and can be seen in a variety of other thyroid neoplasms such as oncocytic neoplasms and non-neoplastic conditions like lymphocytic thyroiditis. Quantification studies have shown that PTC tends to have more nuclear grooves than other lesions, but they have not shown that a specific number of grooves establish a definite diagnosis. For this reason, they should not be relied upon in isolation to make a diagnosis of PTC. In addition, nuclear grooves are useful only when identified within follicular epithelial cells; care must be taken not to misinterpret histiocytes or Langerhans

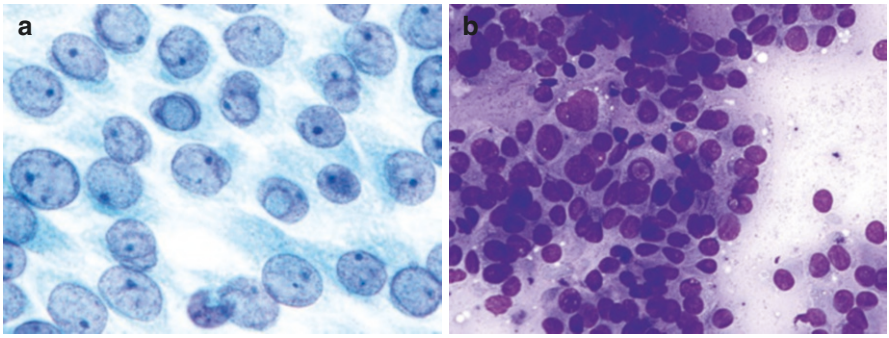

Fig. 8.13 Papillary thyroid carcinoma. (**a**) INPIs and micronucleoli are shown. Note that the two INPIs share the same aqua color and granular texture as the surrounding cytoplasm (smear, Papanicolaou stain). (**b**) A large INPI occupying most of the nucleus is seen in the center. The remaining nuclei show variation in size and shape (smear, Diff-Quik stain)

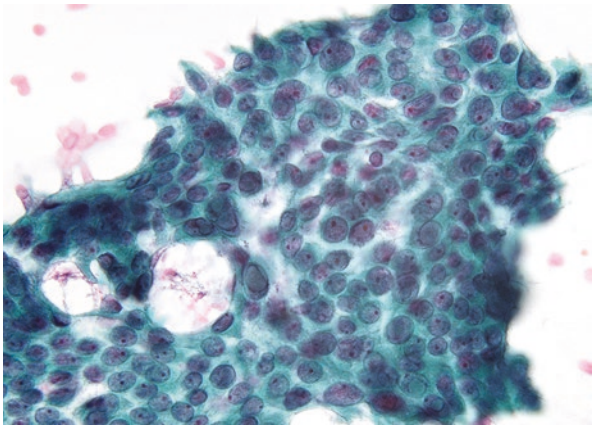

Fig. 8.14 Papillary thyroid carcinoma. Two intranuclear pseudoinclusions are seen. (smear, Papanicolaou stain)

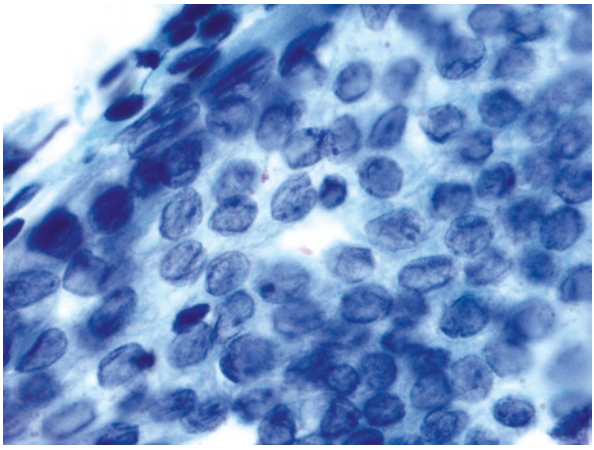

Fig. 8.15 Papillary thyroid carcinoma. Close inspection at high magnification shows frequent nuclear grooves, finely textured (powdery) chromatin, and micronucleoli (smear, Papanicolaou stain)

cells, which are characterized by elongated, oval nuclei with nuclear grooves, for the cells of PTC.

The nuclei of PTC typically display one to three micronucleoli, often positioned marginally underneath the nuclear membrane. On LBP, they are commonly eosinophilic (89%) and associated with a perinucleolar halo ("bare nucleoli") (63%) [12]. The latter has been reported to be very specific for PTC (96%) [12]. The eosinophilic nucleoli, however, are not only observed in PTCs but also in follicular nodular disease or follicular neoplasms, in particular those of the oncocytic type.

Multinucleated giant cells of histiocytic lineage are commonly seen in aspirates of PTC, even when cystic degeneration is not present (Fig. 8.16). Although common, they are not specific for PTC, and similar cells are seen in other conditions, both benign and malignant. The cells can be very large, and their nuclei can vary in number from few to numerous. They are part of the host response to the malignancy, along with other type of immune cells such as Langerhans cells, lymphocytes, and mast cells.

Psammoma bodies (PBs) are seen less frequently in FNA samples of PTC (4–20% of cases) than in histologic specimens (40–60%). They can be solitary or multiple, isolated, or attached to cells (Fig. 8.17). PBs alone (i.e., not associated with altered cells) are nonspecific and can be seen in MTC, lymphocytic thyroiditis, Graves' disease, and even nodular goiter. Calcifications resembling PBs occur in oncocytic neoplasms and represent calcification of colloid. The positive predictive value (PPV) for PTC of PBs in isolation is 50%; when seen in association with the cytologic features of PTC, the PPV is 100% [21].

The background usually contains relatively scant colloid, but some PTC subtypes (see below) can have abundant colloid. Colloid may be watery or dense and stringy with ropy pink strands, the so-called "bubble-gum" colloid (Fig. 8.18). The background is usually clean; the presence of necrotic debris is extremely uncommon in PTC and should raise the possibility of another malignancy. Hemosiderin-laden macrophages, representing hemorrhage and cystic changes, are common in PTC and can be prominent. Variable numbers of lymphocytes can be seen due to an underlying lymphocytic thyroiditis. When lymphocytes predominate, a

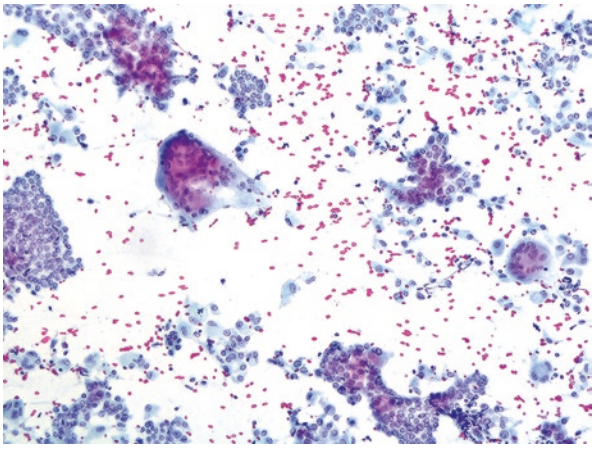

Fig. 8.16 Papillary thyroid carcinoma. Multinucleated giant cells accompany monolayered sheets of tumor cells. Although multinucleated giant cells are often seen in PTCs, they are a nonspecific finding (smear, Papanicolaou stain)

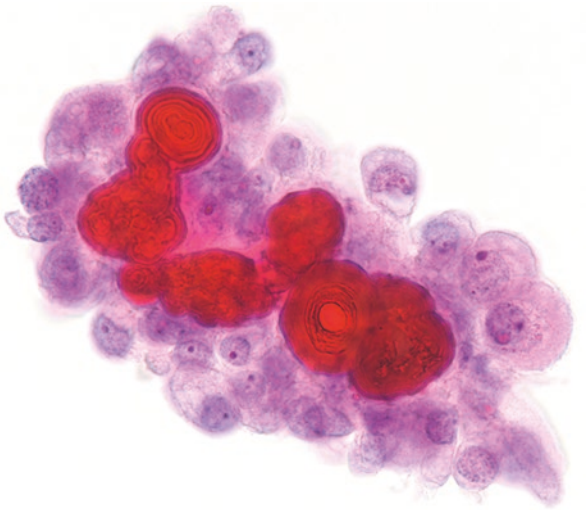

Fig. 8.17 Papillary thyroid carcinoma. Psammoma bodies are concentric rings and are lined here by atypical cells with oval, pale nuclei. Note that the tumor cells surrounding psammoma bodies show hobnail features (ThinPrep, Papanicolaou stain)

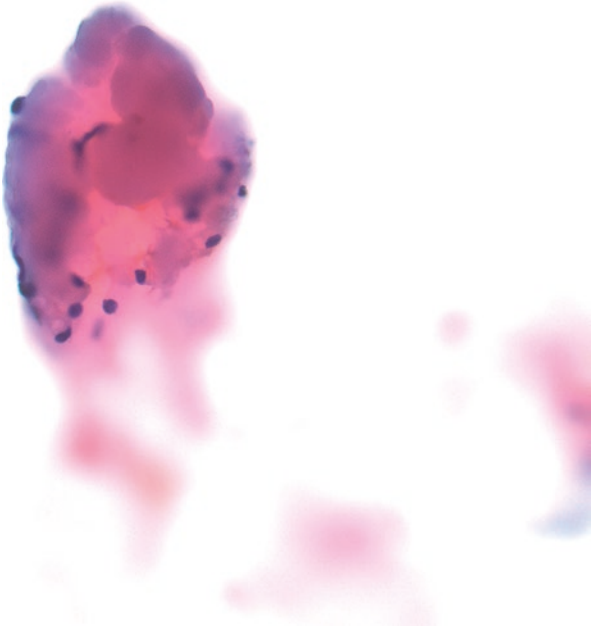

Fig. 8.18 Papillary thyroid carcinoma. The colloid in aspirates of PTC is often dense and stringy, the so-called "bubble-gum" colloid (Cytospin, Papanicolaou stain)

Warthin-like PTC or a diffuse sclerosing PTC should be considered (see below). Caution should be exercised when nuclear abnormalities are seen in follicular cell clusters with intimately admixed lymphocytes, as these nuclear changes may be reactive and not malignant.

Given an adequate sample, the majority of PTCs are straightforward to diagnose by FNA because most or all of the nuclear and architectural changes described

above are clearly identifiable and widespread. Such cases are reliably interpreted as malignant. In some PTCs, however, the nuclear changes are subtle and focal. Other PTCs may be incompletely sampled and yield only a small number of abnormal cells. If only one or two characteristic features of PTC are present, if they are only focal and not widespread throughout the follicular cell population, or if the sample is sparsely cellular, a malignant diagnosis cannot be made with certainty, and such cases are best classified as "Suspicious for Malignancy" (see Chap. 7).

Subtypes (Variants) of Papillary Thyroid Carcinoma (PTC)

Note: *In the latest WHO classification of thyroid tumors* [1], *the term "variant" has been replaced by "subtype" to allow for consistency with other WHO tumor classification schemes and avoid confusion with the molecular diagnostic term "genetic variant(s)."*

However, the term "variant" is still largely used, especially for FVPTC.

A substantial proportion of PTCs exhibit a variety of architectural and/or cytologic features that differ from those of conventional PTC. More than ten subtypes of PTC have been recognized considering: tumor size and delineation (encapsulated, invasive, and diffuse), architecture (follicular, macrofollicular, solid/trabecular, and micropapillary), cell type and shape (tall, spindle, columnar, oncocytic, clear, and hobnail), and associated stromal components (Warthin-like and fibromatosis/fasciitis-like stroma) [1, 2, 22]. Some PTC subtypes are associated with more aggressive and others with more indolent behavior than conventional PTC [1, 2, 22–24]. Columnar cell, hobnail, and tall cell subtypes are recognized as aggressive PTC subtypes by the American Thyroid Association (ATA) and WHO, with diagnosis of these subtypes impacting both risk stratification and clinical management [2]. The solid/trabecular subtype and the diffuse sclerosing subtype may be associated with a less favorable outcome, but the data remain conflicting [1, 2]. In contrast, the noninvasive FVPTC is indolent, with virtually no metastatic or recurrence potential following complete excision, and for this reason has been reclassified as NIFTP, a very low-risk neoplasm (see "Follicular Variant and NIFTP" below and Chap. 5) [1, 5].

Distinction between indolent and aggressive subtypes of PTC at the time of FNA contributes to risk stratification and may influence the management, depending also on the clinico-radiologic features in a given patient [2]. Precise subtyping, however, is rarely possible or reliable, because: (1) The predominant pattern may not have been sampled (many PTCs are heterogeneous with more than one growth pattern and/or cell type). (2) The architectural features of capsular and/or vascular invasion defining some of these subtypes cannot be assessed cytologically, akin to follicular thyroid adenoma/carcinoma. (3) The rarity of some of these subtypes makes it very difficult for the practicing cytopathologist to become familiar with their morphologic features which have significant overlap. (4) The PPV of any "specific" cytomorphologic features (described mostly in retrospective studies) is hard to predict since it is influenced by the incidence of the corresponding subtype in a given population [22, 23]. Nonetheless, the architectural and cytologic features that distinguish these subtypes from conventional PTC histologically are often observed cytologically, and

awareness of the phenotypic characteristics of the various subtypes of PTC can diminish the risk of misdiagnosis. Recognition of PTC subtypes at the time of FNA is generally not required; however, some of the more common subtypes such as tall cell PTC may be at least favored or suggested (see sample reports) [22–24].

Follicular Variant of PTC and NIFTP (See Also Chap. 5)

Definitions

The follicular variant of PTC (FVPTC) is completely or almost completely composed of small to medium-sized follicles lined by cells with variable nuclear features of PTC.

NIFTP is a noninvasive neoplasm with a follicular growth pattern and variable nuclear features of PTC. This terminology was introduced in 2016 to recognize the indolent behavior of thyroid neoplasms previously classified as noninvasive FVPTC and was included as a new entity in the 2017 WHO classification. Rigorous histologic criteria are applied for this diagnosis: the tumor must be well demarcated from surrounding normal thyroid (with or without a capsule) and it must have the nuclear features of PTC, although they are usually more subtle than with the classic PTC [1, 5]. The nuclear features may be focal, patchy, diffuse, or multifocal. Complete examination of the tumor capsule/interface is required to exclude capsular or vascular invasion. There are also several exclusion criteria including: >1% true papillae, PBs, tall cell or columnar cell features, >30% solid/trabecular/insular architecture, necrosis, or increased mitoses (≥3 per 10 high power fields) [1, 5].

Background

There are two distinct groups within FVPTC that differ morphologically, genetically, and clinically.

1. *FVPTC with an infiltrative growth pattern* is associated with frequent lymph node metastases, a risk of recurrence, and *BRAF* V600E mutations, similar to conventional PTC ("BRAF-like PTCs") [1, 2, 25]. *Diffuse FVPTC* is a rare and aggressive variant of infiltrative FVPTC that typically occurs in young females, extensively involving one lobe or both lobes in a multinodular fashion, with frequent distant metastases in the lungs and/or bones with or without concurrent regional lymph node metastases.
2. The *encapsulated FVPTC* is characterized by a follicular growth pattern with no papillae formation and partial or total tumor encapsulation, and the diagnosis rests on finding characteristic nuclear features of PTC. Historically, encapsulated FVPTC has been a controversial entity with poor diagnostic (cytologic and histologic) reproducibility. Most encapsulated FVPTCs show no invasive growth, whereas in about one-third of cases tumor capsular and/or vascular invasion are found [2]. These tumors, which frequently harbor *RAS* mutations, are biologically, genetically, and clinically closer to the follicular adenoma/carcinoma group than the PTC group ("RAS-like PTCs") [1, 25]. Encapsulated FVPTC with invasion tends to spread in a fashion similar to follicular thyroid carcinoma, with

distant lung and bone metastases and infrequent lymph node metastases [1]. In the absence of capsular or vascular invasion, encapsulated FVPTCs have a very low risk of recurrence or extrathyroidal spread, even in patients treated by lobectomy alone, provided that the tumor is completely excised [1, 2, 5]. Therefore, a carefully defined subset of encapsulated FVPTC has been reclassified as NIFTP, using strict histologic inclusion and exclusion criteria (see above) [1, 5].

NIFTP is a very low-risk tumor that likely represents a preinvasive stage of invasive encapsulated FVPTC [1, 5]. The paradigm shift in terminology has important clinical consequences and affects the cytologic diagnosis of thyroid nodules [7–11]. In several European countries and North America, NIFTP comprises approximately 10–20% of all tumors previously classified as thyroid malignancies, with significantly lower prevalence in Asia [1, 7–11]. Accordingly, adoption of this terminology lowers the frequency of a histopathologic diagnosis of thyroid cancer. It also causes an overall decrease in the risk of malignancy associated with thyroid FNA diagnoses, especially in the indeterminate diagnostic categories but also in the Malignant category, since NIFTP comprised a small subset (approximately 3%) of thyroid FNAs that were classified as Malignant in retrospective studies published shortly thereafter (see Chaps. 1 and 5) [7–11].

A NIFTP cannot convincingly be recognized as such by FNA because some of its defining features (like circumscribed margins) cannot be assessed cytologically. Nevertheless, the predominance of follicular architecture and associated nuclear changes (albeit mild) allow most NIFTPs to be recognized as abnormal, with about half of all NIFTPs diagnosed as FN and most of the remaining cases diagnoses as either Suspicious for Malignancy or AUS [7–11]. Because the nuclear changes are subtle (as with many invasive FVPTC), few NIFTPs are interpreted as malignant by FNA. To avoid overtreatment, it is highly desirable to exclude potential NIFTP cases from the Malignant category and limit this category to conventional and other subtypes of PTC. Nevertheless, given the histologic criteria for NIFTP [1, 5], it may not be possible to completely eliminate NIFTP from the Malignant category, even when using more stringent criteria. Thus, some pathologists may prefer to include an educational note to reinforce this limitation (see Chap. 1, Table 1.4, as well as "Sample Reports" below).

How to Distinguish NIFTP from PTC on Cytology?

The degree to which the characteristic nuclear features of PTC are displayed in FVPTC and NIFTP varies from case to case, with a wide quantitative and qualitative spectrum (Figs. 8.19 and 8.20) [9–11, 26–29]. Some FVPTCs, usually those that are infiltrative, have prominent classic nuclear features of PTC, but with others, especially the encapsulated FVPTC (including NIFTP), the features are only partially and focally displayed. Because of the significant overlap in the cytologic features between FVPTC and NIFTP, a definite distinction between these entities is not possible by FNA. FNA specimens from FVPTCs can be separated into two different

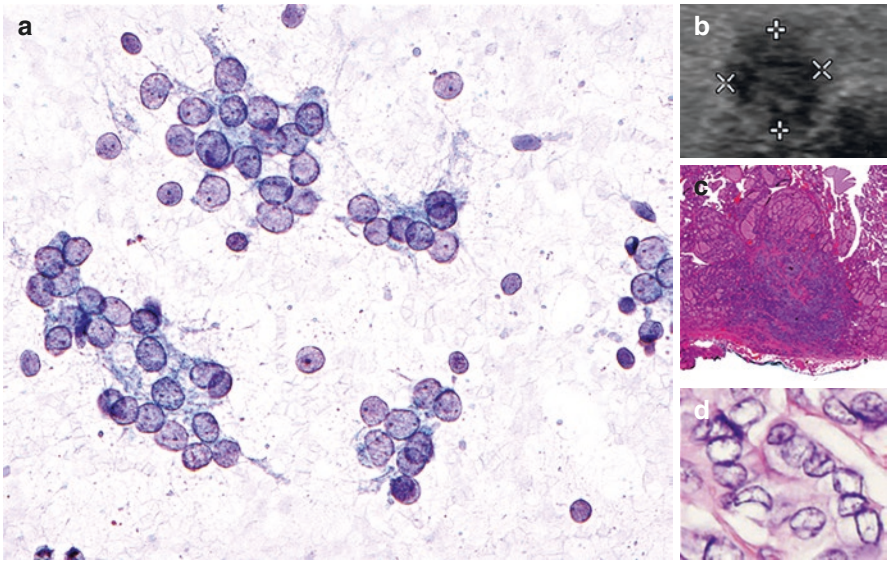

Fig. 8.19 Papillary thyroid carcinoma, follicular variant. (**a**) The aspirate shows microfollicles with crowded, enlarged clear oval nuclei (smear, Papanicolaou stain). (**b**) Ultrasound shows solid nodule with blurred margins. (**c**) This correlates with infiltrative margin on histology. (**d**) Histologically the tumor is composed of microfollicles with "Orphan Annie eye" clear nuclei (hematoxylin and eosin stain)

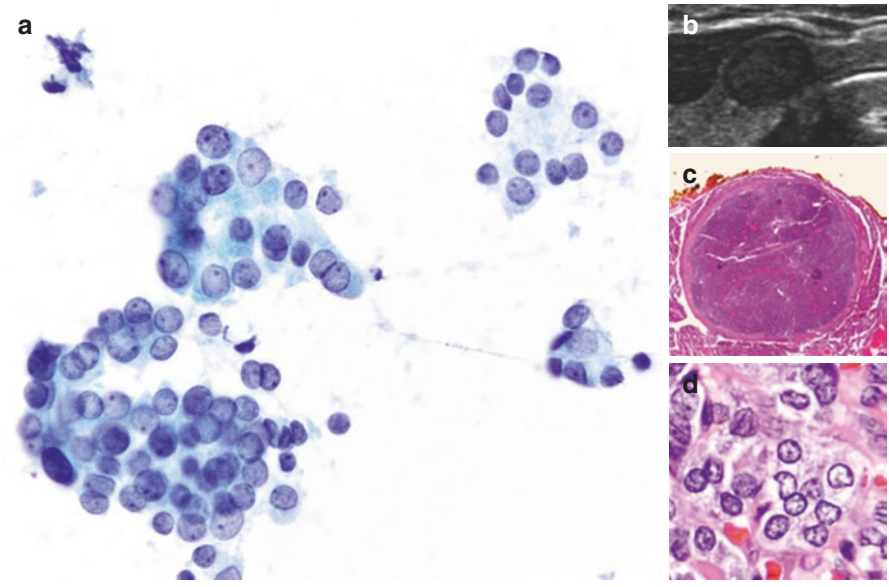

Fig. 8.20 Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (formerly called encapsulated follicular variant of papillary thyroid carcinoma). (**a**) The aspirate shows microfollicles with crowded, enlarged, clear, oval nuclei along with microfollicles with small dark nuclei (smear, Papanicolaou stain). (**b**) Ultrasound shows well-circumscribed solid nodule with a rim, correlating with encapsulation on histology (**c**). (**d**) Histologically, the tumor is composed of microfollicles with "Orphan Annie eye" clear nuclei (hematoxylin and eosin stain)

groups. In the first (30–40% of cases), the FVPTC shows widespread nuclear features of PTC and may be difficult to distinguish from a conventional PTC, especially from those that show a predominant follicular growth pattern. In the second group, which represents the majority of FVPTC and NIFTP cases, the tumor cells show only mild nuclear enlargement and elongation, chromatin clearing, and thick nuclear membranes, with INPIs and nuclear grooves rare or absent. These cytologic samples typically fall into one of the indeterminate categories: Suspicious for PTC (25–35%), FN (25–30%), or AUS (10–20%) [1, 7–11]. NIFTPs are often associated with more subtle nuclear features than classical PTC. Cytomorphologic features which are in favor of classic PTC and against the diagnosis of NIFTP are sheet-predominant architectural pattern, presence of true papillae and PBs, and easily identifiable INPIs. In addition, the nuclei of NIFTP are smaller, less elongated, and more rounded than those of conventional PTC. NIFTP nuclei are also not as crowded and have grooves that are more delicate and focal in comparison to its PTC counterpart [9–11].

In summary, a definitive cytologic diagnosis of PTC can be achieved by applying strict morphologic criteria. These criteria include high cellularity, predominant tumor sheets with papillae or swirls, marked nuclear enlargement with elongation of the nuclei, easily visualized grooves involving the long axis of the nuclei, fine chromatin, nuclear crowding, and the presence of more than rare INPIs (≥3). In contrast, a cytologic specimen raises the differential diagnosis of NIFTP if it exhibits low to moderate cellularity, a follicular architecture, mild nuclear enlargement, and delicate nuclear grooves, but lacks papillae, PBs, or definite INPIs (see also Chap. 5).

Macrofollicular Variant of PTC

Definition

The macrofollicular variant of PTC (MFVPTC) is a FVPTC in which over 50% of the follicles are arranged as macrofollicles (follicles measuring more than 200 μm in diameter).

Criteria

The sample consists of monolayered (two-dimensional) sheets of neoplastic epithelium and/or variably sized follicles.

Convincing nuclear changes of PTC must be present for a definite interpretation of malignancy.

In contrast to conventional PTC, the diagnostic nuclear features are often more subtle as seen in FVPTC.

Papillary structures and psammoma bodies are not seen.

Abundant thin colloid or fragments of thick colloid may be present.

Explanatory Notes

MFVPTC is one of the rarest histologic subtypes of PTC with less than 100 reported cases; it is commonly underdiagnosed as benign, both on histology and cytology,

due to the patchy nuclear features of PTC [30–32]. It is characterized by a low incidence of lymph node metastasis, but when metastases occur the macrofollicular architecture is usually maintained. Most MFVPTCs have an indolent behavior, but multiple bone and lung metastases may occur. The differential diagnosis of MFVPTC includes the benign follicular nodule seen with follicular nodular disease and the follicular adenoma of macrofollicular type. MFVPTC is easily

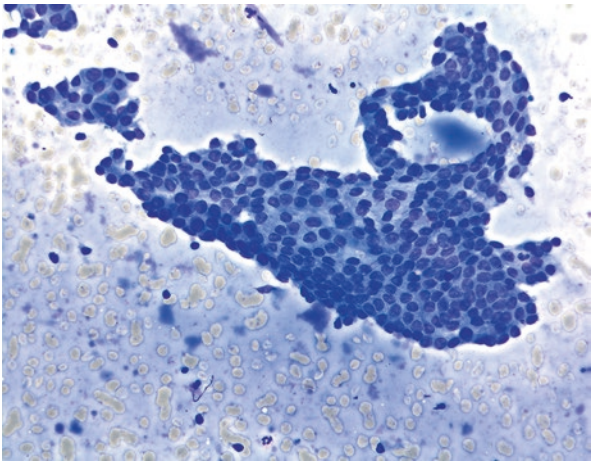

Fig. 8.21 Papillary thyroid carcinoma, macrofollicular. The neoplastic cells resemble those of a benign thyroid nodule at scanning magnification. In such cases there can be abundant thin colloid and relatively few sheets of cells. The difference lies in the nuclear features, which are better appreciated at high magnification (smear, Diff-Quik stain)

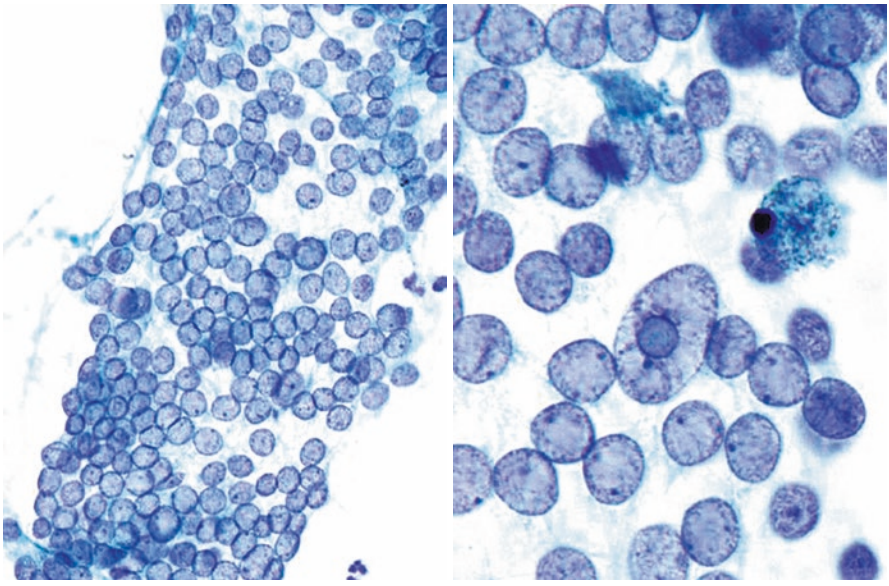

Fig. 8.22 Papillary thyroid carcinoma, macrofollicular. *Left*, There is a large sheet of tumor cells with crowded, "Orphan Annie eye" nuclei; *Right*, An intranuclear pseudoinclusion is present in the large oval nucleus. Note also the marginal micronucleoli (smear, Papanicolaou stain)

underappreciated at low magnification due to the abundance of thin colloid, the low cellularity, and the subtle and focal nuclear atypia. Thus, careful attention to nuclear features is necessary for all benign-appearing thyroid aspirates. Cytologically, the neoplastic cells usually have round/ovoid nuclei, either small or conspicuous eccentrically located nucleoli, chromatin clearing, nuclear overlapping, and nuclear grooves (Figs. 8.21 and 8.22) [30–32]. Only 45% of cases show INPIs, which range from rare to few [31]. Moderate-to-abundant thin and focally thick colloid and macrophages are often present. In contrast, PBs and papillary structures have not been reported. If follicular cells with round/ovoid nuclei, small-to-prominent, eccentrically located nucleoli, nuclear overlapping, and chromatin clearing are present in a background of abundant colloid, it is prudent to consider the possibility of MFVPTC and render a diagnosis of at least AUS, instead of a benign colloid nodule [31].

Cystic PTC

Definition

As the name implies, cystic PTC is a PTC that is predominantly cystic. It is a cytologic variant rather than a true histologic subtype, comprised of thin/watery fluid, abundant histiocytes, and hypervacuolated tumor cells. Cystic PTC on FNA correlates to a subset of the encapsulated (classic) PTC, a recognized PTC subtype in the WHO classification [1], with various stages of cystic degeneration.

Criteria

The neoplastic cells are typically arranged in small groups with irregular borders; sheets, papillae, or follicles may also be present.

Tumor cells look "histiocytoid" (i.e., hypervacuolated).

Macrophages, often containing hemosiderin, are present.

A variable amount of thin or watery colloid.

Convincing nuclear changes of PTC must be present for a definite diagnosis of malignancy.

In contrast to conventional PTC, fine/powdery chromatin is usually less prominent.

Explanatory Notes

The most common cystic lesion of the thyroid is cystic follicular nodular disease. On the other hand, PTC is the most common malignant neoplasm of the thyroid to undergo cystic changes. The amount of cystic change varies from case to case; approximately 10% of PTCs are almost entirely cystic [33, 34]. FNAs of cystic PTC show varying proportions of macrophages, colloid, and vacuolated "histiocytoid" neoplastic cells (Fig. 7.4) [33, 34]. A few small papillae comprised of viable tumor cells are sometimes present. The neoplastic cells of cystic PTC have more abundant, granular, or vacuolated cytoplasm than those of conventional PTC. The tumor cells

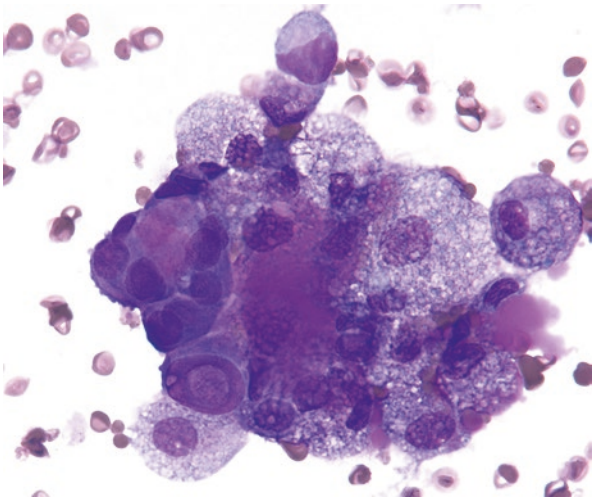

Fig. 8.23 Papillary thyroid carcinoma, cystic. There is prominent cystic change with numerous hemosiderin-laden macrophages. A small cluster of neoplastic cells has smooth, dense cytoplasm, and one cell has a large intranuclear pseudoinclusion (smear, Diff-Quik stain)

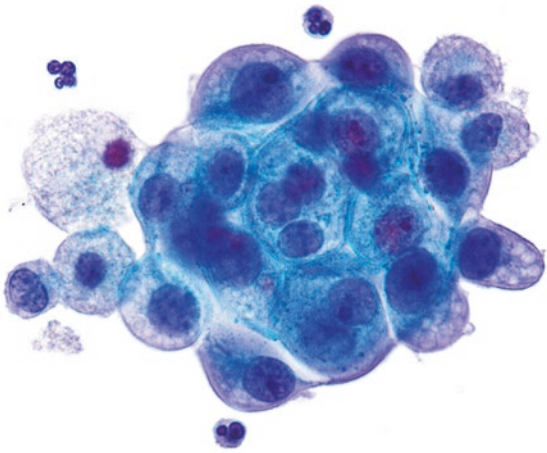

Fig. 8.24 Papillary thyroid carcinoma, cystic. Most of the cells in this image are neoplastic. They have abundant granular cytoplasm, hence the descriptor "histiocytoid." Classic nuclear features of papillary thyroid carcinoma are absent, but there is conspicuous nuclear enlargement (ThinPrep, Papanicolaou stain)

frequently appear more rigid and polygonal than normal follicular cells and display enlarged, oval to irregularly shaped nuclei with prominent nuclear grooves and occasional INPIs (Fig. 8.23). Some of the characteristic nuclear features of PTC, however, like pale, "powdery" chromatin, are often less apparent or even conspicuously absent (Fig. 8.24).

It should be noted that similar atypical cells are sometimes seen in benign follicular nodules with cystic change. These reactive cells may appear "histiocytoid" or they may be arranged in streaming sheets or cyst-lining cells which have enlarged nuclei, nucleoli, nuclear pallor, and occasional nuclear grooves. Their benign nature is betrayed by their elongated shape and the lack of nuclear crowding. In some

cases, however, the nuclear changes of cyst-lining cells can be extreme, and they occasionally show INPIs. Such cases are therefore properly diagnosed as "Suspicious for PTC" or AUS (see Chaps. 7 and 4, respectively).

Whereas some aspirates of cystic PTC are composed of abundant neoplastic cells and are readily interpreted as PTC, others have no neoplastic cells at all and are best interpreted as "Nondiagnostic; cyst fluid only" (see Chap. 2). Indeed, cystic PTC has long been recognized as a possible cause of false-negative thyroid FNAs. This concern may be less common in some centers with the precise sampling of a subcentimeter solid mural nodule within the cyst under high-resolution ultrasound guidance.

Oncocytic PTC

Definition

The oncocytic PTC is a thyroid tumor with nuclear changes characteristic of PTC but composed predominantly of oncocytic cells with variable architecture (follicular, papillary, or solid).

Criteria

The sample is composed predominantly of oncocytic cells (polygonal cells with abundant granular cytoplasm), arranged in papillae, sheets, microfollicles, or as isolated cells.

Convincing diagnostic nuclear changes of PTC must be present for a definite diagnosis of PTC.

Lymphocytes are absent or few in number.

Explanatory Notes

Focal oncocytic change is seen in many PTCs, including the conventional PTC. Only when the oncocytic changes are widespread (>75% of tumor cells) does the tumor

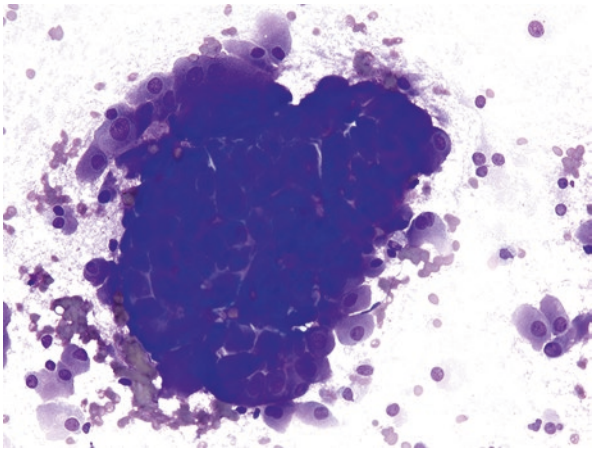

Fig. 8.25 Papillary thyroid carcinoma, oncocytic. The entire neoplasm is composed of oncocytic cells that have abundant granular cytoplasm. The nuclear features of papillary carcinoma are not readily apparent in this image; such cases are good mimics of oncocytic follicular neoplasms (smear, Diff-Quik stain)

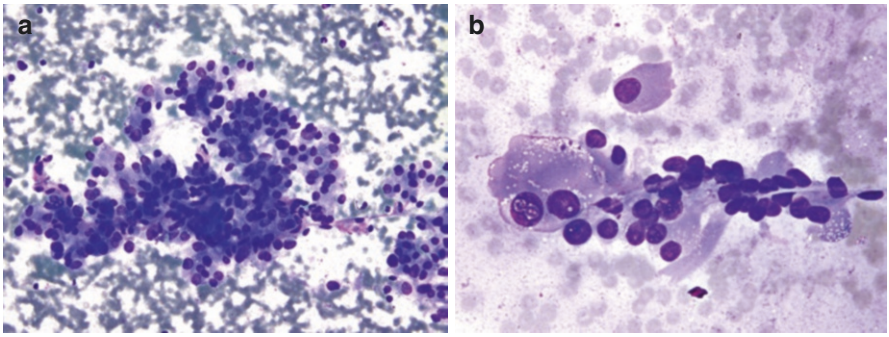

Fig. 8.26 Papillary thyroid carcinoma, oncocytic. (**a**) Loosely cohesive oncocytic cells have atypical, oval-shaped nuclei and rare intranuclear pseudoinclusions without nuclear grooves; such cases are good mimics of oncocytic follicular neoplasm or medullary thyroid carcinoma. (**b**) Multiple small and large intranuclear pseudoinclusions are seen in a large oncocytic cell with abundant granular cytoplasm (smears, Diff-Quik stain)

merit distinction as an oncocytic PTC (Figs. 8.25 and 8.26) [35, 36]. Aspirates of oncocytic PTC resemble those from other follicular cell-derived oncocytic proliferations, oncocytic MTC, and other oncocytic neoplasms (e.g., metastatic renal cell carcinoma). The characteristic nuclear features of PTC, therefore, must be searched for whenever an aspirate is composed predominantly of oncocytes. Non-PTC oncocytic lesions generally have rounder nuclei and more prominent nucleoli than the oncocytic variant of PTC. In addition, non-PTC follicular cell-derived oncocytic proliferations may have nuclear grooves and slight nuclear pallor, but INPIs are very rarely seen. When the full nuclear features of PTC are evident, oncocytic PTC can be readily diagnosed on FNA. When the nuclear features of PTC are not widespread, the case is best classified as "Follicular Neoplasm, Oncocytic Follicular Neoplasm" or as "Suspicious for PTC, oncocytic subtype." Lymphocytes are typically absent in FNAs of the oncocytic subtype of PTC; if present in large numbers, a Warthin-like PTC should be considered.

Warthin-Like PTC

Definition

The Warthin-like PTC (WL-PTC) is a circumscribed thyroid tumor with papillary architecture and lymphoid follicles that resembles a Warthin tumor of the parotid gland. It is often associated with Hashimoto's thyroiditis [1, 37–39]. The neoplastic cells have abundant granular eosinophilic (oncocytic) cytoplasm and the nuclear features of PTC.

Criteria

The neoplastic cells are oncocytic and arranged in papillae, monolayered sheets, and as dispersed cells.

A lymphoplasmacytic background is present; the lymphocytes and plasma cells permeate the fibrovascular stalk and are intimately associated with the tumor cells.

Convincing nuclear changes of PTC must be present for a definite diagnosis of malignancy.

Explanatory Notes

WL-PTC is a rare subtype with a prevalence of 0.2–1.9% of all PTCs, having a unique histomorphology simulating Warthin tumor of the parotid gland. Review of the available literature on cytological features of 28 cases of WL-PTC showed that while most (64.4%) were correctly diagnosed as Malignant-PTC, a smaller but significant percentage (10.7%) were erroneously labeled benign thyroid aspirates (thyroiditis) [39]. The rest were variably described as AUS or Suspicious for PTC. Even though most cases were appropriately diagnosed as PTC, they were not specifically subtyped as WL-PTC on cytology. Because of the mixture of oncocytes and lymphocytes, FNAs from WL-PTC resemble those from Hashimoto thyroiditis (Fig. 8.27) [37]. Also, the tumor itself is associated with Hashimoto thyroiditis more commonly than classical PTC (93% vs. 36%, respectively). The oncocytic cells of Hashimoto thyroiditis, however, typically have a round nucleus with a prominent single nucleolus; the nuclei of PTC (including the WL-PTC), by contrast, are more irregular in contour and nucleoli are less prominent. The oncocytic cells in Hashimoto thyroiditis may show nuclear clearing and grooves, but papillary fragments and INPIs are usually not seen. Processing of samples by LBP technique

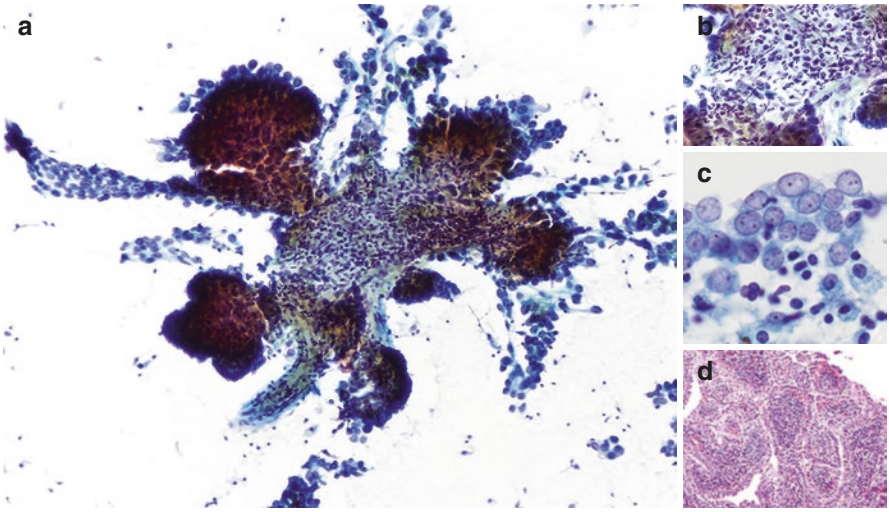

Fig. 8.27 Papillary thyroid carcinoma, Warthin-like. (**a**) The aspirate shows papillary fragments in a lymphocytic background (smear, Papanicolaou stain). (**b**) The fibrovascular cores are engorged with lymphocytes (smear, Papanicolaou stain). (**c**) The epithelial cells are also intimately associated with lymphocytes. The nuclei are enlarged, oval, and clear (smear, Papanicolaou stain). (**d**) Histologically, the tumor resembles a Warthin tumor of the salivary gland, with tumor epithelium surrounding lymphoid aggregates. Typical nuclear features of papillary carcinoma can be seen at high power (not shown) (hematoxylin and eosin stain)

increases the yield of the tumor cells; however, there is loss of the reactive lymphocyte-rich background. It may virtually be impossible to separate a WL-PTC from an oncocytic PTC associated with Hashimoto thyroiditis. Nevertheless, the distinction between WL-PTC and oncocytic PTC does not have any clinical implication in terms of management as well as prognosis [38, 39].

Tall Cell PTC

Definition

The tall cell PTC (TC-PTC) is an aggressive form of PTC composed of elongated "tall" tumor cells (on histologic samples their height is at least three times their width [1]) with abundant dense granular eosinophilic cytoplasm, prominent cell membranes, and the typical nuclear changes of PTC.

Criteria

The neoplastic cells are most commonly polygonal with centrally located nuclei but can be elongated and cylindrical with an eccentrically placed nucleus ("tail-like" cells or "tadpole" cells). They have granular cytoplasm with prominent cytoplasmic borders.

Some lymphocytes may be present.

Convincing nuclear changes of PTC must be present for a definite diagnosis of malignancy.

In contrast to conventional PTC:

- the nuclei tend to be larger and more elongated.
- the nuclear chromatin is sometimes less powdery and more granular.
- the nucleoli can be prominent and centrally placed.
- mitotic figures may be present.
- PBs are fewer in number.
- INPIs tend to be more frequent and more often multiple within a single nucleus, imparting a "soap bubble" appearance to the nucleus.

Explanatory Notes

The TC-PTC is the most common aggressive variant and accounts for 4–16% of all PTC cases. It tends to occur in elderly patients and is more common in men than other PTCs [2, 22, 24]. It frequently presents as a large and bulky tumor, often with extrathyroidal extension and vascular invasion [1, 2]. It is more aggressive than the conventional PTC and has a higher incidence of local recurrence, central neck involvement, and distant metastasis [1, 2, 22, 24]. TC-PTC accounts for a substantial portion of radioactive iodine refractory thyroid carcinomas [1]. According to the WHO classification, tall cells must account for ≥30% of all tumor cells for the diagnosis of TC-PTC [1]. However, if 10% or more of a PTC has tall cell features, the tumor is also associated with an adverse clinical outcome [1, 40]. Therefore, the identification of a minor tall cell component can be clinically significant. Up to 90%

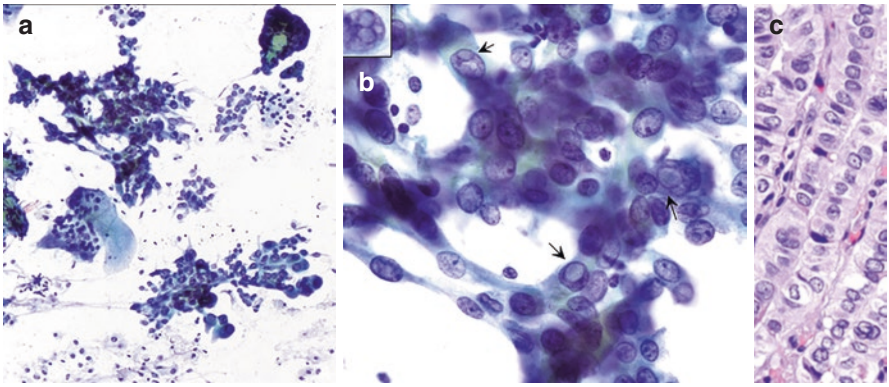

Fig. 8.28 Papillary thyroid carcinoma, tall cell. (**a**) The smear shows elongated cells in loosely cohesive arrangements (smear, Papanicolaou stain). (**b**) The cytoplasm is elongated, with frequent nuclear pseudoinclusions and rare soap bubble nuclei (inset) (smear, Papanicolaou stain). (**c**) Histologically, this variant is comprised of tall rectangular tumor cells with eosinophilic cytoplasm arranged in parallel rows (hematoxylin and eosin stain)

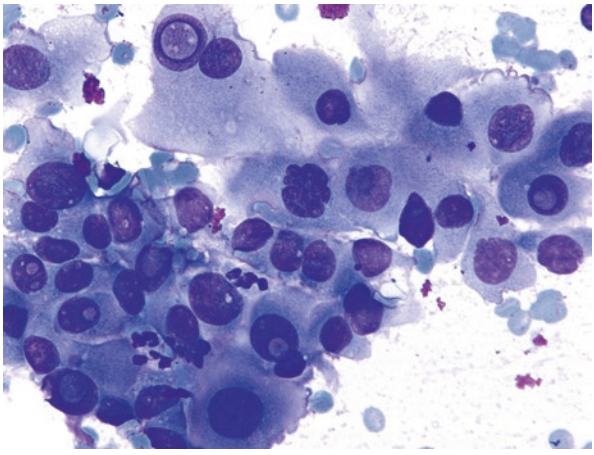

Fig. 8.29 Papillary thyroid carcinoma, tall cell. "Soap bubble-like" intranuclear pseudoinclusions (9 o'clock) are often seen in the tall cell variant of papillary thyroid carcinoma (smear, Diff-Quik stain)

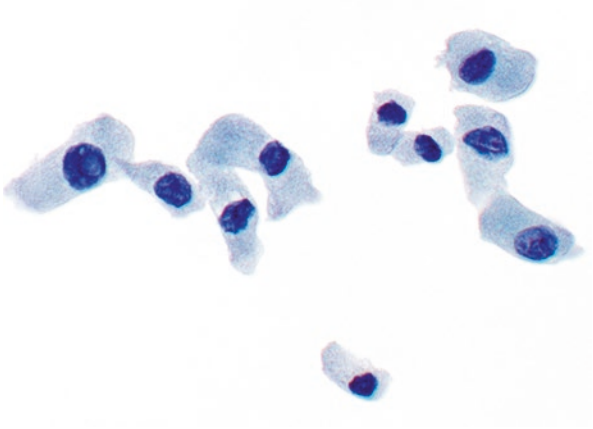

Fig. 8.30 Papillary thyroid carcinoma, tall cell. The "tallness" of these cells is readily appreciated. When this morphology is seen throughout the sample, one can raise the possibility of a tall cell variant in the FNA report (ThinPrep, Papanicolaou stain)

of TC-PTCs harbor the *BRAF* V600E mutation. *TERT* promoter mutations, which are associated with a worse outcome in PTCs, are also significantly more prevalent in TC-PTC (31%) compared to conventional PTC (<10%) [25]. TC-PTC is easily recognized as a PTC due to the prominence of the nuclear features of PTC, especially nuclear grooves and INPIs, which are frequent and easily identified (Figs. 8.28, 8.29, and 8.30) [14, 41–43]. Tall cell features may be easier to assess on LBPs than on conventional smears (Fig. 8.30) [12, 14, 44]. Tall cells are present in the majority of TC-PTC cases and are typically located at the periphery of cell clusters and as single cells [44]. Cytoplasmic cuffing along the periphery of cell clusters and soap bubble INPIs, when present, are highly suggestive of TC-PTC [44]. TC-PTC cases are more likely to show abundant oncocytic cytoplasm and distinct cell borders [44]. Finally, cytoplasmic tails are more likely to be present and more numerous in TC-PTC [44]. Although it is not essential to specify the variant of PTC by FNA in general, a TC-PTC (or tall cell features) may be at least suggested by FNA and it may influence the extent of surgery in a subset of cases along with other clinico-radiological factors.

Columnar Cell PTC

Definition

The columnar cell PTC (CC-PTC) is characterized by columnar cells with hyperchromatic, oval, and pseudostratified nuclei with supranuclear or subnuclear cytoplasmic vacuoles, reminiscent of a colonic adenoma or secretory-type endometrium [1]. The cells are typically arranged in papillae, but trabeculae and follicles can also be seen.

Criteria

Smears are cellular and generally lack colloid.

The neoplastic cells are arranged as papillae, clusters, and flat sheets, sometimes with small tubular structures.

The nuclei are elongated and pseudostratified.

Focal cytoplasmic vacuolization may be present.

Convincing nuclear changes of PTC must be present for a definitive diagnosis of malignancy.

In contrast to conventional PTC:

- the nuclear features of PTC (grooves, INPIs) are much less prominent.
- the nuclear chromatin tends to be hyperchromatic rather than pale and powdery.
- colloid and cystic changes (macrophages) are typically not seen.

Explanatory Notes

The CC-PTC is one of the least common subtypes of PTC (<0.4% of all PTCs). The majority of CC-PTCs occur in older male patients and are large, invasive tumors with extrathyroidal extension that pursue an aggressive clinical course [1, 45]. Rare well-circumscribed/encapsulated and intrathyroidal CC-PTC occur in younger

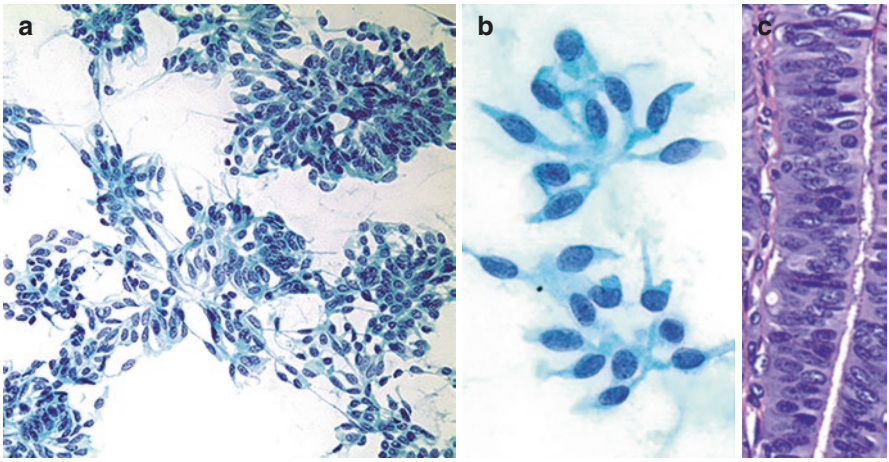

Fig. 8.31 Papillary thyroid carcinoma, columnar cell. (**a**) The aspirate shows loosely cohesive spindle-shaped cells (smear, Papanicolaou stain). (**b**) The cytoplasm is bipolar and wispy, and cigar-shaped nuclei have few characteristic features of papillary thyroid carcinoma (smear, Papanicolaou stain). (**c**) Histologic examination shows rows of pseudostratified columnar cells with elongated hyperchromatic nuclei and scanty cytoplasm (hematoxylin and eosin stain). (Courtesy of Dr. Tamar A. Giordgadze of Medical College of Wisconsin)

female patients and are comparatively indolent [1, 45]. Therefore, the mere presence of columnar cell features on cytology alone may not predict a worse outcome. CC-PTC does not show the typical nuclear features of PTC [1, 45–47]. The cells are usually large with pseudostratified oval or elongated nuclei and powdery chromatin (Fig. 8.31). Hypercellular smears composed almost exclusively of papillary structures with pseudostratified dark nuclei with a paucity of INPIs and nuclear grooves are highly suggestive of CC-PTC [47]. The unique morphology of CC-PTC generally allows it to be recognized as a neoplasm on FNA; however, due to lack of PTC nuclei, it may be underdiagnosed as FN or diagnosed as Malignant, but not typed as PTC. The dark and stratified nuclei of CC-PTC can mimic a metastasis from a colorectal or endometrial primary [46], but the necrotic background commonly present in metastatic disease from these primaries is unusual in CC-PTC. Clinicoradiological correlation, in addition to a limited IHC panel that includes thyroglobulin and TTF-1, can be very helpful. Importantly, PAX8 is expressed in both CC-PTC and gynecological carcinomas, and CDX-2 is expressed in up to 55% of CC-PTC [1], somewhat limiting the diagnostic value of these two markers. Occasionally, the neoplastic cells of CC-PTC may also be mistaken for MTC or even benign respiratory epithelial cells. Most CC-PTC demonstrate activating oncogenic driver alterations in *BRAF* including *BRAF* V600E mutation in 30–44% of cases, with most cases also harboring secondary oncogenic mutations, including *TERT* or *TP53*, and multiple chromosomal gains and losses [45].

Solid/Trabecular PTC

Definition

The solid/trabecular PTC (ST-PTC) is defined histologically by the presence of solid and/or trabecular and/or nested (insular) areas that lack papillae, follicles, and colloid storage and occupy >50% of the tumor [1]. The neoplastic cells have typical nuclear features of PTC.

Criteria

Smears are variably cellular and generally lack colloid.

The neoplastic cells may appear as cohesive, syncytial-type 3-dimensional tissue fragments, microfollicles/trabeculae, or non-cohesive, single cells.

The nuclei usually show the typical nuclear features of PTC, but they may be less elongated (rounder) and darker than those of conventional PTC.

True papillary formations with fibrovascular cores are scant or absent.

Explanatory Notes

ST-PTC is a rare PTC subtype (1–3% of adult PTCs) that is still poorly characterized. It is common in children and has been reported in >30% of children following the Chernobyl accident [1]. This variant is also more common in children without radiation exposure. The prognosis of ST-PTC appears to be less favorable in adults when compared to conventional PTC [1]. In a meta-analysis of 205 ST-PTCs, these tumors manifested a significantly higher risk for vascular invasion, tumor recurrence, and cancer mortality as compared to conventional PTC [48]. The genetic profile of ST-PTC is also distinct from that of conventional PTC. In general, the prevalence of *BRAF* mutations in ST-PTCs is rather low in comparison with those in conventional

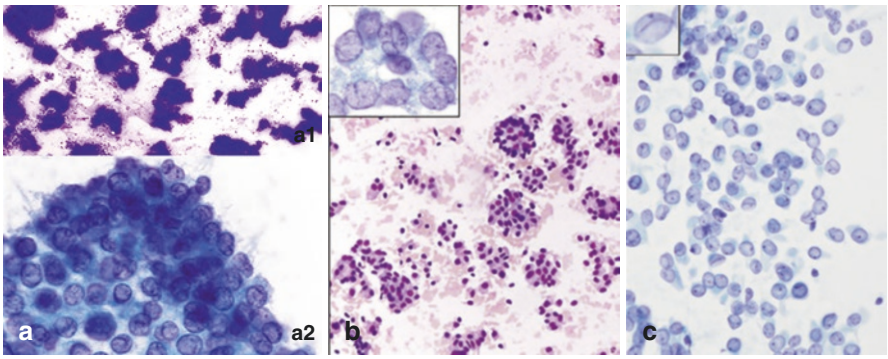

Fig. 8.32 Papillary thyroid carcinoma, solid/trabecular. This subtype may demonstrate three different cytologic patterns: (**a**) a cohesive, syncytial tissue fragment pattern, (**b**) a microfollicular/trabecular pattern, and (**c**) a non-cohesive, single-cell pattern. All three patterns have characteristic nuclear features of papillary carcinoma: convoluted clear nuclei in ***a2***, nuclear clearing and convolution in the inset of **b**, and nuclear clearing and grooves in **c**. (***a1*** and **b**: smears, Diff-Quik stain; ***a2***, **c** and **insets**: smears, Papanicolaou stain)

PTCs. In contrast, gene fusions such as *RET* or *NTRK1/3* are more prevalent in ST-PTCs [48]. The prevalence of *TERT* promoter mutation in ST-PTC is slightly higher than in conventional PTCs [48]. Because of the lack of criteria with high specificity and sensitivity, the preoperative diagnosis of SV-PTC is hardly ever made or suggested on cytology (Fig. 8.32) [49, 50]. Most cases of ST-PTC are diagnosed as Malignant or Suspicious for Malignancy (PTC or FVPTC) [49, 50]. The microfollicular pattern of ST-PTC is difficult to distinguish from other follicular-patterned lesions, including FVPTC and follicular neoplasms, and the typical nuclear features of PTC may be patchy in a subset of cases. In contrast, cohesive, syncytial, three-dimensional tissue fragments appear to be unique to ST-PTC and likely correlate with the nested pattern of the tumor cells observed histologically [49]. This pattern differs from the monolayered sheets typical of conventional PTC. A nonspecific single-cell pattern can also be seen in ST-PTC and may correlate with infiltrative tumor growth and more aggressive behavior [49]. This pattern can mimic MTC, but the two tumors can be distinguished by their nuclear features. There is also significant morphological overlap between ST-PTC and poorly differentiated thyroid carcinoma (PDTC). PDTC may have occasional nuclear grooves and INPIs, but the cells usually have more granular chromatin and scant cytoplasm, with a high nuclear:cytoplasmic ratio. The presence of mitoses and necrosis is helpful to suggest PDTC or differentiated high-grade thyroid carcinomas, but these features are not always present on cytology (see Chap. 10). Clinico-radiological correlation can also be very helpful. Although ST-PTC in children can have significant necrosis, they behave like a PTC and do not have the aggressiveness of a PDTC.

Diffuse Sclerosing PTC

Definition

The diffuse sclerosing PTC (DS-PTC) is characterized by diffuse involvement of one or both thyroid lobes, extensive lymphovascular invasion, numerous PBs, squamous metaplasia, marked lymphocytic infiltration, and prominent fibrosis (Fig. 8.33) [1].

Criteria

The smears are moderately to highly cellular with scant or absent colloid.

The neoplastic cells are arranged in three-dimensional ball-like clusters and cohesive clusters intermingled with inflammatory cells, but conventional monolayered syncytial and papillary clusters may also be present.

The neoplastic cells are round, polygonal, or columnar, with dense cytoplasm and distinct cytoplasmic borders; hobnail cells protruding from cell clusters are often present.

In contrast to conventional PTC:

- there is less chromatin pallor.

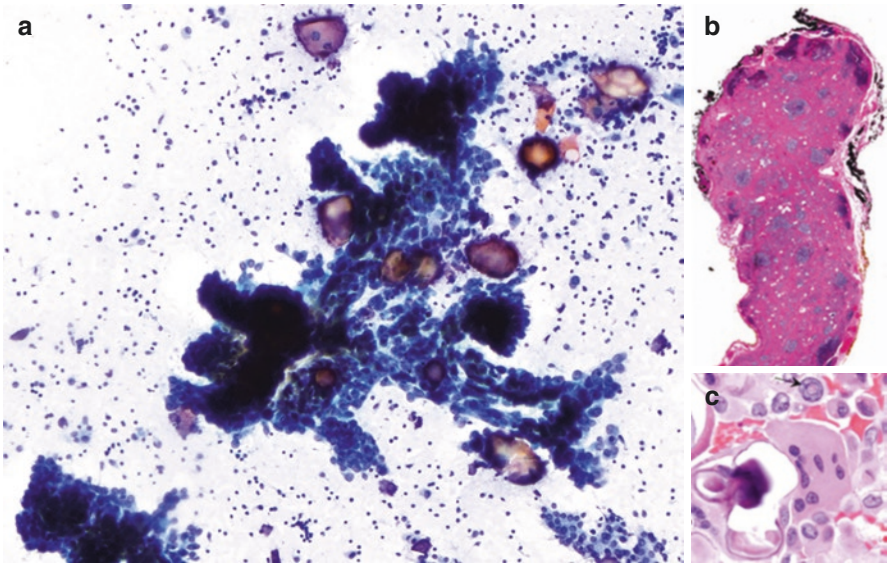

Fig. 8.33 Papillary thyroid carcinoma, diffuse sclerosing. (**a**) The aspirate shows papillary fragments associated with psammoma bodies in a lymphocytic background. The nuclear chromatin is darker than in the conventional papillary thyroid carcinoma (smear, Papanicolaou stain). (**b**) On histologic examination, the thyroid gland shows numerous lymphoid follicles and many small "holes." (**c**) The holes are from popped out psammoma bodies (**b**, **c**: hematoxylin and eosin stain)

- there are fewer INPIs and nuclear grooves (<50% of cases).
- large septate or unilocular cytoplasmic vacuoles are common.
- squamous metaplastic changes are common.
- numerous lymphocytes and PBs are present in the background.

Explanatory Notes

DS-PTC is a relatively uncommon PTC subtype (approximately 3% of all PTCs) [1]. This tumor is common in children and young adults and represents 10% of PTC seen in children exposed to the radioactive iodine following the Chernobyl accident [1]. It typically presents as a goiter without a dominant mass, reflecting a diffuse involvement of the gland that mimics Hashimoto's thyroiditis and/or lymphoma. Sonograms may reveal a characteristic "snowstorm appearance" due to numerous and widespread microcalcifications (PBs). DS-PTC is often associated with extrathyroidal extension, extensive cervical lymph node involvement, and distant metastasis [1]. Although DS-PTC has a lower disease-free survival than conventional PTC, its mortality rate is similar to conventional PTC [1]. Molecular analyses of DS-PTC have revealed *RET* translocations and especially *NCOA4*::*RET* in cases occurring after radiation fallout. *BRAFV600E* mutations are reported in 20% of cases and *ALK* rearrangements in 13% [1]. On FNA, the highly cellular aspirate is

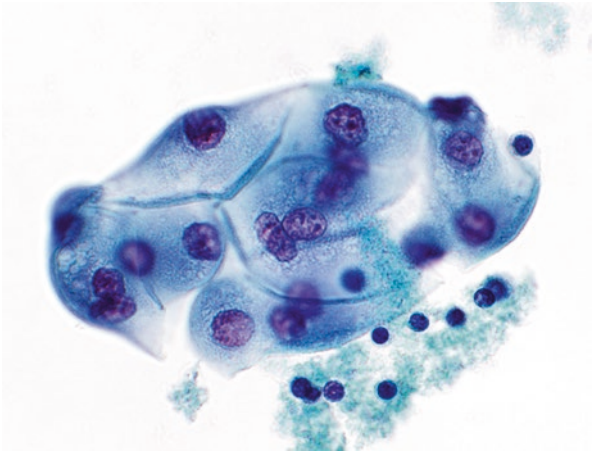

Fig. 8.34 Papillary thyroid carcinoma, diffuse sclerosing. The neoplastic cells in this image are "squamoid": they have a flat, polygonal shape with sharply demarcated cell membranes, and they fit together like jigsaw pieces, but there is no overt keratinization. This squamoid appearance is sometimes encountered as a focal finding in conventional (classic) papillary carcinomas, but in the diffuse sclerosing variant this feature is often widespread. Note that these cells lack the usual nuclear features of papillary carcinoma (ThinPrep, Papanicolaou stain)

notable for numerous monomorphic small lymphocytes (Fig. 8.34) and can be misleading for lymphocytic thyroiditis or malignant lymphoma [51]. It's worth remembering that in lymphocytic thyroiditis, atypical follicular cells are commonly encountered and nuclear grooves and INPIs are sometimes present. Furthermore, there is a lower incidence of characteristic nuclear features of PTC in DS-PTC. Three-dimensional clusters of tumor cells with hobnail features and cytoplasmic vacuoles, abundant PBs, and squamoid differentiation (Fig. 8.34) all suggest the possibility of a DS-PTC [51].

Hobnail PTC

Definition

The hobnail PTC (H-PTC) is an aggressive PTC subtype characterized histologically by complex papillary and micropapillary structures, which are covered with cells showing apically placed nuclei, bulging of the apical cell surface, and loss of cellular polarity/cohesiveness (hobnail features) [1]. Hobnail features must account for ≥30% of the tumor for the diagnosis of the hobnail variant of PTC [1].

Criteria

The neoplastic cells show loss of polarity and cohesiveness.

Single cells with eccentric nuclei and tapering cytoplasm (comet-like or tear drop-like cells) are present.

Neoplastic cells with an apically or eccentrically placed nucleus (hobnail features) can be seen in papillary or micropapillary clusters.

Multiple soap bubble-like INPIs and typical nuclear features of PTC are present.

Cell blocks may reveal papillary or micropapillary fragments lined by hobnail cells.

Explanatory Notes

H-PTC is a rare PTC subtype (<1% of all PTCs), first described in 2010 by Asioli et al. [18, 52]. Most patients with H-PTC demonstrate rapid disease progression and many die of disease within 5 years [1, 52]. As such, H-PTCs are extremely rare in a pure form and are usually associated with other aggressive subtypes of PTC (e.g., TC-PTC, CC-PTC, ST-PTC) and/or intermixed with areas showing progression to poorly differentiated or anaplastic thyroid carcinoma [1, 52]. Conversely, hobnail cells/features can be seen in conventional PTC with an indolent course, sometimes in >30% of the tumor where they are often associated with cystic and/or degenerative changes [53]. In contrast to H-PTC, these "hobnail-like" PTC occur in younger patients, have a low mitotic rate, and lack gross extra-thyroid extension and secondary pathogenic mutations [1, 53]. The *BRAF* V600E mutation is found in most (70–80%) cases, while *TP53* mutations, *TERT* promoter mutations, and *PIK3CA* mutations are also common [1]. On FNA, most H-PTC cases can be diagnosed as Malignant-PTC. However, the cytologic findings of H-PTC, described in a few retrospective studies, are essentially nonspecific and there is significant cytomorphological overlap with other aggressive subtypes of PTC such as the TC-PTC, CC-PTC, and DS-PTC [17, 18]. Hobnail morphology may occur also in the context of oncocytic, cystic/degenerative, and clear cell changes. As a result, a preoperative diagnosis of the H-PTC based on cytomorphology alone is not realistic. Even on histology, a diagnosis of H-PTC without the presence of aggressive clinico-pathologic features (such as extrathyroidal extension, vascular invasion, necrosis, and high mitotic count) should be rendered with caution [1]. The H-PTC also needs to be differentiated from metastases to the thyroid gland (or lymph nodes) that have hobnail and/or micropapillary growth patterns (e.g., breast, lung, ovary).

Related Tumors

In the fifth edition of the WHO Classification of Endocrine and Neuroendocrine Tumors that relate to the thyroid gland, the cribriform-morular thyroid carcinoma (CMTC) is no longer classified as a subtype/variant of PTC but as a malignant thyroid tumor of uncertain histogenesis, while hyalinizing trabecular tumor (HTT) is classified as a low-risk follicular cell-derived neoplasm, along with NIFTP and thyroid tumors of uncertain malignant potential [1].

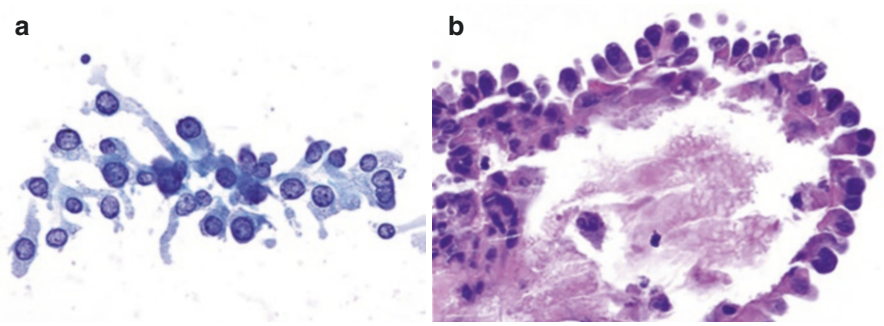

Fig. 8.35 Papillary thyroid carcinoma, hobnail subtype. (**a**) The tumor cells in this subtype are characterized by an eccentric location of the nucleus in elongated cytoplasm (hobnail-like) (smear, Papanicolaou stain). (**b**) The histologic counterpart shows similar features (hematoxylin and eosin)

Cribriform-Morular Thyroid Carcinoma

Definition

The CMTC is a rare, distinct thyroid malignancy characterized histologically by cribriform and solid architecture lacking colloid. The cells are tall and columnar or spindle-shaped, and squamoid morules are present. The tumor cell nuclei are often hyperchromatic and pseudostratified, although several nuclear features of PTC are also found. Some nuclei within the morules contain a peculiar nuclear clearing caused by biotin accumulation (Fig. 8.35).

Criteria

The smears are hypercellular.

Colloid is absent.

The tall, columnar neoplastic cells have a papillary-like arrangement.

Round to oval slit-like empty spaces formed by spindle to ovoid cells within cell clusters are present (cribriform pattern).

Cell clusters with eddy formation (morules) are present.

Spindle-shaped tumor cells are present in the background.

Pale staining nuclei with thickened nuclear membranes are present focally.

Nuclear grooves are present, but INPIs are less common than in the conventional PTC (58% of cases).

Foamy or hemosiderin-laden histiocytes are often present in the background.

Hyaline material can be seen within cell clusters or in the background.

PBs and multinucleated giant cells are absent.

The neoplastic cells usually express TTF-1; however, PAX8 immunoreactivity is weak, focal or negative, and tumors usually lack thyroglobulin reactivity.

The neoplastic cells show diffuse nuclear and cytoplasmic positivity for β-catenin in both inherited and sporadic forms of this tumor (due to germline or somatic alterations in the Wnt/beta-catenin pathway).

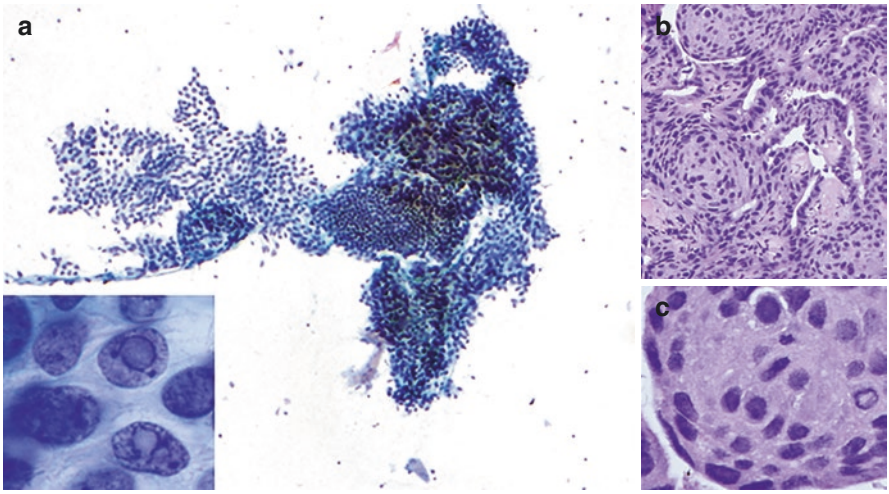

Fig. 8.36 Cribriform-morular thyroid carcinoma. (**a**) The aspirate shows large fragments of cohesive epithelium with a complicated arrangement (smear, Papanicolaou stain). The nuclear chromatin is dark, but intranuclear pseudoinclusions are present (inset). (**b**) Histologically, the tumor is characterized by cribriform morula formation (hematoxylin and eosin stain). (**c**) Higher magnification shows the characteristic morules (hematoxylin and eosin stain)

Explanatory Notes

CMTC was traditionally considered as a variant of PTC. Recent studies, however, showed that CMTC constitutes a clinicopathologically distinct category of thyroid carcinoma of uncertain histogenesis driven by Wnt/beta-catenin pathway activation [54, 55]. CMTC occurs almost exclusively in young women (97% of cases) and is frequently associated (up to 53%) with familial adenomatous polyposis (FAP) or Gardner syndrome and often precedes by several years the development of polyposis coli [1, 54–57]. A sporadic form occurs in patients who do not carry a germline mutation of *APC* gene. Generally, FAP-associated CMTC occurs in younger patients and is multifocal, whereas sporadic CMTC presents as a solitary thyroid nodule. CMTC is generally an indolent tumor, especially in its sporadic form. CMTC is associated with lymph node metastases at presentation in 12% and distant metastases in 3%, with overall mortality of 2% [1]. Most (95%) of CMTC aspirates showed features either diagnostic or suspicious of thyroid carcinoma [54, 57]. There is significant overlap between the architectural and nuclear features of CMTC and some PTC subtypes (conventional, TC-PTC, CC-PTC) (Fig. 8.36). Diffuse nuclear and cytoplasmic positivity for β-catenin is the hallmark of CMTC in both FAP-associated or non-FAP-associated cases, in contrast with other tumors and normal thyroid cells that show diffuse membranous β-catenin expression [1, 54, 55]. In addition, the neoplastic cells usually express TTF-1; however, PAX8 immunoreactivity is weak, focal or negative, and tumors usually lack thyroglobulin reactivity [1, 54, 55]. These findings raise questions about tumor cell origin and may indicate that these are not of thyroid follicular epithelial differentiation [54, 55]. Thus, in the appropriate

settings such as the presence of characteristic cytological features, relative young age of patients, clinical suspicious or confirmation of FAP as well as the presence of material for β-catenin IHC (nuclear and cytoplasmic positivity), the diagnosis of CMTC can be made or at least suggested preoperatively [56, 57]. The diagnosis of CMTC should alert the clinician for a possible diagnosis of FAP and initiation of genetic screening.

Hyalinizing Trabecular Tumor

Definition

The hyalinizing trabecular tumor (HTT) is a follicular cell-derived neoplasm composed of large trabeculae of elongated/polygonal cells with hyaline cytoplasm admixed with intra-trabecular hyaline material, and with nuclear features of PTC including prominent grooves, INPIs, and membrane irregularities [1].

Criteria

Cohesive neoplastic cells are radially oriented around amyloid-like hyaline stromal material.

Cells can be round or spindle-shaped.
INPIs and nuclear grooves are numerous.
Occasional PBs may be present.
Cytoplasmic paranuclear yellow bodies may be present.
Papillary and sheet-like fragments are absent.

Explanatory Notes

HTT represents <1% of thyroid neoplasms, has a strong female predominance (>80% of cases), and a mean age of 50 years (range: 21–79 years) [1]. Despite significant morphologic similarities with PTC, HTT is characterized by its unique

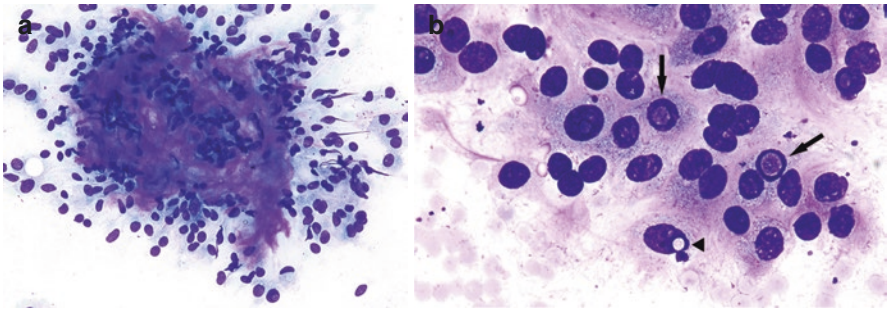

Fig. 8.37 Hyalinizing trabecular tumor. (**a**) A core of metachromatic hyaline material insinuates among cells with oval nuclei, anisonucleosis, and abundant cytoplasm (smear, Diff-Quik stain). (**b**) Oval neoplastic nuclei have occasional intranuclear pseudoinclusions (*arrows*). Note the clear hole in one of the adjacent nuclei (*arrowhead*), a mimic of INPIs, but recognizable as an artifact because the hole is white rather than the color and texture of cytoplasm (smear, Papanicolaou stain)

genetic profile with the presence of *GLIS* rearrangement (*PAX8::GLIS3* in most cases, less commonly *PAX8::GLIS1*) in virtually all cases analyzed and not in other thyroid tumors, when stringent diagnostic criteria are applied [1, 58, 59]. In contrast to PTC, *RAS* and *BRAF* V600E mutations have not been found in HTT. HTT is considered as a low-risk neoplasm, akin to NIFTP, and patients with HTT follow a benign clinical course in the vast majority of cases (>99%) even after long follow-up; complete excision is usually curative [1, 58–63]. Total thyroidectomy and/or radioiodine treatment are usually not warranted for HTT [1]. Because the morphologic features of HTT overlap significantly with those of PTC and MTC (see Chap. 9), HTT is very difficult to recognize as such in an FNA specimen (Fig. 8.37) [61–63]. Most HTTs are interpreted as PTC or Suspicious for PTC. Despite the presence of nuclear grooves, INPIs and irregular nuclear borders, all of which mimic PTC, the following diagnostic clues favor HTT: the presence of hyaline or amyloid-like material, loosely cohesive groups of tumor cells with a trabecular or syncytial pattern, radiating arrangement of neoplastic cells around a hyaline core, abundant eosinophilic or amphophilic cytoplasm, lack of papillae, and calcifications [61–63]. The presence of hyaline material may be misinterpreted as amyloid, therefore leading to an incorrect diagnosis of MTC, or may even thought to be colloid causing a false-negative diagnosis. It is important to remember that in MTC the tumor cells have eccentrically located nuclei with granular "salt and pepper" chromatin and inconspicuous nucleoli (see Chap. 9). IHC may be of help in discriminating HTT and MTC. HTT cells are positive for thyroglobulin and TTF-1 while they are negative for calcitonin. A peculiar cell membrane reactivity of the monoclonal MIB-1 to Ki-67, rather than nuclear staining, can further support the diagnosis of HTT. The specific *GLIS* fusion product can be identified by molecular techniques and also by IHC. While this biomarker is largely unavailable in most laboratories, the detection of a *GLIS* rearrangement or *GLIS* protein expression enables a preoperative diagnosis of HTT in cytology specimens [1, 62, 63]. The ultrasound findings of HTT usually show a well-defined iso- or hypoechoic solid nodule without microcalcifications that more closely resembles a follicular neoplasm or FVPTC than a classic PTC [1, 62].

Management

As a group, PTCs tend to be biologically indolent and have an excellent prognosis; survival rates of 96% at 5 years, 93% at 10 years, and >90% at 20 years have been reported [1]. Surgical consultation is recommended for patients with an FNA interpretation that is conclusive for PTC; subtyping the PTC cytologically is not essential and generally doesn't affect management [2]. The decision to perform surgery and the extent of surgery (lobectomy vs. total thyroidectomy) depend on the patient's age and overall health status and the size and sonographic characteristics of the tumor [2]. A cytologic diagnosis of PTC almost always leads to thyroid surgery. Active surveillance is an alternative to immediate surgery in a subset of patients, including those with very low-risk tumors (e.g., papillary microcarcinomas without

clinically evident metastases or local invasion, and no convincing cytologic or molecular evidence of aggressive disease) and patients at high surgical risk because of comorbidities, patients with an expected short remaining life span, or patients with concurrent medical or surgical issues that are more pressing than thyroid surgery [2]. For patients with thyroid cancer between 1 and 4 cm in diameter without extrathyroidal extension and without clinical evidence of lymph node metastases (cN0), the initial surgical procedure can be either a near-total/total thyroidectomy or a lobectomy [2]. Thyroid lobectomy alone may be sufficient initial treatment for low-risk PTCs, but the treatment team may choose total thyroidectomy to enable radioiodine therapy or to enhance follow-up based upon disease features and/or patient preferences [2]. If surgery is chosen for patients with microcarcinomas (<1 cm) without extrathyroidal extension and cN0, the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe [2]. Thyroid lobectomy alone is sufficient treatment for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck irradiation, familial thyroid carcinoma, or clinically detectable cervical nodal metastases [2].

Sample Reports

The general category "Malignant" is used whenever the cytomorphologic features are conclusive for malignancy. If an aspirate is interpreted as Malignant, it is implied that the sample is adequate for evaluation. An explicit statement of adequacy is optional. Descriptive comments that follow are used to subclassify the malignancy and summarize the results of special studies, if any. If the findings are suspicious but not conclusive for malignancy, the general category "Suspicious for malignancy" should be used (see Chap. 7).

The positive predictive value of a conclusive malignant diagnosis of PTC is approximately 97–99%. This drops slightly, to 94–96%, if NIFTP is excluded from malignancies. Much of this drop in positive predictive value can be eliminated if the malignant category is limited to those cases with classical or tall cell PTC features.

Example 1
MALIGNANT.
Papillary thyroid carcinoma.

Example 2
MALIGNANT.
Papillary thyroid carcinoma.
Note: With the reclassification of a subset of indolent thyroid malignancies as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)," the positive predictive value of the malignant category for thyroid FNA

is expected to drop from 97–99% to about 94–96%. Thus, a small proportion of cases interpreted as malignant by FNA may prove to be NIFTP upon histologic examination.

Example 3
MALIGNANT.
Papillary thyroid carcinoma, favor tall cell variant.

Example 4
MALIGNANT.
Papillary thyroid carcinoma.
Note: Some cytologic features raise the possibility of a tall cell variant.

Example 5
MALIGNANT.
Thyroid carcinoma, most consistent with cribriform-morular thyroid carcinoma.
Note: The cytologic features and the immunoprofile (diffuse nuclear and cytoplasmic positivity for β-catenin, negativity for thyroglobulin) are compatible with the cribriform-morular thyroid carcinoma. Correlation with clinico-radiological findings is recommended. Genetic consultation should be considered to rule out the possibility of a familial syndrome.

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