Papillary Thyroid Carcinoma, Variants, and Related Tumors

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Background

Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the thyroid gland, accounting for approximately 85% of all cancers at this site. It occurs in all age groups, including children, with a peak incidence in the third to fourth decades, and an M/F ratio of 1:4. The incidence of thyroid carcinomas has nearly tripled in the last three decades, with PTC accounting for most of the surge [1–3]. The mortality rate remained stable during this time, however, suggesting that the more indolent forms of PTC are increasingly diagnosed. Although traditionally considered the most common type of PTC, conventional (classic) PTC has diminished in relative frequency compared to PTC variants, especially in view of the increasing awareness and recognition of the follicular variant of PTC (FVPTC) [3].

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Given the revision in nomenclature that reclassified the noninvasive FVPTC as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) [4], this trend in the increase of PTC and FVPTC diagnosis may be reversed in the future. Risk factors for PTC include external radiation to the neck during childhood, exposure to ionizing radiation, and genetic susceptibility [1]. 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, 5], the majority of them PTCs. When a definite diagnosis of PTC is made by FNA, 94–96% prove to be PTC on histologic follow-up, taking into consideration the reclassification of some PTCs as NIFTP [2, 5]. Conventional 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 variant architectural and/or cytologic features from those of conventional PTC. Furthermore, some PTC variants have different genetics and biological behavior than conventional (classic) PTC. An awareness of the cytomorphologic spectrum of PTC variants helps prevent misdiagnosis, but it is not necessary to specify the subtype of PTC on an FNA specimen. In the following sections, conventional (classic) PTC and its variants are described separately to highlight some of the morphologic heterogeneity in this family of tumors.

Given the reclassification of some follicular variants of PTC as "neoplasms" rather than overt malignancies, it is desirable to eliminate from the malignant category tumors likely to harbor a NIFTP. To accomplish this goal, a suspected PTC with an exclusively follicular architecture, especially one that lacks intranuclear cytoplasmic pseudoinclusions and psammoma bodies (e.g., many follicular variants of PTC), is best interpreted as "suspicious for malignancy" rather than malignant. This approach leaves other subtypes of PTC in the malignant category but minimizes the contribution of FVPTC and NIFTP. It is unlikely that NIFTPs can be completely eliminated from the malignant category, however, and some pathologists may prefer to include an educational note to reinforce this limitation (see "Sample Reports" below).

Conventional (Classic) Papillary Thyroid Carcinoma

Definition

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

Criteria

Cells arranged in papillae and/or monolayers
Cellular swirls ("onion-skin" or "cartwheel" patterns) (some cases)
Enlarged and crowded nuclei, often molded
Oval or irregularly shaped nuclei
Longitudinal nuclear grooves
Intranuclear cytoplasmic pseudoinclusions (INCIs)
Pale nuclei with powdery chromatin
Thick nuclear membranes
Marginally placed micronucleoli, solitary or multiple
Psammoma bodies
Multinucleated giant cells
Variable amount of colloid; may be stringy, ropy, or "bubblegum"-like
"Hobnail" cells
Oncocytic (Hürthle cell) metaplasia
Squamoid metaplasia
"Histiocytoid" cells
There are some minor differences between smears and liquid-based preparations (LBP) with regard to the diagnosis of conventional (classic) PTC [6–8]. Awareness of the cytomorphological features observed with the use of the LBP method is helpful.

Cytological Features More Frequent in LBP Compared to Smears

Convoluted nuclei
Eosinophilic nucleoli
Perinucleolar halo
Trabecular and hobnail patterns
Tall cells
Collagenous stroma
Naked capillaries
Intercellular spaces

Cytological Features Less Frequent in LBP Compared to Smears

Pale nuclei
Papillary pattern and tissue fragments

Explanatory Notes

Although several nuclear alterations are characteristic, none of them is diagnostic of PTC in isolation or low frequency. Only when relatively widespread and in combination are they diagnostic of PTC, whether one is examining smears or LBP [6, 7]. 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 INCIs) 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" or "Atypia (or Follicular Lesion) of Undetermined Significance (AUS/FLUS)" (see Chaps. 7 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 (classic) PTC are typically arranged in syncytial-like flat sheets ("monolayers") with crowded and overlapping nuclei (Figs. 8.1, 8.2, and 8.3). The latter feature often leads to conspicuous nuclear molding (Fig. 8.3). 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 (classic) PTC and mimics the flat sheet of a macrofollicular fragment typical of benign follicular nodules, such

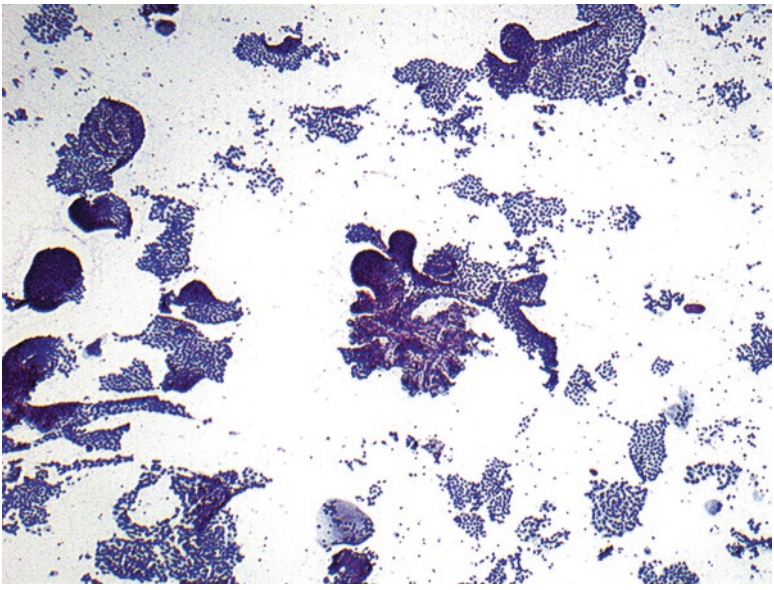

Fig. 8.1 Papillary thyroid carcinoma. Preparations are often highly cellular and composed of numerous monolayer sheets and occasional papillary-like fragments (smear, Papanicolaou stain).

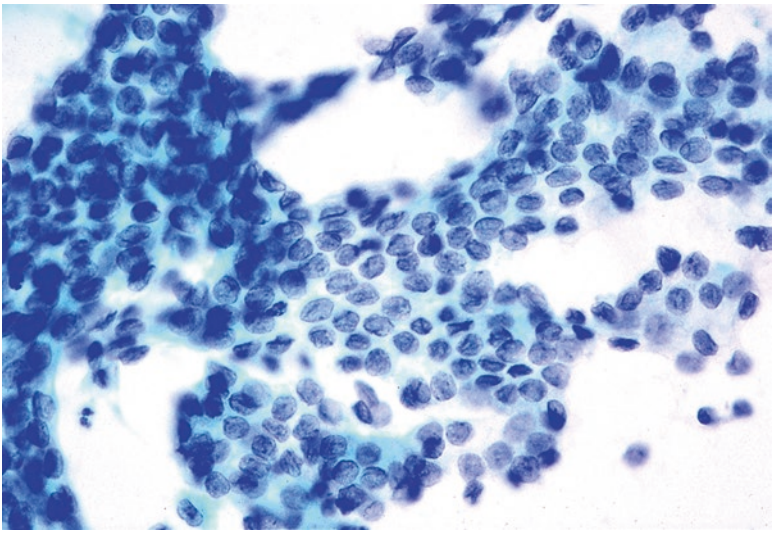

Fig. 8.2 Papillary thyroid carcinoma. Monolayer sheets with a syncytial-like appearance are characteristic of papillary thyroid carcinoma. These flat sheets resemble those of benign follicular nodules; attention to the nuclear features is essential for this distinction (smear, Papanicolaou stain).

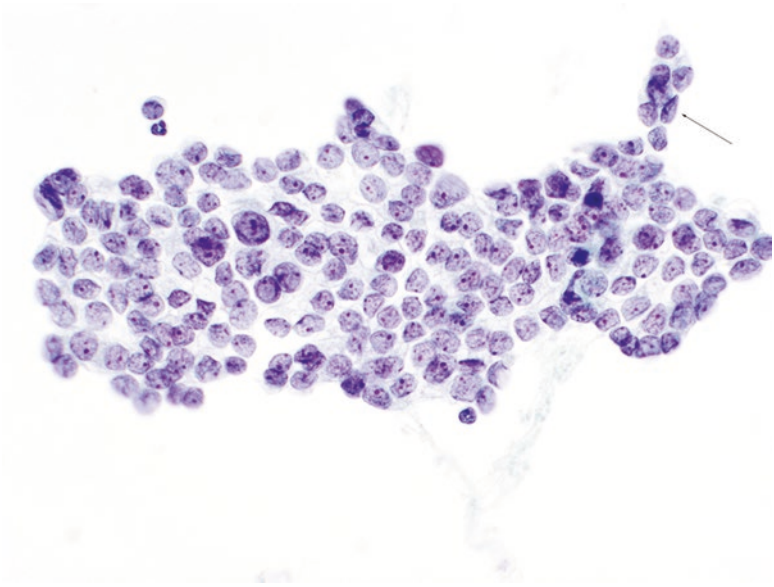

Fig. 8.3 Papillary thyroid carcinoma. This monolayer sheet is comprised of cells with irregular nuclei that show focal molding (*arrow*) (ThinPrep, Papanicolaou stain).

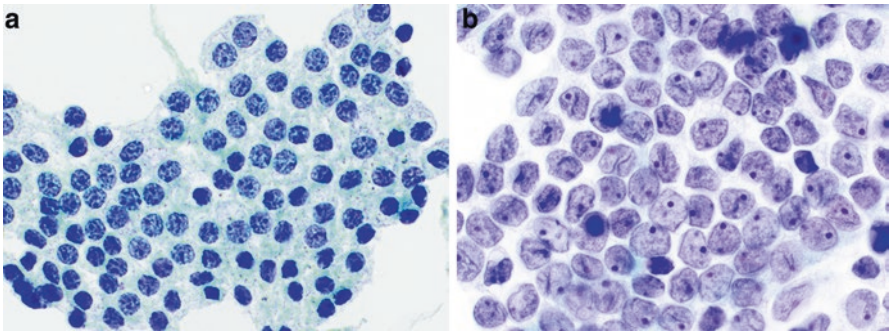

Fig. 8.4 Comparison of benign follicular cells with the cells of papillary thyroid carcinoma. (**a**) Benign follicular cells (nodular goiter). (**b**) Compared with those of the benign follicular cells, the nuclei of papillary carcinoma are larger, paler, more crowded, and more irregular in contour (**a**, **b**, ThinPrep, Papanicolaou stain).

as those commonly seen in nodular hyperplasia (Fig. 8.4). The distinction requires particular attention to the arrangement of the cells in the sheets (evenly spaced vs. crowded) and their nuclear features to avoid a false-negative diagnosis. The architectural pattern varies depending on the type of PTC (see below), but FNAs from a conventional PTC often display true papillary fragments (i.e., with a fibrovascular core) (Figs. 8.5 and 8.6), papillary-like fragments (rounded shape with smooth edges but lacking a fibrovascular core) (Fig. 8.7), and cellular swirls. Cellular swirls (Fig. 8.8) 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 (sometimes also called an "onion-skin" pattern) [9]. Cellular swirls are a distinctive feature of the conventional (classic) PTC, seen in about 17% of cases (smears and LBP) and have not been reported in benign thyroid nodules [7, 9]. Although individually dispersed neoplastic cells are seen in PTC, a pattern of predominantly isolated cells is highly unusual (in contrast to medullary carcinoma).

The cells of PTC vary in size (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 also vary greatly. In some cases, the cells have scant cytoplasm, but abundant oncocytic (granular) cytoplasm is common, although usually a focal finding. When extensive, it signals an oncocytic variant of PTC. A hobnail pattern was recently suggested as a useful diagnostic criterion, especially on LBP [6, 7], and has been reported in several variants 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 [7, 10, 11]. The hobnail pattern is usually associated with a loss of cellular polarity and cohesiveness and, when extensive, may be associated with aggressive behavior

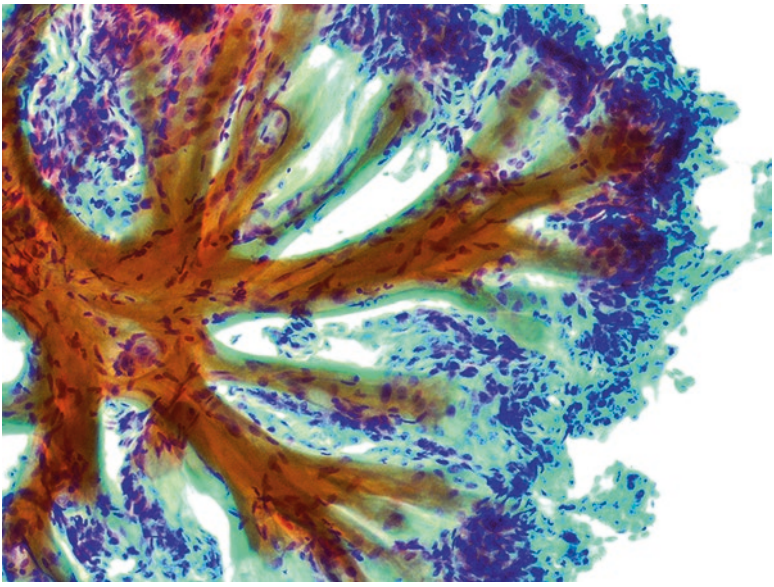

Fig. 8.5 Papillary thyroid carcinoma. True papillary tissue fragments, comprised of fibrovascular cores lined by neoplastic cells, are seen in the conventional type of papillary thyroid carcinoma (smear, Papanicolaou stain).

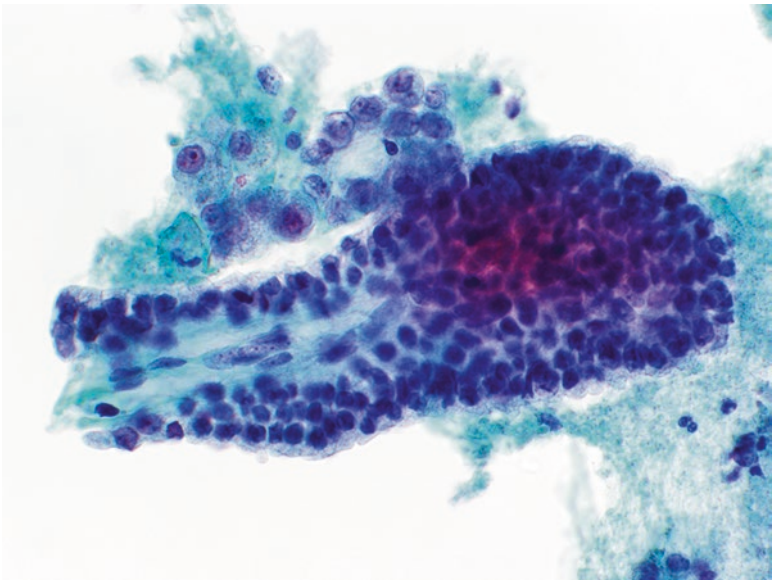

Fig. 8.6 Papillary thyroid carcinoma. The neoplastic cells surround a fibrovascular core (ThinPrep, Papanicoalou stain).

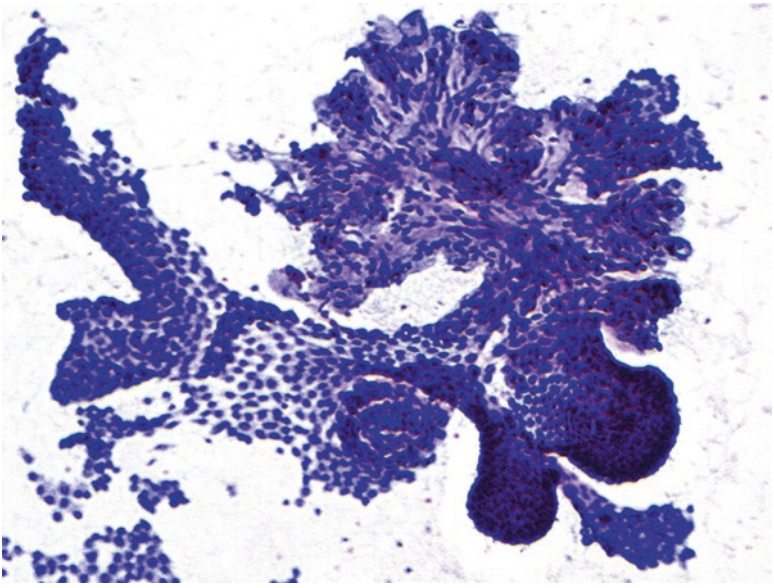

Fig. 8.7 Papillary thyroid carcinoma. There is a mixture of flat sheets and rounded, papillary-like fragments without fibrovascular cores (ThinPrep, Papanicoalou stain).

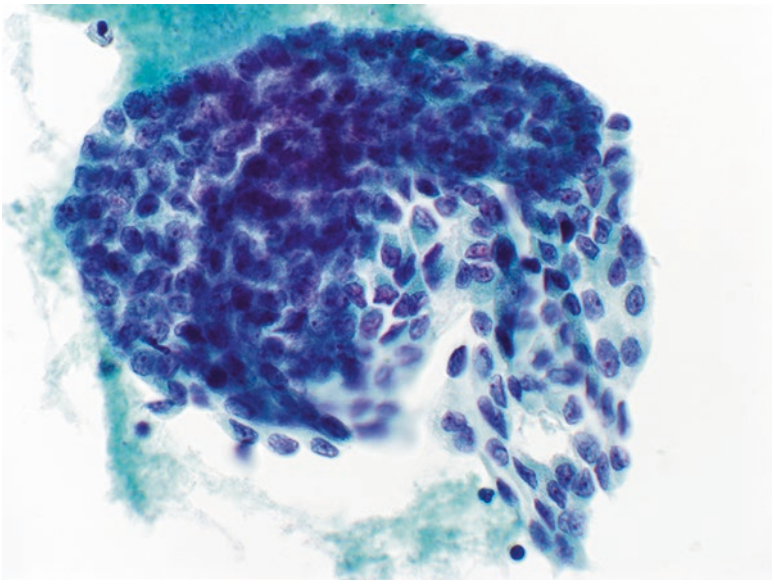

Fig. 8.8 Papillary thyroid carcinoma. Cellular swirls are highly characteristic of the conventional (classic) papillary thyroid carcinoma. They are a concentric aggregate of tumor cells in which many of the peripheral cells have ovoid (rather than round) nuclei and are oriented perpendicular to the radius of the swirl (ThinPrep, Papanicolaou stain).

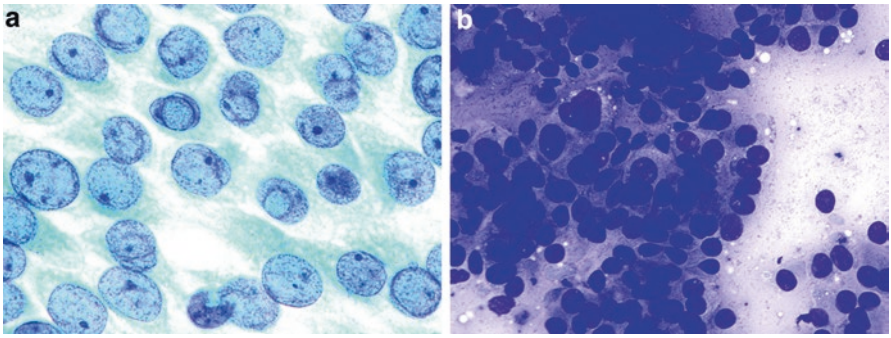

Fig. 8.9 Papillary thyroid carcinoma. (**a**) Intranuclear cytoplasmic pseudoinclusions (INCIs) and micronucleoli are shown. Note that the two INCIs share the same aqua color and granular texture as the surrounding cytoplasm (smear, Papanicolaou stain). (**b**) A large INCI occupying most of the nucleus is seen in the center. The remaining nuclei show variation in size and shape (smear, Diff-Quik stain).

(see "Hobnail Variant" below) [10, 11]. Changes resembling squamous metaplasia (moderate-to-abundant dense cytoplasm and cells that fit together like pavement stones) are also seen, usually only as a focal finding in conventional (classic) PTC. Hyperkeratinized squamous cells (orangeophilic cytoplasm on Papanicolaou stain) and keratin pearls, however, are rare. Histiocytoid cells are characterized by extensive cytoplasmic vacuolation (like that of benign histiocytes) and typically arise in a PTC that has undergone cystic changes (see Fig. 7.4).

The defining features of PTC are seen in the nuclei. They 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 (Fig. 8.4b). Convoluted nuclei, where more than half of the nuclear membrane is wrinkled, are very specific for PTC on LBP (97.3%) [6]. 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. 8.4b). 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 variants of PTC (e.g., columnar cell). 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 cytoplasmic pseudoinclusions (INCIs) are seen in 50–100% of aspirates of PTC, depending on the subtype of PTC (Figs. 8.9 and 8.10). For example, INCIs are most frequent and florid in the tall cell variant, whereas they are often rare or absent in the follicular variant. INCIs are not specific for PTC; they can be seen in aspirates of medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, anaplastic thyroid carcinoma, hyalinizing trabecular tumor, NIFTP, and very rarely, benign thyroid nodules (e.g., nodular goiter, follicular adenoma) and lymphocytic thyroiditis. INCIs should therefore always be interpreted in light of the

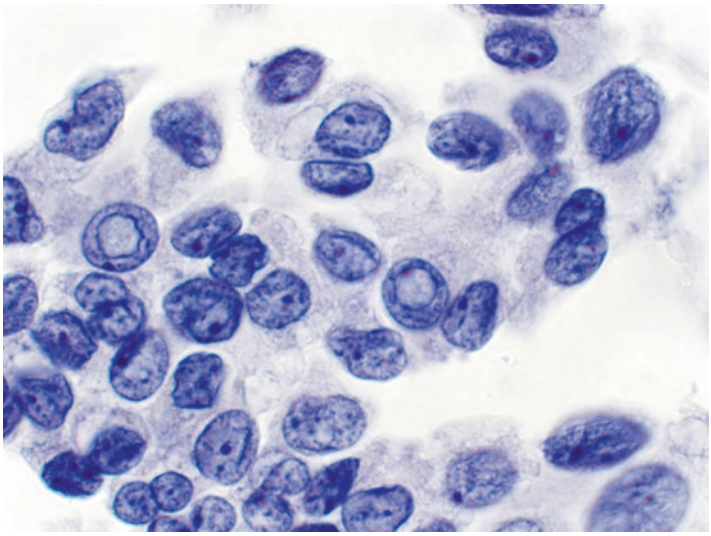

Fig. 8.10 Papillary thyroid carcinoma. Two intranuclear cytoplasmic pseudoinclusions (INCIs) are seen. (ThinPrep, Papanicoalou stain).

other architectural and nuclear features in a given FNA. Ultrastructurally, INCIs are membrane-bound spheroidal masses of cytoplasm that protrude into the nuclei. Thus, a true INCI displays the same color/texture of adjacent cytoplasm and is sharply bordered by a rim of condensed chromatin, like a "wire loop." These features help distinguish INCIs from common mimics: degenerative and artifactual vacuoles, fixation artifacts, and superimposed red blood cells.

Nuclear grooves are another hallmark of PTC [12]. Akin to INCIs, they are best seen with alcohol-fixed, Papanicolaou-stained preparations (Fig. 8.11) and are less conspicuous with air-dried Romanowsky-stained smears (e.g., Diff-Quik). Nuclear grooves and INCIs are manifestations of nuclear membrane redundancy; a nuclear groove, for example, results from a nucleus folded onto itself [13]. 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 nonneoplastic 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 establishes 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 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 underneath the nuclear membrane ("marginal"). On LBP, they are commonly eosinophilic (89%) and associated with a perinucleolar halo ("bare nucleoli") (63%) [6]. The latter has been reported to be very specific for PTC (96%) [6].

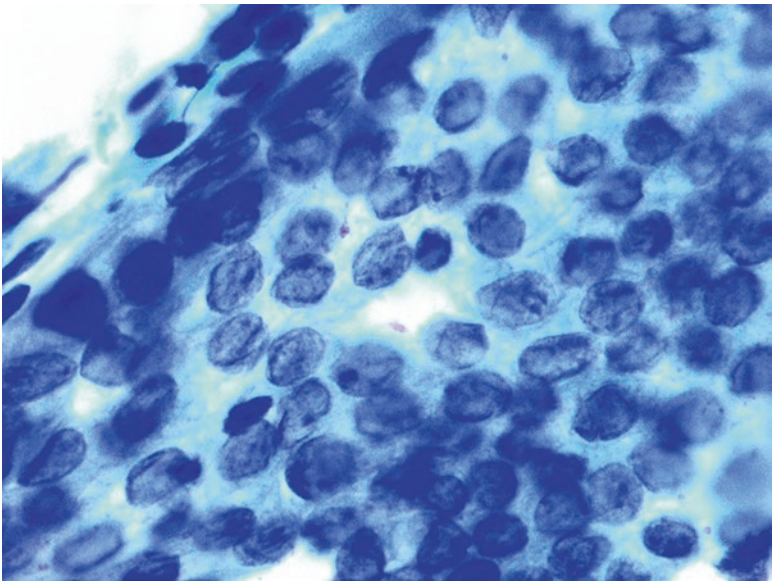

Fig. 8.11 Papillary thyroid carcinoma. Close inspection at high magnification shows frequent nuclear grooves, finely textured (powdery) chromatin, and micronucleoli (smear, Papanicolaou stain).

Multinucleated giant cells of histiocytic lineage are commonly seen in aspirates of PTC, even when cystic degeneration is not present (Fig. 8.12). 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 (e.g., 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 and isolated or attached to cells (Fig. 8.13). PBs alone (i.e., not associated with altered cells) are nonspecific and can be seen in medullary thyroid carcinoma, 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% [14].

The background usually contains relatively scant colloid, but some variants (see below) can have abundant colloid. Colloid may be watery or dense and stringy with ropy strands ("bubblegum" colloid). The background is usually clean; necrotic debris is extremely uncommon. 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 Warthin-like or diffuse sclerosing variant (DSV)

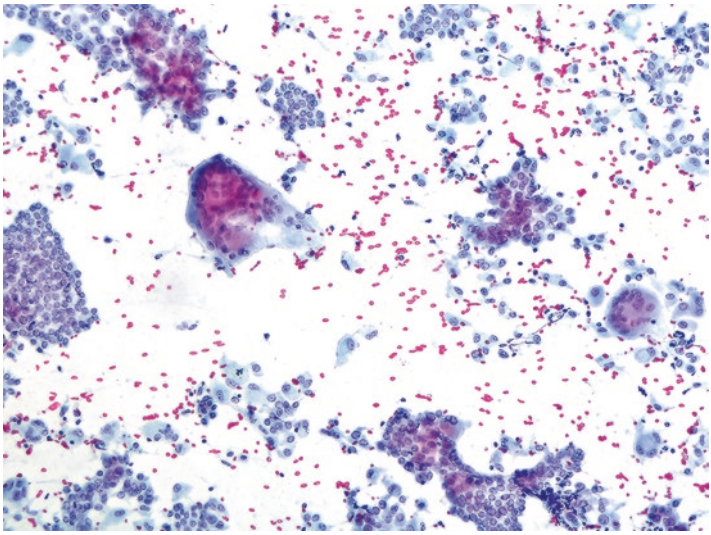

Fig. 8.12 Papillary thyroid carcinoma. Multinucleated giant cells accompany monolayered sheets of tumor cells. Although multinucleated giant cells are often seen in PTCs, they are a nonspecific finding (smear, Papanicolaou stain).

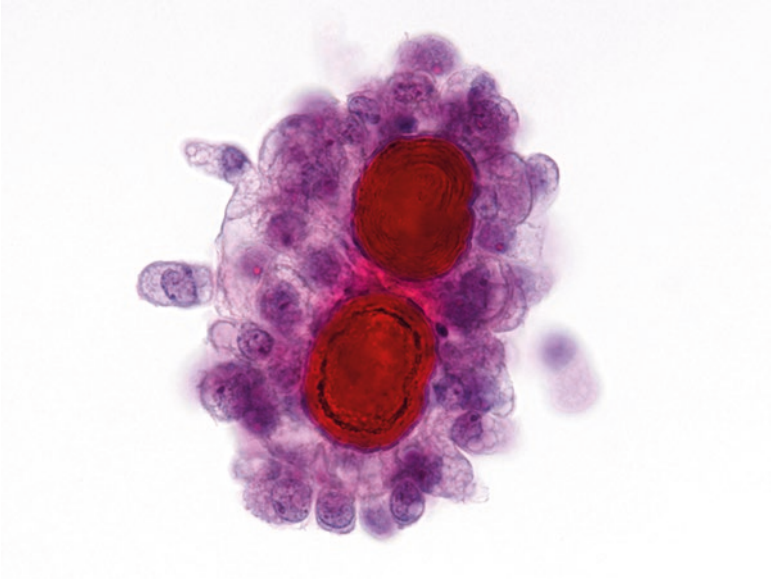

Fig. 8.13 Papillary thyroid carcinoma. Psammoma bodies are concentric rings and are lined here by atypical cells with oval, pale nuclei. Note that the tumor cells surrounding psammoma bodies show hobnail features (ThinPrep, Papanicolaou stain).

of 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, it is relatively straightforward to diagnose conventional (classic) PTC by FNA. Although false-negative and false-positive diagnoses occasionally occur, they can be minimized by adopting a conservative approach to a sparsely cellular or otherwise suboptimal specimen. This recommendation applies as well to cases with focal or limited nuclear changes.

Variants of Papillary Thyroid Carcinoma

A substantial proportion of PTCs exhibit variant architectural and/or cytologic features from those of conventional (classic) PTC. Variants of PTC, by definition, have at least some of the essential nuclear features of PTC but a different architectural pattern, unusual cytoplasmic features, or different background characteristics, such as the quantity and texture of the colloid, the type of stroma, and the presence or absence of a prominent lymphoplasmacytic infiltrate. More than ten variants of PTC have been documented [1, 2]. Some are associated with more aggressive and others with more indolent behavior than conventional PTC [1, 2]. The variants with less favorable outcomes are the tall cell, columnar cell, and hobnail variants [2]. The solid variant and the diffuse sclerosing variant may be associated with a less favorable outcome, but the data remain conflicting [2]. In contrast, the noninvasive FVPTC is indolent, with virtually no metastatic or recurrence potential, and for this reason has been reclassified as NIFTP (see "Follicular Variant and NIFTP" below) [4].

Recognition of PTC variants at the time of FNA is generally unnecessary [2]. Precise subtyping is rarely possible or reliable, because the predominant pattern may not have been sampled (many PTCs show more than one growth pattern and/or cell type). Furthermore, because some of these variants are very rare, familiarity with their morphologic features may be impractical, and the PPV of any set of specific features (described mostly in retrospective studies) is hard to predict. Nonetheless, the architectural and cytologic features that distinguish these lesions from conventional PTC histologically are often observed cytologically, and awareness of the phenotypic characteristics of the various subtypes can diminish the risk of misdiagnosis.

Follicular Variant and NIFTP

Definition

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.

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is an encapsulated or well-demarcated neoplasm with follicular-patterned

morphology and variable nuclear features of PTC, without capsular or vascular invasion. This term was introduced to recognize the indolent behavior of thyroid neoplasms previously classified as noninvasive FVPTC.

Background

It has long been recognized that some PTCs are composed primarily if not exclusively of follicles rather than papillae. FVPTC is now the most common variant of PTC and represents nearly 30% of PTCs in some series [3, 15–20]. FVPTC consists of several distinct subtypes. The vast majority of these tumors are composed of microfollicles; however, some FVPTCs are composed of normal-sized follicles. Tumors composed predominantly of macrofollicles are a different and distinct subset of PTC (see "Macrofollicular Variant" below) [1].

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") [2, 21]. *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 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 is found [2]. At the present time, 50–75% of all FVPTC belong to this subtype [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") [21]. Encapsulated FVPTC with invasion tend to spread in a fashion similar to follicular thyroid carcinoma, with distant lung and bone metastases and infrequent lymph node metastases. 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 [2, 4]. Therefore, a carefully defined subset of encapsulated FVPTC has been reclassified as NIFTP, using strict histologic inclusion and exclusion criteria [4].

NIFTP is a very low risk tumor that likely represents a preinvasive stage of invasive encapsulated FVPTC [4]. The paradigm shift in terminology has important clinical consequences and affects the cytologic diagnosis of thyroid nodules [15, 16, 22–24]. NIFTP comprises approximately 20–25% of all tumors previously classified as thyroid malignancies [15, 16, 22–24]. 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 (ROM) associated with thyroid FNA diagnoses, especially in the indeterminate diagnostic categories but also in the malignant category, because NIFTP comprises a subset, albeit small (3–4%), of thyroid FNAs currently classified as malignant [15, 16, 22–24].

Criteria

Samples are usually hypercellular, with syncytial-like fragments containing microfollicles ("rosettes"). Dispersed microfollicular clusters, isolated neoplastic follicles, and some sheets with branched irregular contours may also be present.

Some colloid may be present, typically dense-staining, thick, and sometimes within neoplastic follicles.

In contrast to conventional PTC, the nuclear changes are often subtle. The following features are usually absent or inconspicuous: papillary and papillary-like fragments, multinucleated giant cells, INCIs, psammoma bodies, and marked cystic change.

Explanatory Notes

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. 8.14 and 8.15). Some FVPTCs, usually those that are infiltrative, have prominent classic nuclear features of PTC, but with others, especially the

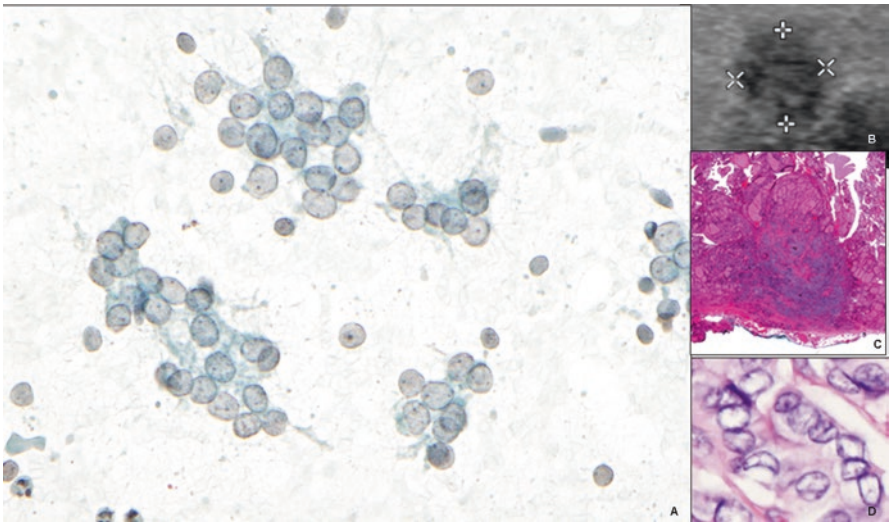

Fig. 8.14 Papillary thyroid carcinoma, follicular variant. (**a**) The aspirates show microfollicles with crowded, enlarged clear oval nuclei (smear, Papanicolaou stain). (**b**) Ultrasound shows solid nodule with blurred margins (**c**) correlating with infiltrative margin in histology. (**d**) Histologically, the tumor is composed of microfollicles with "Orphan Annie eye" "clear nuclei (hematoxylin and eosin stain).

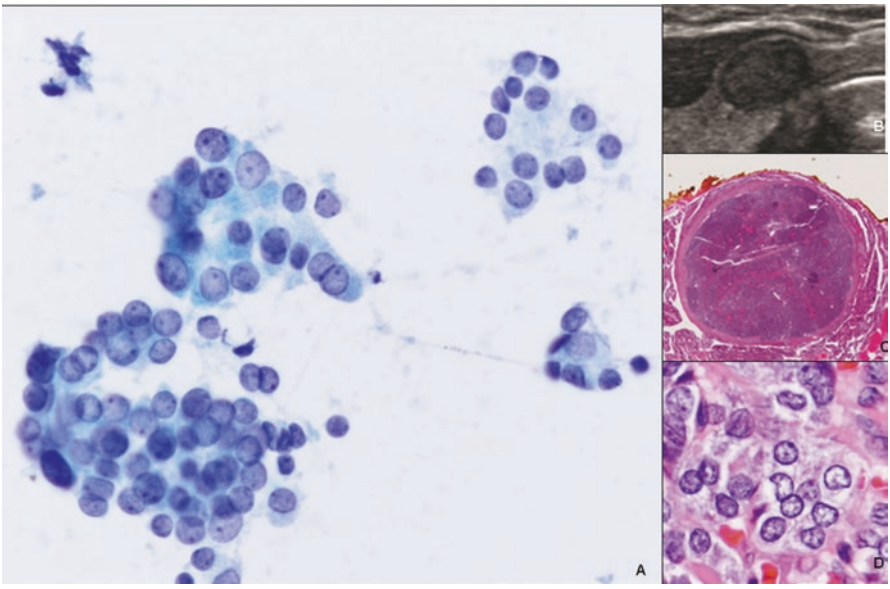

Fig. 8.15 Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (formerly called encapsulated follicular variant of papillary thyroid carcinoma). (**a**) The aspirate shows microfollicles with crowded, enlarged, clear, oval nuclei along with microfollicles with small dark nuclei (smear, Papanicolaou stain). (**b**) Ultrasound shows well-circumscribed solid nodule with a rim, correlating with encapsulation (**c**). (**d**) Histologically, the tumor is composed of microfollicles with "Orphan Annie eye" clear nuclei (hematoxylin and eosin stain).

encapsulated FVPTC (including NIFTP), the features are only partially and focally displayed. For this reason, a distinction among the various "follicular-patterned" lesions of the thyroid (e.g., nodular goiter, follicular adenoma, NIFTP, FVPTC) is sometimes troublesome [17]. FVPTC is, in fact, one of the most problematic variants of PTC to diagnose, both cytologically and histologically. 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 in two different groups. In the first (30–40% of cases), the FVPTC is easily recognizable as malignant due to widespread nuclear features of PTC but difficult to distinguish from a conventional PTC. 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, and INCIs and nuclear grooves are rare or absent. These cytologic samples typically fall into one of the indeterminate categories: suspicious for PTC (25–35%), FN/SFN (25–30%), or AUS/FLUS (10–20%) [15, 16, 22–24]. Particular attention must be paid to the presence of ovoid, pear-shaped, and cerebriform (or raisin-shaped) nuclei. NIFTPs are often associated with more subtle nuclear features than infiltrative FVPTC and classical PTC [22–24]. To avoid overtreatment, it is highly desirable to exclude potential NIFTP cases from the

malignant category and limit this category to conventional and other variants of PTC. Preliminary data suggest that a definitive ("malignant") diagnosis of PTC should be reserved for cases that have, in addition to other characteristic features, at least one of the following: papillary architecture, psammoma bodies, and INCIs [22–24]. Nevertheless, given the histologic criteria for NIFTP [4], it is unlikely that NIFTPs can be completely eliminated from the malignant category. Thus, some pathologists may prefer to include an educational note to reinforce this limitation (see Chap. 1, Table 1.3, as well as "Sample Reports" below).

Molecular and ultrasonographic features can be helpful to suggest noninvasive FVPTC or NIFTP at the time of FNA diagnosis. Because *RAS* mutations are the most commonly identified genetic abnormality in noninvasive FVPTC and NIFTP, these neoplasms show a very high association with other follicular-patterned neoplasms [4, 21]. *PAX8/PPARγ* translocations, *THADA* fusions, and $BRAF^{K601E}$ mutations are also found on occasion [21]. In contrast, $BRAF^{V600E}$ mutations and *RET* fusions, common in conventional PTC, are absent in NIFTP [4, 21]. Sequencing with large multigene panels may one day assist in the detection of NIFTP. On ultrasound, most NIFTPs are benign-appearing, round-to-oval, circumscribed nodules with a hypoechoic rim [17]. The definite diagnosis of a FVPTC or NIFTP, however, can only be made after complete histological analysis of the tumor and its capsule.

Macrofollicular Variant

Definition

The macrofollicular variant is a PTC 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 with FVPTC).

Papillary structures and psammoma bodies are not seen.

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

Explanatory Notes

The macrofollicular variant of PTC (MFVPTC) is one of the rarest histologic variants of PTC [1]. It is characterized by a low incidence of lymph node metastasis, but when metastases occur, the macrofollicular architecture is usually maintained. The differential diagnosis of MFVPTC includes the benign follicular nodule seen with nodular goiter and the follicular adenoma of macrofollicular type. MFVPTC is easily underappreciated at low magnification due to the abundance of thin colloid, the

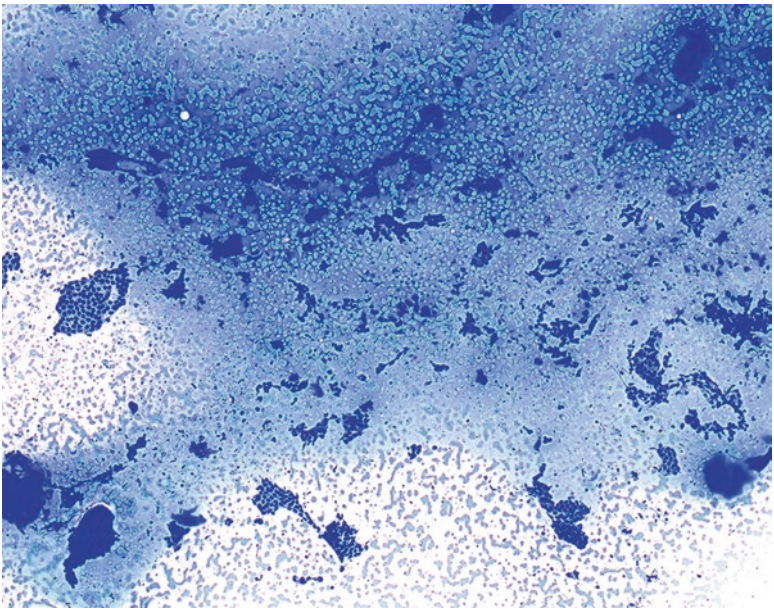

Fig. 8.16 Papillary thyroid carcinoma, macrofollicular variant. The neoplastic cells resemble those of a benign thyroid nodule at scanning magnification. In such cases, there can be abundant thin colloid and relatively few sheets of cells. The difference lies in the nuclear features, which are better appreciated at high magnification (smear, Diff-Quik stain).

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. 8.16 and 8.17) [25, 26]. Only 45% of cases show INCIs, which range from rare to few [25]. Moderate-to-abundant thin and focally thick colloid and macrophages are often present. In contrast, psammoma bodies 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/FLUS (instead of a benign colloid nodule) [25].

Cystic Variant

Definition

The cystic variant is a PTC that is predominantly cystic, comprised of thin, watery fluid, abundant histiocytes, and hypervacuolated tumor cells.

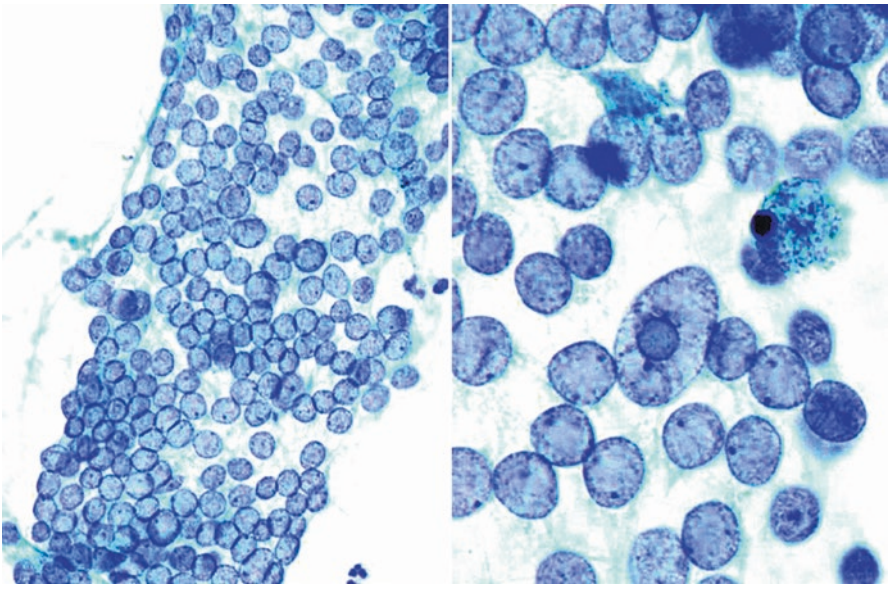

Fig. 8.17 Papillary thyroid carcinoma, macrofollicular variant. *Left*, There is a large sheet of tumor cells with crowded, "Orphan Annie eye" nuclei; *Right*, An intranuclear pseudoinclusion is present in the large oval nucleus. Note also the peripheral micronucleoli (smear, Papanicolaou stain).

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" (hypervacuolated).

Macrophages, often containing hemosiderin, are present.

There is 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

PTC is the most common malignant neoplasm of the thyroid to undergo cystic change. The amount of cystic change varies from case to case; approximately 10% of PTCs are almost entirely cystic [27, 28]. FNAs of cystic PTC show varying proportions of macrophages, colloid, and vacuolated "histiocytoid" neoplastic cells (see Fig. 7.4) [27, 28]. A few small papillae comprised of viable tumor cells are sometimes present. The neoplastic cells have more abundant, granular, or vacuolated cytoplasm than those of conventional PTC. The tumor cells frequently appear more rigid and polygonal than normal follicular cells and display enlarged, oval- to irregularly

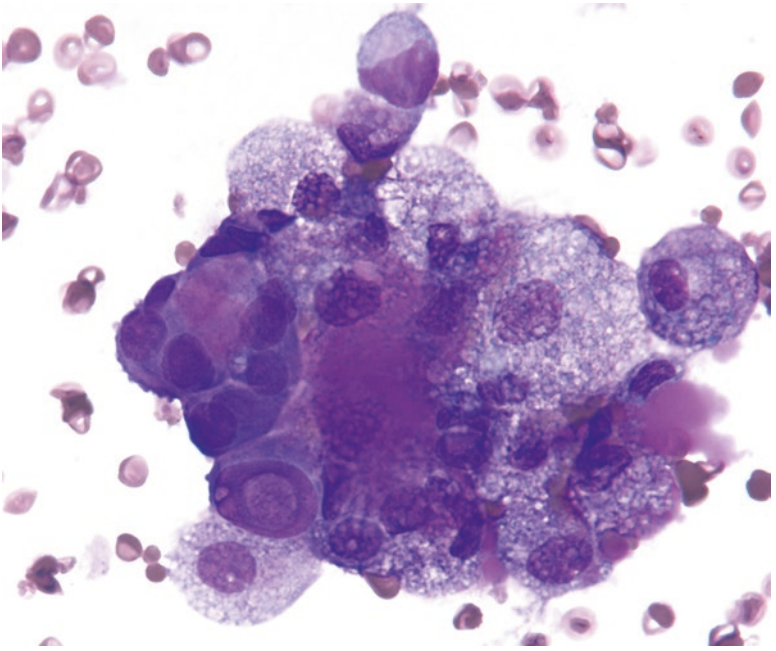

Fig. 8.18 Papillary thyroid carcinoma, cystic variant. There is prominent cystic change with numerous hemosiderin-laden macrophages. A small cluster of neoplastic cells has smooth, dense cytoplasm, and one cell has a large intranuclear cytoplasmic pseudoinclusion (smear, Diff-Quik stain).

shaped nuclei with prominent nuclear grooves and occasional INCIs (Fig. 8.18). Some of the characteristic nuclear features of PTC, however, like pale, "powdery" chromatin, are often less apparent or even conspicuously absent (Fig. 8.19).

It should be noted that similar atypical cells are sometimes seen in entirely benign follicular nodules with cystic change. These reactive cells may appear "histiocytoid" or they may be arranged in streaming sheets ("cyst lining cells"). Cyst lining cells 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 INCIs. Such cases are therefore properly diagnosed as "suspicious for papillary carcinoma" or AUS/FLUS (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." Indeed, cystic PTC has long been recognized as a possible cause of false-negative thyroid FNAs. This concern is less common with the precise sampling of the subcentimeter solid mural nodule within the cyst under high-resolution ultrasound guidance.

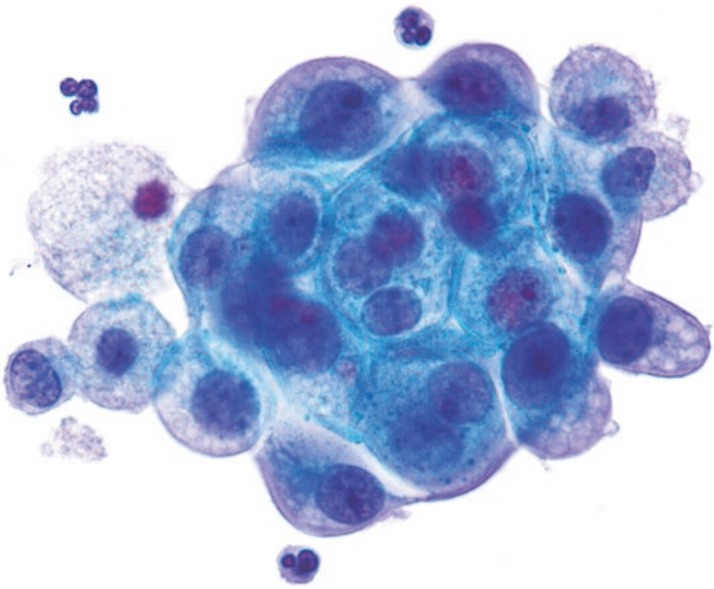

Fig. 8.19 Papillary thyroid carcinoma, cystic variant. Most of the cells in this image are neoplastic. They have abundant granular cytoplasm, hence the descriptor "histiocytoid." Classic nuclear features of papillary thyroid carcinoma are absent, but there is conspicuous nuclear enlargement (ThinPrep, Papanicolaou stain).

Oncocytic Variant

Definition

The oncocytic variant is a thyroid tumor with nuclear changes characteristic of PTC but composed predominantly of oncocytic cells with variable architecture (follicular, papillary, 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 (classic) PTC. Only when the changes are widespread does the tumor merit distinction as an oncocytic variant of PTC (Figs. 8.20 and 8.21) [29, 30]. Aspirates of the oncocytic variant of PTC resemble those from other follicular cell-derived

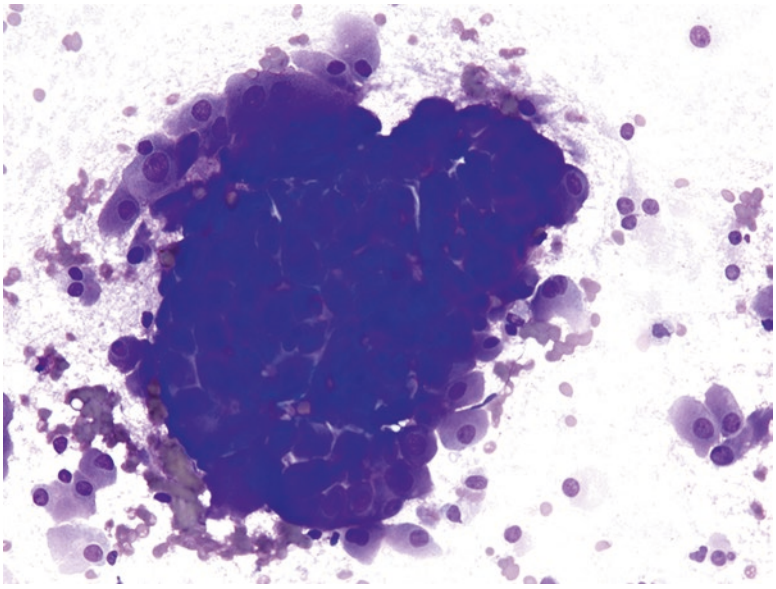

Fig. 8.20 Papillary thyroid carcinoma, oncocytic variant. The entire neoplasm is composed of oncocytic (Hürthle-like) cells that have abundant granular cytoplasm. The nuclear features of papillary carcinoma are not readily apparent in this image; such cases are good mimics of Hürthle cell neoplasms (smear, Diff-Quik stain).

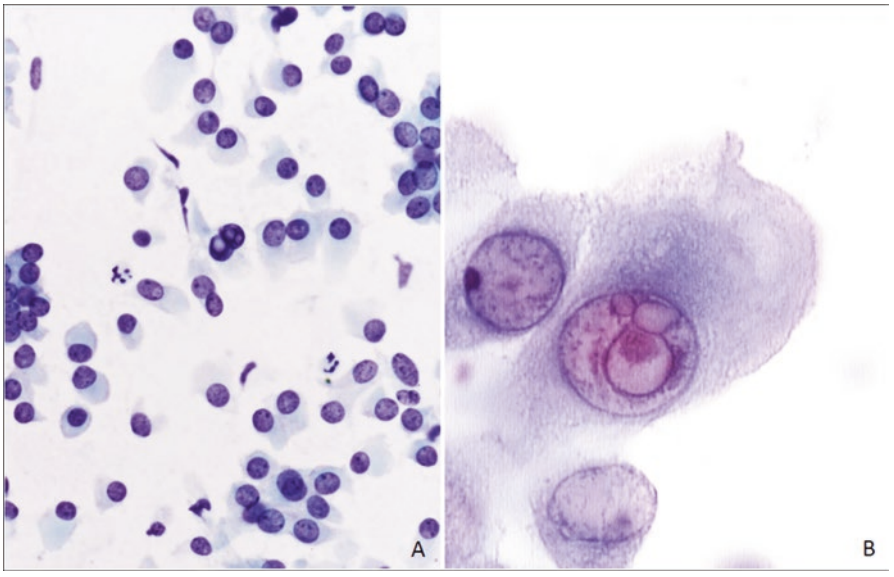

Fig. 8.21 Papillary thyroid carcinoma, oncocytic variant. (**a**) Loosely cohesive polygonal to plasmacytoid oncocytic (Hürthle-like) cells have atypical, clear nuclei with eccentric micronucleoli and rare intranuclear pseudoinclusions without nuclear grooves; such cases are good mimics of medullary thyroid carcinoma. (**b**) Multiple small and large intranuclear pseudoinclusions are seen in a large oncocytic cell with abundant granular cytoplasm (smears, Papanicolaou stain).

oncocytic proliferations, the oncocytic variant of medullary thyroid carcinoma, 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 (Hürthle cells). 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 INCIs are very rarely seen. When the full nuclear features of PTC are evident, PTC can be readily diagnosed on FNA. When the nuclear features of PTC are not widespread, the case is best classified as suspicious for a follicular neoplasm/follicular neoplasm, Hürthle cell (oncocytic) type, or as suspicious for PTC, oncocytic type. Lymphocytes are typically absent in FNAs of the oncocytic variant of PTC; if present in large numbers, a Warthin-like variant of PTC should be considered.

Warthin-Like Variant

Definition

The Warthin-like variant of 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 thyroiditis [1, 31]. The neoplastic cells have abundant granular cytoplasm and the nuclear features of PTC.

Criteria

The neoplastic cells are oncocytic and arranged in papillae 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

Because of the mixture of oncocytes and lymphocytes, FNAs from the Warthin-like variant of PTC resemble those from Hashimoto thyroiditis (Fig. 8.22) [31]. The oncocytic cells of Hashimoto thyroiditis, however, typically have a round nucleus with a prominent single nucleolus; the nuclei of PTC (including the Warthin-like variant), 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 INCIs are usually not seen.

Tall Cell Variant

Definition

The tall cell variant (TCV) is an aggressive form of PTC composed predominantly of elongated (“tall”) tumor cells (their height is at least three times their width) with abundant dense granular cytoplasm and the typical nuclear changes of PTC.

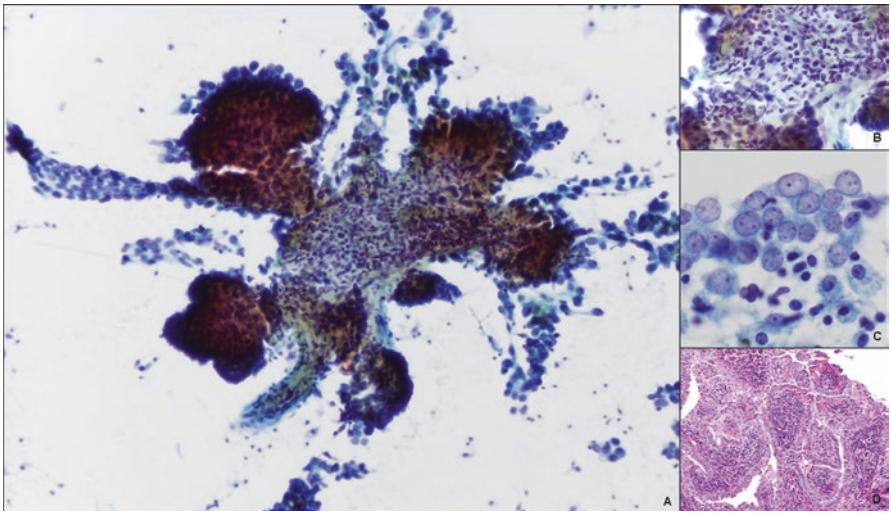

Fig. 8.22 Papillary thyroid carcinoma, Warthin-like variant. (**a**) The aspirate shows papillary fragments in a lymphocytic background (smear, Papanicolaou stain). (**b**) The fibrovascular cores are engorged with lymphocytes (smear, Papanicolaou stain). (**c**) The epithelial cells are also intimately 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).

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.
- Psammoma bodies are fewer in number.
- INCIs tend to be more frequent and more often multiple within one nucleus, imparting a "soap-bubble" appearance to the nucleus.

Explanatory Notes

The TCV tends to occur in elderly patients and is more common in men than other PTCs [1, 2]. It frequently presents as a large and bulky tumor, often with extrathyroidal extension and vascular invasion [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]. If 10% or more of a PTC has tall cell features, the tumor is associated with an adverse clinical outcome. Therefore, the identification of a minor tall cell component is important for histologic classification. Up to 90% of TCVs harbor the *BRAF*^{V600E} mutation. *TERT* promoter mutations, which are associated with a worse outcome in PTCs, are also significantly more prevalent in TCV (31%) compared to conventional (classic) PTC (<10%).

The TCV is easily recognized as a PTC due to the prominence of the nuclear features of PTC, especially nuclear grooves and INCIs, which are frequent and easily identified (Figs. 8.23, 8.24, and 8.25) [32, 33]. Tall cell features may be easier to assess on LBPs than on conventional smears (Fig. 8.25) [6, 8], but, as with all PTCs, it is not essential to specify the variant by FNA.

Columnar Cell Variant

Definition

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

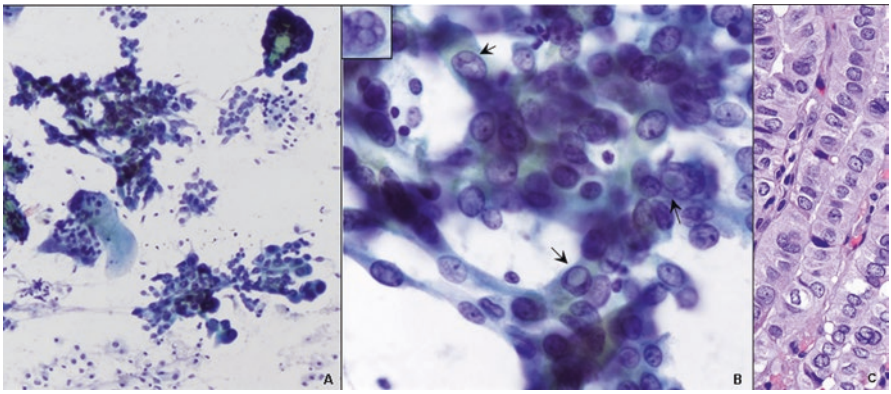

Fig. 8.23 Papillary thyroid carcinoma, tall cell variant. (**a**) The smear shows elongated cells in loosely cohesive arrangements (smear, Papanicolaou stain). (**b**) The cytoplasm is elongated, with frequent nuclear pseudoinclusions and rare soap-bubble nuclei (*inset*) (smear, Papanicolaou stain). (**c**) Histologically, this variant is comprised of tall rectangular tumor cells with eosinophilic cytoplasm arranged in parallel rows (hematoxylin and eosin stain).

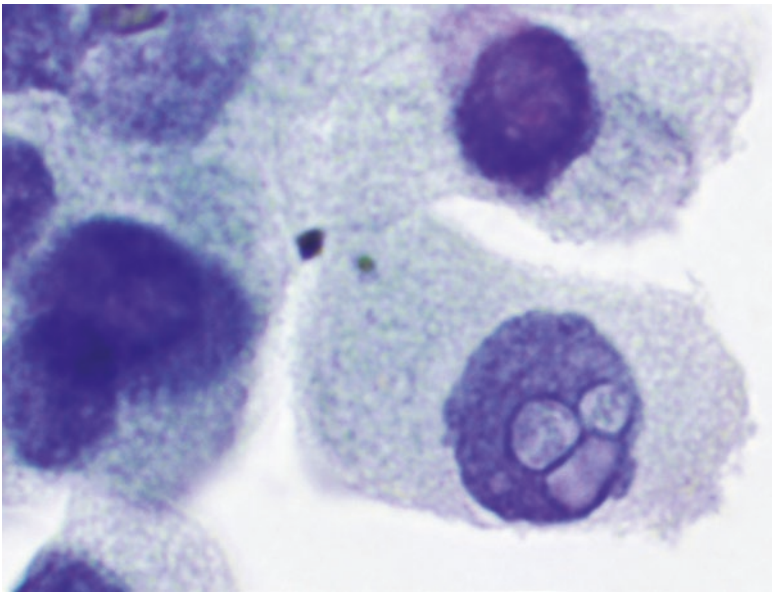

Fig. 8.24 Papillary thyroid carcinoma, tall cell variant. "Soap-bubble-like" intranuclear pseudoinclusions are often seen in the tall cell variant of papillary thyroid carcinoma (ThinPrep, Papanicolaou stain).

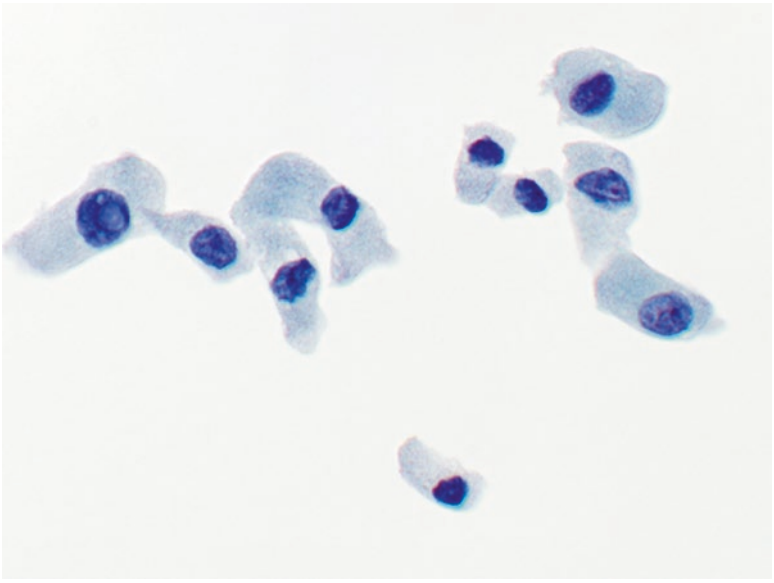

Fig. 8.25 Papillary thyroid carcinoma, tall cell variant. The "tallness" of these cells is readily appreciated. When this morphology is seen throughout the sample, one can raise the possibility of a tall cell variant in the FNA report (ThinPrep, Papanicolaou stain).

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, INCIs) 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 CCV is one of the least common variants of PTC and occurs primarily in males. It is an aggressive tumor associated with a higher risk of distant metastases and tumor-related mortality, especially in cases with extrathyroidal extension [1, 2]. The *BRAF*^{V600E} mutation is found in one-third of cases [2].

Because the nuclei of the columnar cell variant are darker than those of the typical PTC, and because the other typical nuclear features of PTC are less pronounced (Fig. 8.26), the neoplastic cells of the CCV may be mistaken for benign respiratory epithelial cells (seen when the trachea is penetrated), but cilia are not identified.

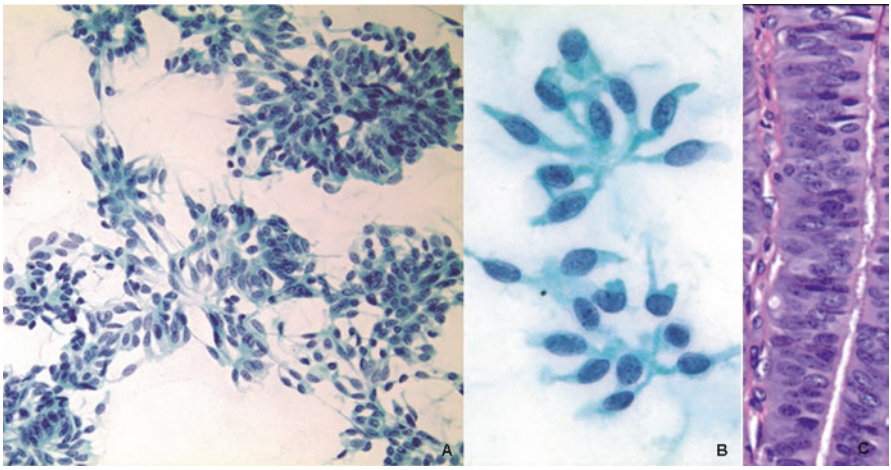

Fig. 8.26 Papillary thyroid carcinoma, columnar cell variant. (**a**) The aspirate shows loosely cohesive spindle-shaped cells (smear, Papanicolaou stain). (**b**) The cytoplasm is bipolar and wispy, and cigar-shaped nuclei have few characteristic features of papillary thyroid carcinoma (smear, Papanicolaou 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 Giorgadze, MD, PhD of Medical College of Wisconsin).

The dark and stratified nuclei of CCV can also mimic a metastasis from a colorectal or endometrial primary [34], but the necrotic background commonly present in metastatic disease from these primaries is unusual in CCV. Clinico-radiological correlation, in addition to a limited immunocytochemical panel that includes thyroglobulin and TTF1, can be very helpful. Importantly, PAX8 is expressed in both CCV and gynecological carcinomas, and CDX2 is expressed in up to 50% of CCV, limiting the diagnostic value of these two markers.

Solid Variant

Definition

The solid variant of PTC (SVPTC) is defined histologically by the presence of solid areas that lack papillae, follicles, and colloid storage and occupy at least 50% of the lesion. 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 three-dimensional tissue fragments, microfollicles/trabeculae, or noncohesive, 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

SVPTC is a rare variant (approximately 3% of PTCs) that is still poorly characterized. Its prevalence is high among survivors of the Chernobyl nuclear incident (up to 30%), where it is associated with *RET/PTC3* rearrangements (radiation-induced). This variant is also more common in children without radiation exposure. There are conflicting reports about its behavior [2, 35]. Because of the lack of criteria with high specificity and sensitivity, the preoperative diagnosis of SVPTC is hardly ever made or suggested on cytology (Fig. 8.27). Most cases of SVPTC are diagnosed as malignant or suspicious for malignancy (PTC or FVPTC) [35]. The microfollicular pattern of SVPTC 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 SVPTC and likely correlate with the nested pattern of the tumor cells observed histologically [35]. This pattern differs from the monolayered sheets typical of conventional (classic) PTC. A nonspecific single-cell pattern can also be seen in SVPTC and may correlate with infiltrative tumor growth and more aggressive behavior [35]. This pattern can mimic medullary thyroid carcinoma, but the two tumors can be distinguished by their nuclear features. There is also significant morphological overlap between SVPTC and poorly differentiated thyroid carcinoma (PDTC). PDTC may have occasional nuclear grooves and INCIs 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,

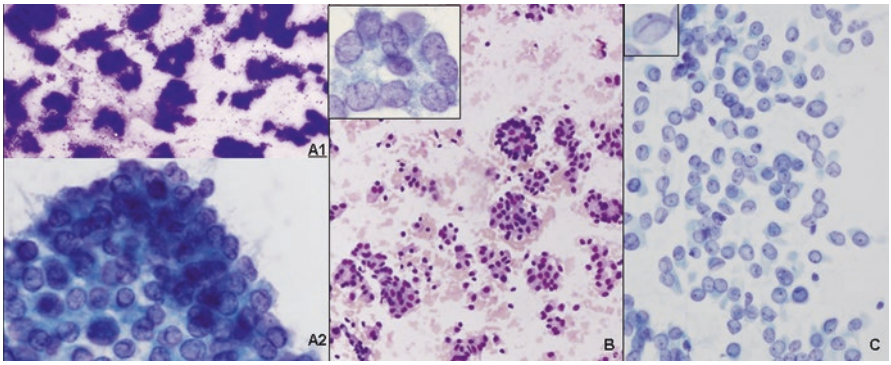

Fig. 8.27 Papillary thyroid carcinoma, solid variant. This variant may demonstrate three different cytologic patterns: (**a**) a cohesive, syncytial tissue-fragment pattern, (**b**) a microfollicular/trabecular pattern, and (**c**) a noncohesive, single-cell pattern. All three patterns have characteristic 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, **b**: smears, Diff-Quik stain; a2, **c** and *insets*: smears, Papanicolaou stain).

but these features are not always present (see Chap. 10). Clinico-radiological correlation can also be very helpful. Although SVPTC in children can have significant necrosis, they behave like a PTC and do not have the aggressiveness of a PDTC.

Diffuse Sclerosing Variant

Definition

The diffuse sclerosing variant (DSV) is characterized by diffuse involvement of one or both thyroid lobes, extensive lymphovascular invasion, numerous psammoma bodies, squamous metaplasia, marked lymphocytic infiltration, and prominent fibrosis.

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.
- There are fewer INCIs and nuclear grooves (<50% of cases).
- Large septate or unilocular cytoplasmic vacuoles are common.
- Squamous metaplastic changes are common.
- Numerous lymphocytes and psammoma bodies are present in the background.

Explanatory Notes

This relatively uncommon variant occurs in young patients, especially women, and typically presents as a goiter without a dominant mass, reflecting a diffuse involvement of the gland that mimics Hashimoto thyroiditis and/or lymphoma. Sonograms reveal a characteristic "snowstorm appearance" due to numerous and widespread microcalcifications. There is a higher incidence of lymph node and lung metastases at presentation, and the prognosis may be less favorable than for conventional PTC, although the data remain controversial [1, 2]. On FNA, the highly cellular aspirate is notable for numerous monomorphic small lymphocytes (Fig. 8.28) and can be misleading for lymphocytic thyroiditis or malignant lymphoma. It's worth remembering that in lymphocytic thyroiditis, atypical follicular cells are commonly encountered, and nuclear grooves and INCIs are sometimes present [36]. Furthermore, there is a lower incidence of characteristic nuclear features of PTC in DSV. Three-dimensional clusters of tumor cells with hobnail features and cytoplasmic vacuoles, abundant psammoma bodies, and squamoid differentiation (Fig. 8.29) all suggest the possibility of a DSV.

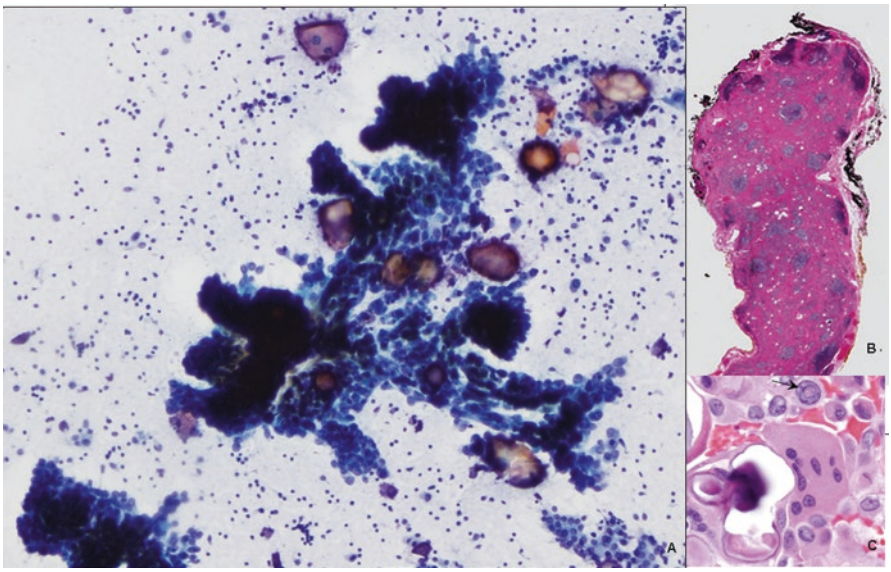

Fig. 8.28 Papillary thyroid carcinoma, diffuse sclerosing variant. (**a**) The aspirate shows papillary fragments associated with psammoma bodies in a lymphocytic background. The nuclear chromatin is darker than in the conventional papillary thyroid carcinoma. (**b**) On histologic examination, the thyroid gland shows numerous lymphoid follicles and many small "holes." (**c**) The holes are from popped out psammoma bodies.

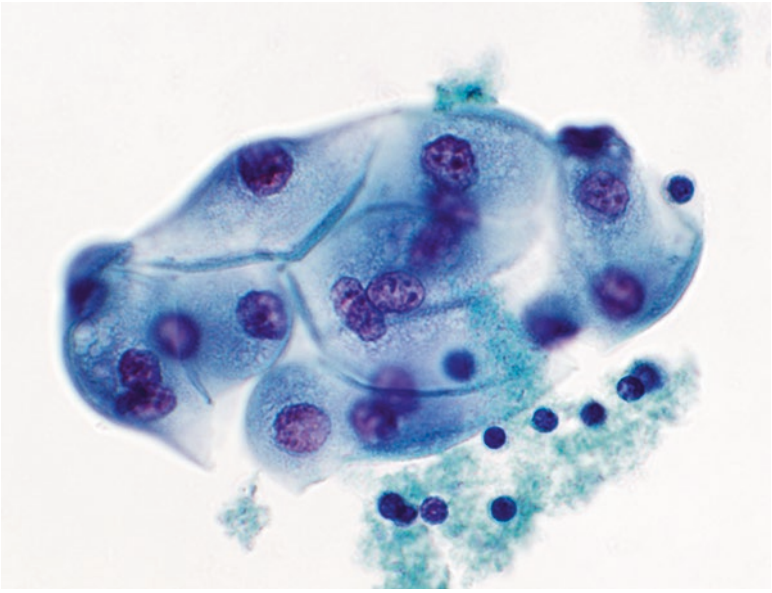

Fig. 8.29 Papillary thyroid carcinoma, diffuse sclerosing variant. The neoplastic cells in this image are "squamoid": they have a flat, polygonal shape with sharply demarcated cell membranes, and they fit together like jigsaw pieces (but there is no overt keratinization.) This squamoid appearance is 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).

Cribriform-Morular Variant

Definition

The cribriform-morular variant of PTC (CMV-PTC) is characterized 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 typical nuclear features of PTC are also found. Some nuclei within the morules contain a peculiar nuclear clearing caused by biotin accumulation.

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 (peculiar nuclear clearing) is present focally.
Nuclear grooves are present, but INCIs 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.
Psammoma bodies and multinucleated giant cells are absent.
The neoplastic cells show nuclear and cytoplasmic positivity for β-catenin (in the FAP-associated CMV-PTCs only).

Explanatory Notes

CMV-PTC is an uncommon variant of PTC with a very frequent association with familial adenomatous polyposis (FAP) or Gardner syndrome and often precedes by several years the development of polyposis coli [2, 37, 38]. A sporadic form occurs in patients who do not carry a germline mutation of *APC* gene. Generally, FAP-associated CMV-PTC occurs in younger patients and is multifocal, whereas sporadic CMV-PTC presents as a solitary thyroid nodule. CMV-PTC is generally an indolent tumor, especially in its sporadic form. There is significant overlap between the architectural and nuclear features of CMV-PTC and other variants of PTC (conventional, tall cell, columnar cell) (Fig. 8.30). Nevertheless, CMV-PTC demonstrates several peculiar cytologic findings, which, when combined with an aberrant positive β-catenin nuclear immunostain (seen in the FAP-associated CMV-PTC cases only), can allow a preoperative diagnosis of CMV-PTC, ruling out more aggressive variants like the tall cell variant [37, 38].

Hobnail Variant

Definition

The hobnail variant of PTC is characterized by the loss of cellular polarity/cohesiveness, with apically placed nuclei and bulging of the apical cell surface (hobnail features) in more than 30% of neoplastic cells.

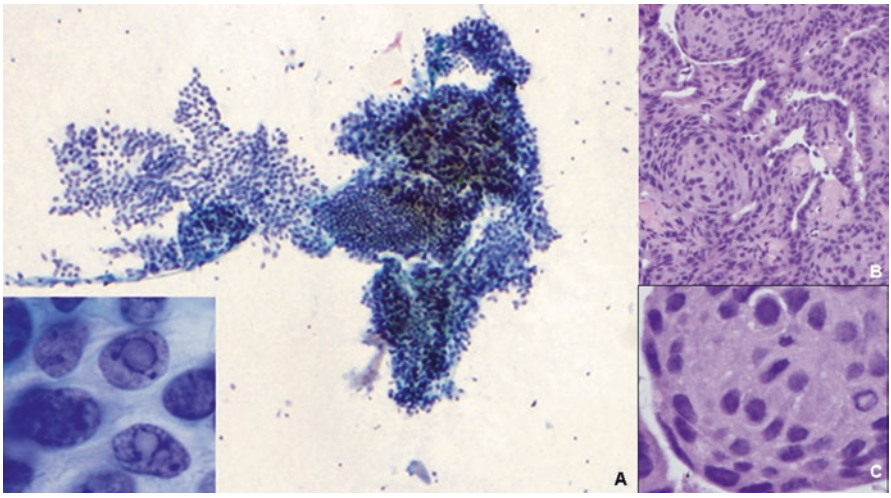

Fig. 8.30 Papillary thyroid carcinoma, cribriform-morular variant. (**a**) The aspirate shows large fragments of cohesive epithelium with a complicated arrangement (smear, Papanicolaou stain). The nuclear chromatin is dark, but nuclear pseudoinclusions are present (*inset*). (**b**) Histologically, the tumor is characterized by cribriform morula formation ((hematoxylin and eosin stain). (**c**) Higher magnification shows the characteristic morules (hematoxylin and eosin stain).

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 INCIs and typical nuclear features of PTC are present.

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

Explanatory Notes

The hobnail variant is a recently described rare variant associated with frequent distant metastases (typically to the lungs) and an increased risk of tumor-related death in small series (Fig. 8.31) [2, 10, 11]. The *BRAF*^{V600E} mutation is found in 70–80% of cases [10]. These tumors may require more aggressive treatment than conventional PTCs. There is significant morphological overlap with other aggressive variants of PTC such as the tall cell, columnar cell, and diffuse sclerosing variants. Hobnail morphology can be identified in LBPs and may occur also in the context of oncocytic, cystic, and clear cell changes. The hobnail variant also needs to be differentiated from metastases to the thyroid gland that have hobnail and/or micropapillary growth patterns (e.g., breast, lung, ovary). Additional studies with

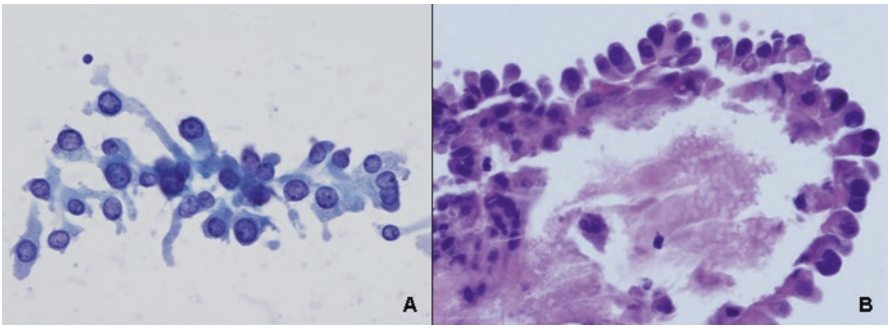

Fig. 8.31 Papillary thyroid carcinoma, hobnail variant. (**a**) The tumor cells in this variant are characterized by an eccentric location of the nucleus in elongated cytoplasm (hobnail-like) (smear, Papanicolaou stain). (**b**) The histologic counterpart shows similar features (hematoxylin and eosin).

large patient cohorts are needed to further clarify the biological behavior of this variant and the relevance of hobnail morphology in the context of cystic and/or encapsulated tumors and other variant growth patterns.

Related Tumors

Hyalinizing Trabecular Tumor/Hyalinizing Trabecular Adenoma

Definition

The hyalinizing trabecular tumor (HTT) or hyalinizing trabecular adenoma is a rare tumor of follicular cell origin characterized by trabecular growth, marked intratrabecular hyalinization, and the nuclear changes of PTC.

Criteria

Cohesive neoplastic cells are radially oriented around amyloid-like hyaline stromal material.
Cells can be round- or spindle-shaped.
INCIs and nuclear grooves are numerous.
Occasional psammoma bodies may be present.
Cytoplasmic paranuclear yellow bodies may be present.
Papillary and sheetlike fragments are absent.

Explanatory Notes

HTT is a controversial entity. Despite significant morphologic and genetic similarities with PTC, it may be better regarded as a variant of follicular adenoma rather than PTC [39, 40]. Patients with HTT follow a benign clinical course in the vast majority of cases (>99%) [40]. A total thyroidectomy and/or radioiodine treatment are usually not warranted for HTT. Because the morphologic features of HTT overlap significantly with those of PTC [39, 40], HTT is very difficult to recognize as

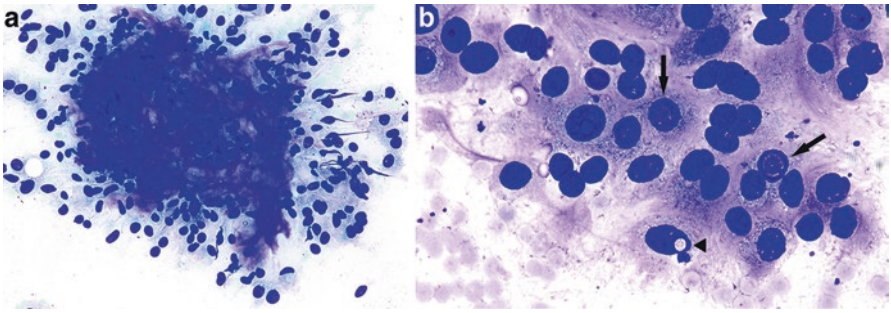

Fig. 8.32 Hyalinizing trabecular tumor/adenoma. (**a**) A core of metachromatic hyaline material insinuates among cells with oval nuclei, anisonucleosis, and abundant cytoplasm (smear, Diff-Quik stain). (**b**) Oval neoplastic nuclei have occasional intranuclear cytoplasmic pseudoinclusions (INCIs, *arrows*). Note the clear hole in one of the adjacent nuclei (*arrowhead*), a mimic of INCIs, but recognizable as an artifact because the hole is white rather than the color and texture of cytoplasm (smear, Papanicolaou stain).

such in an FNA specimen (Fig. 8.32). Most HTTs are interpreted as PTC or "suspicious for PTC." The demonstration of aberrant cytoplasmic expression of MIB-1 by immunohistochemistry supports the diagnosis of HTT. In contrast to PTC, *BRAF*^{V600E} mutations have not been found in HTT, but HTT harbors a *RET/PTC* rearrangement in a significant subset of cases (up to 62%), rekindling a possible relationship to PTC. The ultrasound findings of HTT usually show a well-defined iso- or hypoechoic solid nodule that more closely resembles a follicular neoplasm or FVPTC than a classic PTC.

Management

Surgical consultation is recommended for patients with an FNA interpretation that is conclusive for PTC; subtyping the PTC cytologically is not necessary 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 diagnostic 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) [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 a 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 a 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).

Example 1
MALIGNANT.
Papillary thyroid carcinoma.

Example 2
MALIGNANT.
Papillary thyroid carcinoma. See note.

Note: With the recent 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 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.

References

1. LiVolsi VA, Albores-Saavedra J, Asa SL. Papillary carcinoma. In: Lellis D, Lloyd R, Heitz PU, Eng C, editors. WHO classification of tumours. Pathology and genetics of tumours of endocrine organs. Lyon: IARC Press; 2004. p. 57–66.
2. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26:1–133.

3. Jung CK, Little MP, Lubin JH, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. J Clin Endocrinol Metab. 2014;99:E276–85.
4. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma. A paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol. 2016;2:1023–9.
5. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda system for reporting thyroid cytopathology: a meta-analysis. Acta Cytol. 2012;56:333–9.
6. Suzuki A, Hirokawa M, Higuchi M, et al. Cytological characteristics of papillary thyroid carcinoma on LBC specimens, compared with conventional specimens. Diagn Cytopathol. 2015;43:108–13.
7. Lee JS, Choi HS, Park IA, Ryu HS. Liquid-based fine needle aspiration biopsy of papillary thyroid carcinoma: logistic regression analysis with conventional and new cytomorphologic features. Acta Cytol. 2013;57:233–40.
8. Lee SH, Jung CK, Bae JS, Jung SL, Choi YJ, Kang CS. Liquid-based cytology improves preoperative diagnostic accuracy of the tall cell variant of papillary thyroid carcinoma. Diagn Cytopathol. 2014;42:11–7.
9. Szporn AH, Yuan S, Wu M, Burstein DE. Cellular swirls in fine needle aspirates of papillary thyroid carcinoma: a new diagnostic criterion. Mod Pathol. 2006;19:1470–3.
10. Lee YS, Kim Y, Jeon S, Bae JS, Jung SL, Jung CK. Cytologic, clinicopathologic, and molecular features of papillary thyroid carcinoma with prominent hobnail features: 10 case reports and systematic literature review. Int J Clin Exp Pathol. 2015;8:7988–97.
11. Asioli S, Maletta F, Pagni F, et al. Cytomorphologic and molecular features of hobnail variant of papillary thyroid carcinoma: case series and literature review. Diagn Cytopathol. 2014;42:78–84.
12. Rupp M, Ehya H. Nuclear grooves in the aspiration cytology of papillary carcinoma of the thyroid. Acta Cytol. 1989;33:21–6.
13. Papotti M, Manazza AD, Chiarle R, Bussolati G. Confocal microscope analysis and tridimensional reconstruction of papillary thyroid carcinoma nuclei. Virchows Arch. 2004;444:350–5.
14. Ellison E, Lapuerta P, Martin SE. Psammoma bodies in fine-needle aspirates of the thyroid: predictive value for papillary carcinoma. Cancer. 1998;84:169–75.
15. Strickland KC, Howitt BE, Marqusee E, et al. The impact of non-invasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnostic categories. Thyroid. 2015;25:987–92.
16. Faquin WC, Wong LQ, Afrogheh AH, et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in the Bethesda system for reporting thyroid cytopathology. Cancer Cytopathol. 2016;124:181–7.
17. Yang GC, Fried K, Yakoushina TV, Schreiner AM. Encapsulated follicular variant of papillary thyroid carcinoma: fine-needle aspiration with ultrasound and histologic correlation of 41 cases. Acta Cytol. 2013;57:26–32.
18. Gallagher J, Oertel YC, Oertel JE. Follicular variant of papillary carcinoma of the thyroid: fine-needle aspirates with histologic correlation. Diagn Cytopathol. 1997;16:207–13.
19. Mesonero CE, Jugle JE, Wilbur DC, et al. Fine-needle aspiration of the macrofollicular and microfollicular subtypes of the follicular variant of papillary carcinoma of the thyroid. Cancer Cytopathol. 1998;84:235–44.
20. Baloch ZW, Gupta PK, Yu GH, et al. Follicular variant of papillary carcinoma: cytologic and histologic correlation. Am J Clin Pathol. 1999;111:216–22.
21. Cancer Genome Atlas Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159:676–90.
22. Maletta F, Massa F, Torregrossa L, et al. Cytological features of “non-invasive follicular thyroid neoplasm with papillary-like nuclear features” and their correlation with tumor histology. Hum Pathol. 2016;54:134–42.

23. Strickland K, Vivero M, Jo VY, et al. Pre-operative cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a prospective analysis. Thyroid. 2016;26:1466–1471. [Epub ahead of print].
24. Howitt BE, Chang S, Eszlinger M, et al. Fine-needle aspiration diagnoses of noninvasive follicular variant of papillary thyroid carcinoma. Am J Clin Pathol. 2015;144:850–7.
25. Policarpio-Nicolas ML, Sirohi D. Macrofollicular variant of papillary carcinoma, a potential diagnostic pitfall: A report of two cases including a review of literature. Cytojournal. 2013;10:16.
26. Chung D, Ghossein RA, Lin O. Macrofollicular variant of papillary carcinoma – a potential thyroid FNA pitfall. Diagn Cytopathol. 2007;35:560–4.
27. Goellner JR, Johnson DA. Cytology of cystic papillary carcinoma of the thyroid. Acta Cytol. 1982;26:797–808.
28. Yang GC, Stern CM, Messina AV. Cystic papillary thyroid carcinoma in fine needle aspiration may represent a subset of the encapsulated variant in WHO classification. Diagn Cytopathol. 2010;38:721–6.
29. Moreira AL, Waisman J, Cangiarella JF. Aspiration cytology of the oncocytic variant of papillary adenocarcinoma of the thyroid gland. Acta Cytol. 2004;48:137–41.
30. Doria MI Jr, Attal H, Wang HH, Jensen JA, DeMay RM. Fine needle aspiration cytology of the oxyphil variant of papillary carcinoma of the thyroid. A report of three cases. Acta Cytol. 1996;40:1007–11.
31. Baloch ZW, LiVolsi VA. Warthin-like papillary carcinoma of the thyroid. Arch Pathol Lab Med. 2000;124:1192–5.
32. Guan H, Vandenbussche CJ, Erozan YS, et al. Can the tall cell variant of papillary thyroid carcinoma be distinguished from the conventional type in fine needle aspirates? A cytomorphologic study with assessment of diagnostic accuracy. Acta Cytol. 2013;57:534–42.
33. Solomon A, Gupta PK, LiVolsi VA, Baloch ZW. Distinguishing tall cell variant of papillary thyroid carcinoma from usual variant of papillary thyroid carcinoma in cytologic specimens. Diagn Cytopathol. 2002;27:143–8.
34. Jayaram G. Cytology of columnar-cell variant of papillary thyroid carcinoma. Diagn Cytopathol. 2000;22:227–9.
35. Giorgadze TA, Scognamiglio T, Yang GC. Fine-needle aspiration cytology of the solid variant of papillary thyroid carcinoma: a study of 13 cases with clinical, histologic, and ultrasound correlations. Cancer Cytopathol. 2015;123:71–81.
36. Takagi N, Hirokawa M, Nobuoka Y, Higuchi M, Kuma S, Miyauchi A. Diffuse sclerosing variant of papillary thyroid carcinoma: a study of fine needle aspiration cytology in 20 patients. Cytopathology. 2014;25:199–204.
37. Hirokawa M, Maekawa M, Kuma S, Miyauchi A. Cribriform-morular variant of papillary thyroid carcinoma – cytological and immunocytochemical findings of 18 cases. Diagn Cytopathol. 2010;38:890–6.
38. Boonyaarunnate T, Olson MT, Bishop JA, Yang GC, Ali SZ. Cribriform morular variant of papillary thyroid carcinoma: clinical and cytomorphological features on fine-needle aspiration. Acta Cytol. 2013;57:127–33.
39. Casey MB, Sebo TJ, Carney JA. Hyalinizing trabecular adenoma of the thyroid gland: cytologic features in 29 cases. Am J Surg Pathol. 2004;28:859–67.
40. Carney JA, Hirokawa M, Lloyd RV, Papotti M, Sebo TJ. Hyalinizing trabecular tumors of the thyroid gland are almost all benign. Am J Surg Pathol. 2008;32:1877–89.