High-Grade Follicular Cell-Derived Non-Anaplastic Thyroid Carcinoma

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Background

This chapter was called "poorly-differentiated thyroid carcinomas" in the previous editions of TBSRTC. The latest 5th edition of the WHO classification of thyroid neoplasms has now included poorly differentiated thyroid carcinoma (PDTC) in the same group as differentiated high-grade thyroid carcinoma (DHGTC) under the umbrella of "Follicular cell-derived non-anaplastic carcinomas, high-grade" in the chapter on malignant neoplasms [1]. This was the result of studies highlighting how non-anaplastic thyroid carcinomas that show necrosis and high mitotic activity have an aggressive clinical behavior intermediate between that of well differentiated thyroid carcinomas (WDTC) (papillary carcinoma, follicular carcinoma, and oncocytic carcinoma) and undifferentiated (anaplastic) thyroid carcinomas, despite the morphological architectural arrangement (follicular, papillary, or oncocytic) [2].

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Poorly differentiated thyroid carcinoma (PDTC) was first proposed as a distinct subtype of thyroid malignancy by Carcangiu et al. [3] These authors reinterpreted the original observation made in 1907 by Langhans, who described a locally aggressive tumor with a peculiar architecture: tumor cells arranged in large, round to oval formations, the so-called "insulae" [4].

In the past, high mitotic activity and tumor necrosis were necessary for the histologic diagnosis of PDTC [5]. To qualify histologically as PDTC, tumors must have a solid, trabecular, and/or insular pattern of growth; conventional nuclear features of papillary thyroid carcinoma should not be present throughout the tumor; and at least one of the following features must be present: mitotic activity ≥3/10 high-power fields (HPFs), tumor necrosis, and convoluted nuclei (known as the Turin criteria). Others considered PDTC as having ≥5 mitoses/10 HPF and/or tumor necrosis, independently from growth pattern (known as the Memorial Sloan Kettering Cancer Center criteria) [6]. PDTCs can also have prominent oncocytic features [7, 8].

DHGTC are carcinomas with high mitotic activity and necrosis and in which papillary or follicular architecture is still present and well identified (in contrast to PDTC, where usually these architectural features are lacking and solid, trabecular, and insular features are most common) [9].

PDTC and DHGTC are rare malignancies, accounting for 1–6.7% of all thyroid cancers [1, 10]. Both entities often present at an advanced stage, have a propensity for local recurrence, tend to metastasize to regional lymph nodes, and do not respond to radioactive iodine therapy. The disease-specific survival of patients with PDTC and DHGTC varies from 50% to 56% [1, 10]. A focal (10% or greater) PDTC component in an otherwise well-differentiated thyroid carcinoma designates a more aggressive clinical course than standard well-differentiated carcinomas of the thyroid [11].

Definition

PDTC is a thyroid carcinoma of follicular cell origin characterized by an insular, solid, or trabecular growth pattern with minimal colloid. The most classic architectural form of PDTC is the insular type, defined by its "cellular nests" or insular cell groups outlined by a thin fibrovascular border. In its pure form, PDTC lacks conventional nuclear features of papillary thyroid carcinoma and is distinguished from other well-differentiated thyroid neoplasms by the presence of poorly differentiated features: necrosis, mitoses, or small, round hyperchromatic nuclei with convoluted and irregular nuclear membranes [6]. The quantity and quality of cytoplasm of the tumor cells can vary, as a subset can have oncocytic features. While most PDTCs

contain a relatively monotonous population of malignant cells with limited pleomorphism, some are characterized by larger, more pleomorphic cells. However, there is no frank anaplasia as that seen in cases of undifferentiated (anaplastic) thyroid carcinoma. In cases where there is prominent pleomorphism, progression to undifferentiated (anaplastic) thyroid carcinoma should be a diagnostic consideration.

DHGTC still retain conventional nuclear features and structures of papillary thyroid carcinoma (or follicular architecture in a lesser percentage of cases), but are associated with more atypical cellular features, such as nuclear enlargement and/or pleomorphism and necrosis. Mitoses, which are almost never observed in well differentiated thyroid carcinomas, are more frequently present in DHGTC.

Criteria

Cellular preparations display an insular, solid, or trabecular cytoarchitecture (Figs. 10.1, 10.2, 10.3, and 10.4) suggestive of a PDTC morphology.

There is a uniform population of malignant follicular cells with scant cytoplasm, sometimes plasmacytoid (Fig. 10.5), or with oncocytic features (Fig. 10.6) and frequently arranged in microfollicles (Fig. 10.7).

The cells have a high nuclear/cytoplasmic (N/C) ratio with variable nuclear atypia (Figs. 10.8 and 10.9).

Colloid is scant/absent.

Apoptosis and mitotic activity are present (Fig. 10.10).

Necrosis is often present (Fig. 10.11).

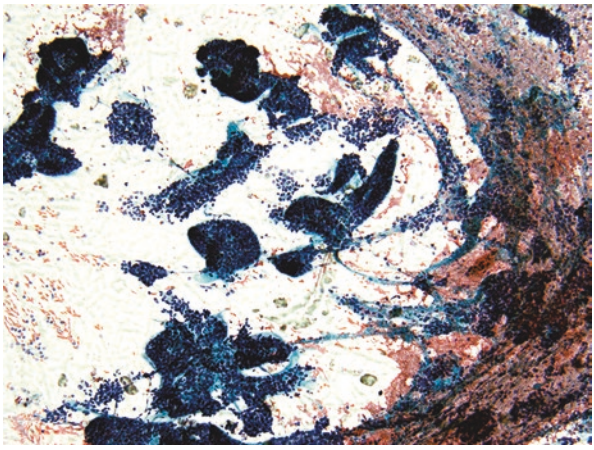

Fig. 10.1 Poorly differentiated thyroid carcinoma. A low magnification view reveals small follicular cells arranged in crowded insulae (smear, Papanicolaou stain)

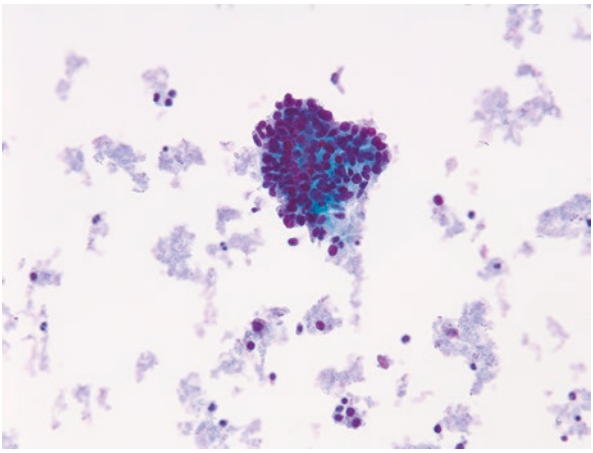

Fig. 10.2 Poorly differentiated thyroid carcinoma. The monomorphic cells are arranged in crowded 3-dimensional groups and scattered as isolated cells (ThinPrep, Papanicolaou stain)

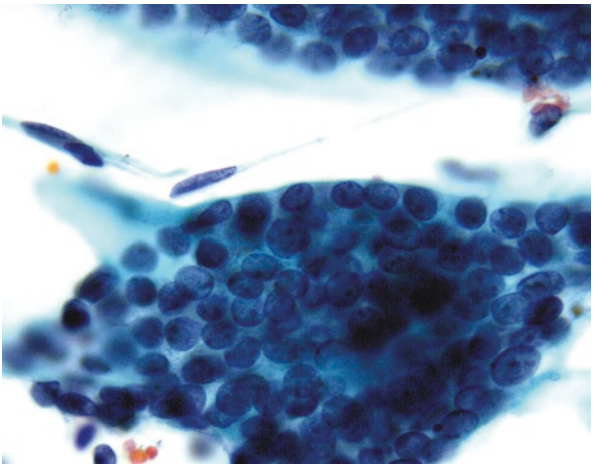

Fig. 10.3 Poorly differentiated thyroid carcinoma. Endothelium wrapping around cell groups can often be found highlighting the insular arrangements (smear, Papanicolaou stain)

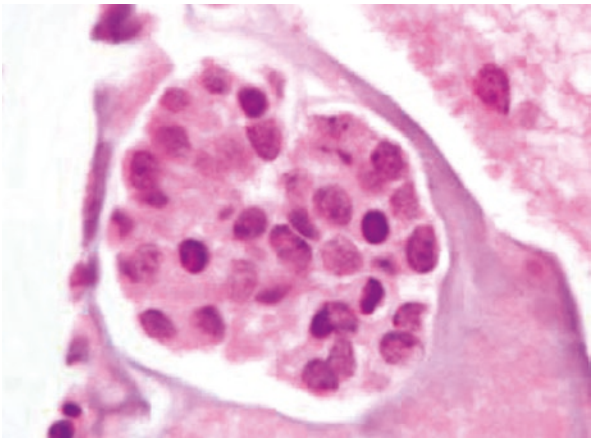

Fig. 10.4 Poorly differentiated thyroid carcinoma. The cell block demonstrates the arrangement of cells in insular groups (cell block, H&E stain)

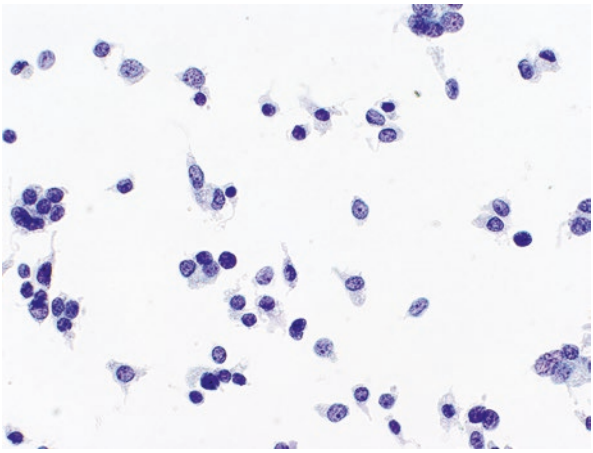

Fig. 10.5 Poorly differentiated thyroid carcinoma. In some cases, the malignant cells are arranged predominantly as isolated cells. They can have a plasmacytoid cytomorphology, as seen here (ThinPrep, Papanicolaou stain)

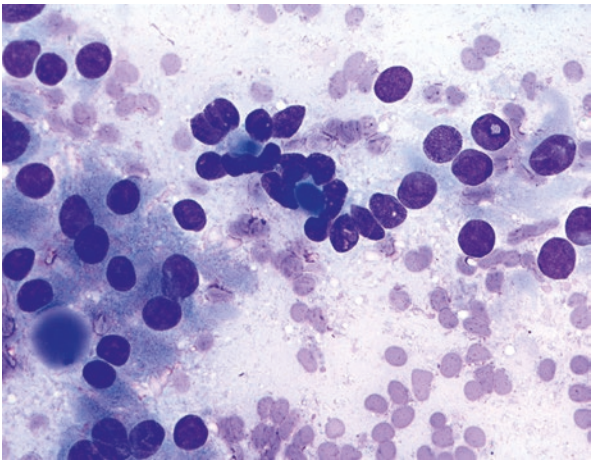

Fig. 10.6 Poorly differentiated thyroid carcinoma. In some cases, the cells have oncocytic cytoplasm. Some bare nuclei are also present (smear, Diff-Quik stain)

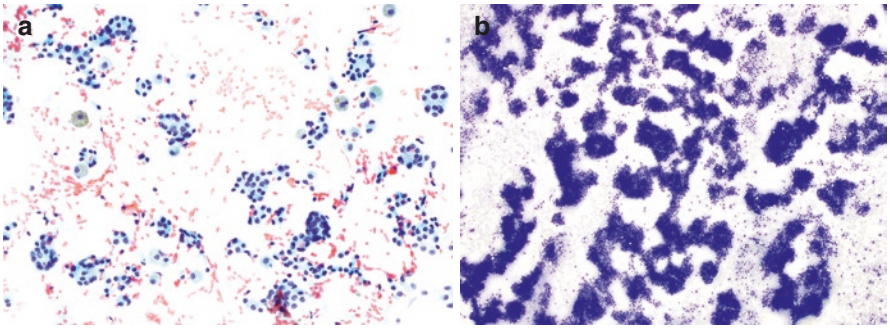

Fig. 10.7 High-grade follicular carcinoma. (**a**) The presence of microfollicles does not preclude the possibility of a poorly differentiated thyroid carcinoma or a high-grade follicular thyroid carcinoma (smear, Papanicolaou stain). (**b**) A hypercellular smear without colloid and large groups of follicular cells with an insular/solid component can be the only cytomorphological feature of a poorly differentiated thyroid carcinoma (smear, Diff-Quik stain)

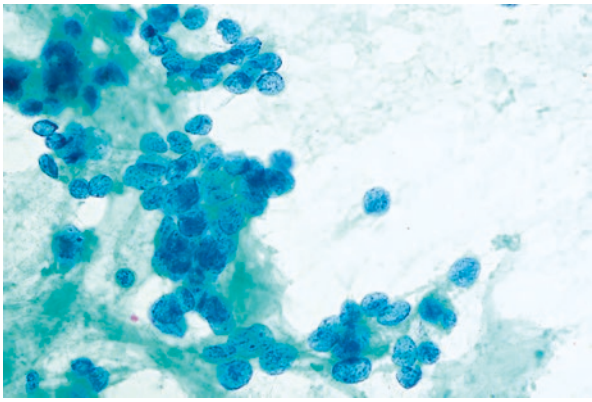

Fig. 10.8 Poorly differentiated thyroid carcinoma. Occasional tumors demonstrate only mild nuclear atypia, with small nucleoli and delicate chromatin (smear, Papanicolaou stain)

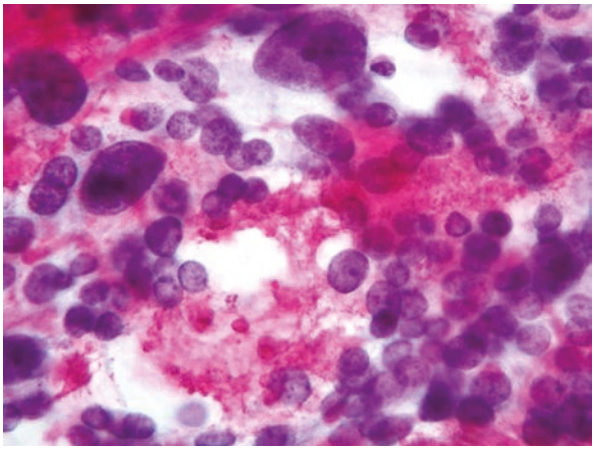

Fig. 10.9 Poorly differentiated thyroid carcinoma. Some aspirates exhibit marked nuclear atypia. In this example, there is impressive anisonucleosis (smear, Papanicolaou stain)

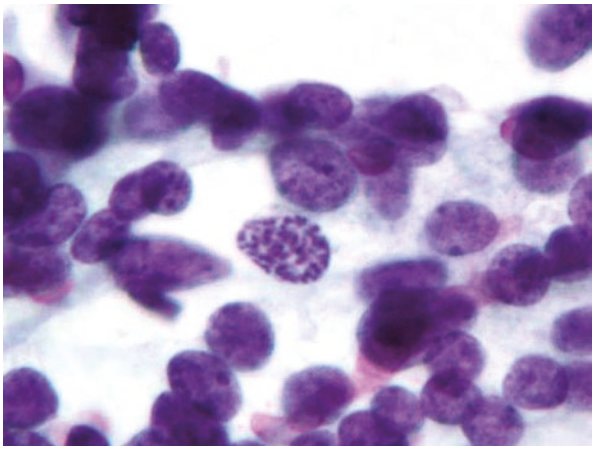

Fig. 10.10 Poorly differentiated thyroid carcinoma. Aspirates often contain mitotically active cells (smear, Papanicolaou stain)

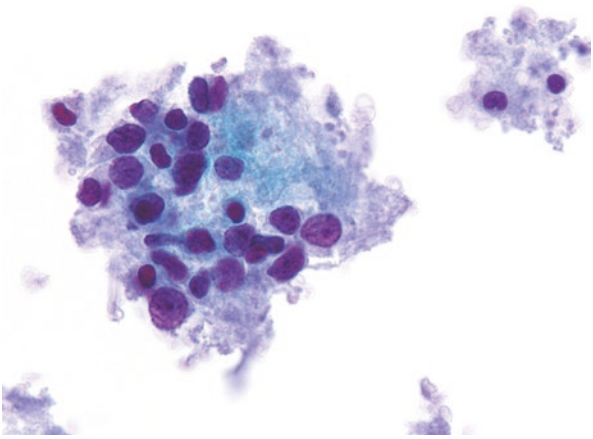

Fig. 10.11 Poorly differentiated thyroid carcinoma. Necrotic debris (cytoplasmic and nuclear fragments) is seen in occasional cases (smear, Papanicolaou stain)

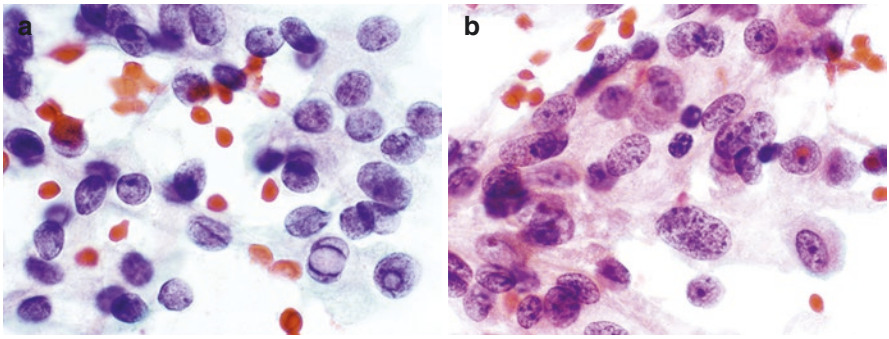

Fig. 10.12 High-grade follicular carcinoma. (**a**) In some cases, high-grade thyroid carcinomas show features of papillary carcinoma, including nuclear grooves and intranuclear pseudoinclusions. (**b**) There can be significant nuclear pleomorphism (smears, Papanicolaou stain)

Clearly malignant papillary carcinoma cells can display significant nuclear pleomorphism often accompanied by necrosis or necrotic debris (Figs 10.12 and 10.13).

In case of a predominant population of monotonous cell with plasmacytoid appearance, immunohistochemistry can be useful to exclude a medullary thyroid carcinoma or a metastasis (Figs. 10.14, 10.15, and 10.16).

In liquid-based cytology, PDTC exhibits the same cytomorphology, typically characterized by a population of cells with a high N/C ratio and focal nuclear atypia (Figs. 10.2 and 10.5).

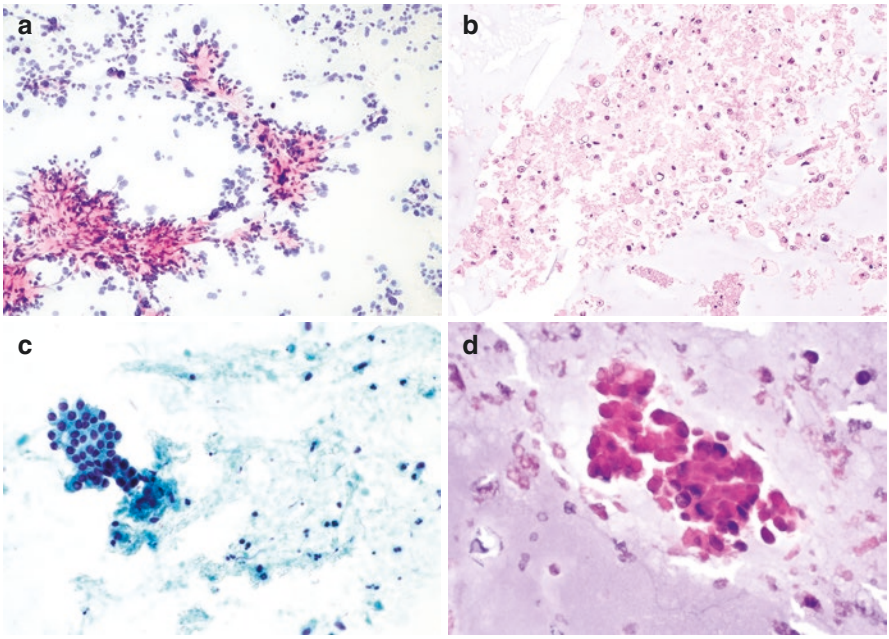

Fig. 10.13 High-grade follicular carcinoma. (**a**) High-grade tumors can show classic features of papillary carcinoma, including papillary architecture and intranuclear pseudoinclusions, but are associated with significant nuclear pleomorphism and dissociated cells (smear, Papanicolaou stain). (**b**) The cell block of the same case shows necrotic debris, cellular pleomorphism, and an oncocytic appearance of cells. Necrosis and pleomorphic tumor cells can also be the hallmark of anaplastic thyroid carcinoma, which should also enter in the differential diagnosis (cell block, H&E stain). (**c**) In a different case, papillary thyroid carcinoma cells lie in a necrotic background (smear, Papanicolaou stain) and (**d**) the corresponding cell block also shows necrotic cells (cell block, H&E stain)

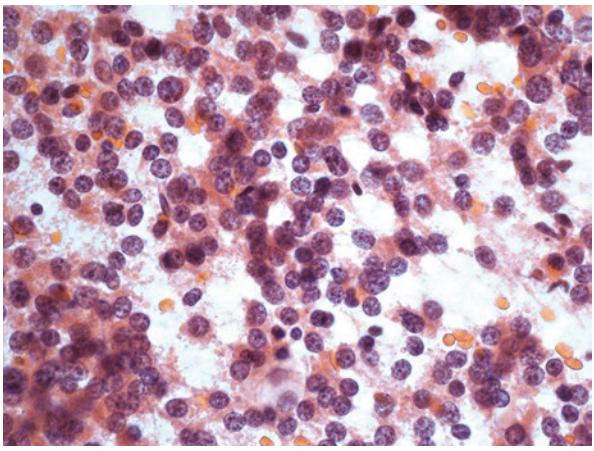

Fig. 10.14 Poorly differentiated thyroid carcinoma. Because some aspirates are comprised predominantly of isolated cells with granular chromatin, they mimic both medullary thyroid carcinoma and metastatic neoplasms (smear, Papanicolaou stain)

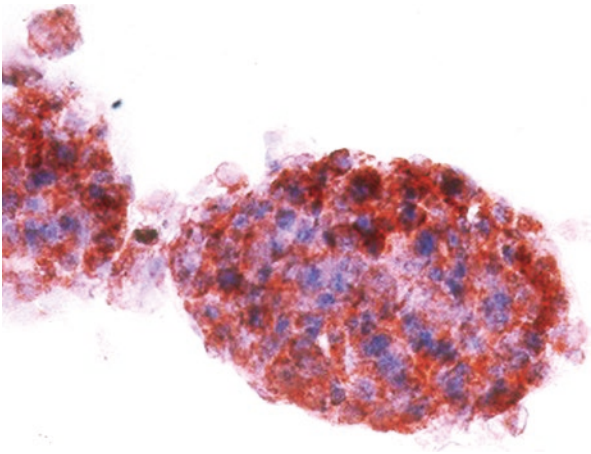

Fig. 10.15 Poorly differentiated thyroid carcinoma. Poorly differentiated thyroid carcinomas are positive for thyroglobulin, which helps to distinguish them from medullary thyroid carcinoma and metastatic tumors (ThinPrep, thyroglobulin IHC)

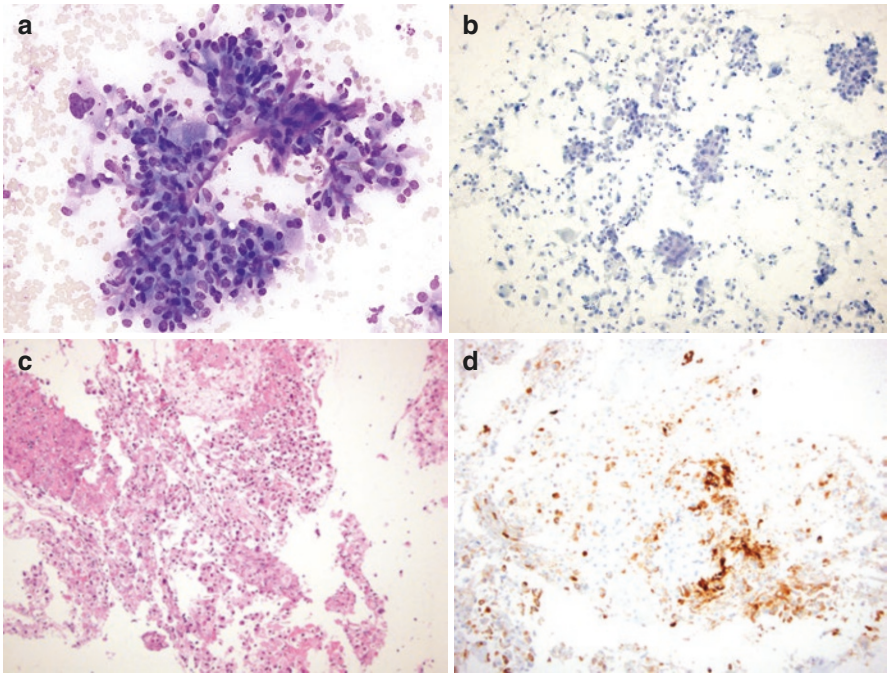

Fig. 10.16 High-grade follicular carcinoma. (**a**) Papillary architecture, plasmacytoid cells with nuclear pleomorphism (smear, Diff-Quik stain), (**b**) a more dissociated population of cells (smear, Papanicolaou stain) with (**c**) foci of necrosis (left corner) of the cell block, mimic medullary thyroid carcinoma (cell block, H&E). (**d**) Positive immunostaining for thyroglobulin confirms a high-grade papillary carcinoma (cell block, thyroglobulin immunostain)

Explanatory Notes

The below discussion will concentrate on the cytomorphological features of PDTC. On fine needle aspiration, PDTCs are difficult to recognize as such because they are rare and have cytomorphologic features that overlap with those of follicular neoplasms. DHGTC are more easily recognized from a cytological point of view, given the presence of characteristic papillary thyroid carcinoma nuclei and structures and/or follicular architecture; distinguishing from WDTC can be more challenging if tumor necrosis and mitotic activity are not readily apparent. Characteristic PDTC features on aspirate specimens do not have great specificity. A limited number of published case reports, small series, and institutional reviews yield just over 100 cases of PDTC, the aspirates of which are often hypercellular with scant amounts of colloid [12–23]. The tumor cells often have a monomorphic appearance at low magnification and consist of small to medium-sized cells with high N/C ratios. However, at higher magnification, variable degrees of atypia can be found along with abrupt nucleomegaly. While many PDTC cases show a single cell dispersion pattern, larger cell nests, trabeculae, sheets, and occasional follicular arrangements of neoplastic cells can be appreciated. The proportion of isolated cells versus larger fragments varies from case to case. As mentioned previously, the insular form of PDTC is identified histologically by its characteristic arrangement of cells in insulae with peripheral endothelial wrapping and peripheral alignment of nuclei and a similar pattern can be recognized in a subset of PDTC aspirates. Less frequently, some PDTC cases exhibit microfollicles (Fig. 10.7), nuclear grooves, and intranuclear pseudoinclusions (Fig. 10.12). Variable mitotic activity and apoptotic or necrotic debris can be appreciated but may be more frequently visualized on cell block or histologic material. Although necrosis is a concerning feature, it is important to differentiate tumor necrosis from that of infarct-type necrosis which can be seen after prior FNA. Morphologic findings such as a fibrovascular proliferation and/or the presence of hemosiderin-laden macrophages may be helpful in differentiating between these two etiologies of necrosis.

In the majority of preoperative FNAs, PDTCs are diagnosed cytologically as “Follicular Neoplasm” or “Malignant” as a well-differentiated thyroid carcinoma. In two large FNA series of PDTCs, approximately 35% of cases were prospectively recognized as PDTC or “poorly differentiated carcinoma, NOS” [23, 24]. The other cases were diagnosed mostly as “suspicious for a follicular neoplasm” or as “carcinoma,” either papillary carcinoma, follicular variant of papillary carcinoma, or not otherwise specified. Using logistic regression analysis, Bongiovanni et al. noted that a combination of cytoarchitecture, single cell dispersion pattern, significant crowding, and high N/C ratio was most predictive of PDTC [23].

The combination of cytomorphologic features described above, however, is suggestive of PDTC in FNA specimens. Clinical and ultrasonographic correlation is also helpful in further clarification of the FNA diagnosis, as PDTCs are usually large tumors with extrathyroidal extension.

Other primary thyroid tumors and metastatic malignancies should be considered in the differential diagnosis. A subset of PDTCs exhibits a predominantly isolated cell pattern in FNA samples (Fig. 10.13). When this occurs, together with

a "salt and pepper-like" chromatin pattern, the possibility of medullary thyroid carcinoma should be excluded with immunohistochemical stains. In contrast to medullary thyroid carcinoma, most PDTCs are immunoreactive for thyroglobulin (Fig. 10.14) and PAX8, are negative for calcitonin and CEA [25], and are only rarely immunoreactive for the neuroendocrine markers like synaptophysin and chromogranin. Medullary thyroid carcinomas are most often positive for calcitonin, CEA, and neuroendocrine markers. They only rarely show positivity for PAX8 and are negative for thyroglobulin. TTF-1 is not useful for this distinction as it will be positive in both PDTC and medullary thyroid carcinoma. PDTC and DHGTC can display oncocytic features, raising the possibility of oncocytic neoplasms. Unfortunately, immunohistochemistry is not helpful in differentiating these two entities and clear delineation is deferred to subsequent resection specimens. Undifferentiated (anaplastic) thyroid carcinomas are also characterized by a variety of cytomorphologic patterns (see Chap. 11) together with necrosis and increased mitotic activity. In contrast, PDTCs lack the marked nuclear pleomorphism, high-grade features, and sarcomatoid features of undifferentiated (anaplastic) thyroid carcinomas. Additionally, undifferentiated (anaplastic) thyroid carcinomas only rarely stain positively for thyroglobulin and usually show focal TTF-1 positivity in contrast to the typical diffuse staining of both of these markers in PDTCs and DHGTCs [26].

Based purely on cytomorphology, a PDTC may resemble a metastasis from an extrathyroidal primary tumor: both typically yield cellular specimens with nuclear atypia and necrosis, and colloid is scant. The positive immunoreactivity of PDTCs for thyroglobulin and TTF-1 helps to exclude a metastasis. The subset of PDTCs with a predominantly isolated cell pattern and plasmacytoid cytomorphology can suggest a lymphoproliferative disorder, but PDTCs are negative for CD45 and markers of B cells (e.g., CD19, CD20) and plasma cells (e.g., CD138).

Molecular Genetics

High-grade follicular cell-derived non-anaplastic thyroid carcinomas most often develop from three distinct pathways: partial dedifferentiation or high-grade transformation of a papillary thyroid carcinoma, partial dedifferentiation or high-grade transformation from a follicular or oncocytic carcinoma, or de novo [27]. As expected, these tumors show a mutational burden that is higher than well-differentiated tumors but is less than observed in anaplastic carcinomas. Furthermore, these tumors show characteristic early somatic mutations that correspond to a well-differentiated counterpart. For example, tumors arising from PTC often show *BRAF* V600E mutations, tumors arising from a follicular carcinoma often show *RAS* mutations, and tumors arising from oncocytic carcinomas often show somatic copy number alterations and mutations in mitochondrial DNA [28, 29]. However, HGFDTCs are enriched for additional late event mutations that drive the process of high-grade transformation. These most commonly include *TP53* and telomerase reverse transcriptase (*TERT*) mutations, which are also detected in higher proportions in

Table 10.1 Common driver alterations and functions in poorly differentiated thyroid carcinomas

Gene	Hotspots/fusion Partner	Function	Prevalence
RAS	Point mutations in codon 61 of NRAS or HRAS	Activation of MAPK and PI3K/AKT signaling pathways	20–40% [30–32]
BRAF	V600E	Activation of MAPK signaling pathway	5–30% [28, 33, 34]
EIF1AX	Point mutations in codons 9–15 in exon 2 or at a splice site between exons 5 and 6	Typically, co-existing with RAS and causes altered initiation of protein translation; only 1–2% of conventional PTCs (26878173)	10% [28, 35]
PIK3CA	Point mutations in codons 542, 545, or 1047	PI3K/AKT signaling pathway	5–20% [28, 31]
PTEN	Inactivating mutations, insertions, deletions	PI3K/AKT signaling pathway	5–20% [27, 28]
AKT1	*AKT1*49G>A	PI3K/AKT signaling pathway	<5% [31]
TERT	C228T and C250T	Encodes catalytic subunit of telomerase which maintains the lengths of telomeres to preserve chromosome during replication	30–50% [28, 36–38]
TP53	Exons 5–8	Tumor suppressor that regulates the cell cycle, DNA repair, and apoptosis	10–30% [28, 39, 40]
ALK fusions	*ALK::STRN*	Receptor tyrosine kinase that activates multiple downstream signaling pathways, such as MAPK, PI3K/AKT, and JAK-STAT	5–10% [28, 41–43]
PPARG fusions	*PPARG::PAX8*	Fusion product is an oncoprotein which accelerates growth and decreases apoptosis	5–7% [28, 44, 45]
RET fusions	*RET::PTC1* and *RET::PTC3*	Receptor tyrosine kinase that activates multiple downstream signaling pathways, such as MAPK and PI3K/AKT	0–5% [28, 46, 47]

anaplastic carcinomas. The most common driver molecular alterations are shown in Table 10.1, along with a note about gene hotspots, gene function, and prevalence in PDTC. As molecular diagnostic testing continues to play an increasing role for patient management, particularly in thyroid FNA samples, it is important to have a basic understanding of the molecular alterations present in conventional differentiated thyroid carcinomas, as well as HGFDTCs.

Management

Because of their poor clinical prognosis and radioactive iodine resistance, HGFDTCs are usually managed more aggressively than well differentiated thyroid carcinomas, with total thyroidectomy and lymph node dissection. Currently, additional therapies based on molecular signature are available [48, 49].

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). Many PDTCs overlap morphologically with follicular neoplasms and are therefore inevitably interpreted as "Follicular Neoplasm."

Example 1
MALIGNANT.
Most consistent with differentiated high-grade thyroid carcinoma.
Note: Highly cellular aspirate with atypical follicular cells, necrosis, and scant colloid, most consistent with differentiated high-grade thyroid carcinoma. However, a poorly differentiated thyroid carcinoma cannot be excluded.

Example 2
MALIGNANT.
Papillary thyroid carcinoma with focal poorly differentiated features, suggestive of differentiated high-grade thyroid carcinoma.

Example 3
FOLLICULAR NEOPLASM.
Note: Atypical follicular cells are present with a prominently isolated cell component, focal necrosis, and mitotic activity. Immunostains on cell block sections are positive for thyroglobulin and TTF-1 and negative for calcitonin. The findings raise the possibility of a poorly differentiated thyroid carcinoma.

Example 4
MALIGNANT.
Papillary thyroid carcinoma.
Note: Papillary carcinoma cells are present in groups and isolated patterns with background necrosis. A differentiated (papillary) high-grade thyroid carcinoma could not be excluded.

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