Poorly Differentiated Thyroid Carcinoma

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Background

Poorly differentiated thyroid carcinoma (PDTC) was first proposed as a distinct subtype of thyroid malignancy by Carcangiu et al. [1]. 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 [2]. Currently, there are two recognized subtypes of PDTC – insular and non-insular [3].

In 2006, formal criteria (known as the Turin criteria) were established for the histologic diagnosis of PDTC [4]. 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. Some PDTCs have prominent oncocytic (Hürthle cell) features [5, 6].

PDTC is a rare malignancy, accounting for 0.3–6.7% of all thyroid cancers [3]. The age at presentation is between 18 and 63 years with a slight female predilection. It has an aggressive clinical behavior intermediate between that of the well-differentiated thyroid carcinomas (papillary carcinoma, follicular carcinoma, and

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Hürthle cell carcinoma) and undifferentiated (anaplastic) thyroid carcinoma. PDTCs often present at an advanced stage, have a propensity for local recurrence, and tend to metastasize to regional lymph nodes, lung, and bones. The mean 5-year survival of patients with PDTC is approximately 50% [3, 4]. Well-differentiated thyroid carcinomas with a focal (10% or greater) PDTC component follow a more aggressive clinical course than standard well-differentiated carcinomas of the thyroid [7].

Definition

PDTC is a thyroid carcinoma of follicular cell origin characterized by an insular, solid, or trabecular growth pattern. In its pure form, PDTC lacks conventional nuclear features of papillary thyroid carcinoma and is distinguished from the latter by the presence of poorly differentiated features: mitoses, necrosis, or small convoluted nuclei. The most classic form of PDTC is the insular type, defined by its "cellular nests" or insular cell groups outlined by a thin fibrovascular border. In a subset of cases, PDTCs can also be associated with a better differentiated component showing typical microscopic features of papillary or follicular carcinoma variably admixed with poorly differentiated cells. The presence of oncocytic (Hürthle cell) features does not exclude a diagnosis of PDTC.

Criteria

Cellular preparations display an insular, solid, or trabecular cytoarchitecture (Figs. 10.1, 10.2, 10.3, and 10.4).

There is a uniform population of malignant follicular cells with scant cytoplasm (sometimes plasmacytoid) (Fig. 10.5) or with oncocytic features (Fig. 10.6).

The cells have a high nuclear/cytoplasmic (N/C) ratio with variable nuclear atypia (Figs. 10.7 and 10.8).

Colloid is scant.

Apoptosis and mitotic activity are present (Fig. 10.9).

Necrosis is often present (Fig. 10.10).

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

Explanatory Notes

Cytologically, PDTCs are difficult to recognize as such because they are rare; their cytomorphologic features overlap with those of follicular neoplasms; and their characteristic FNA features do not have great specificity. Based upon a limited number of published case reports and small series, aspirates of PDTC are often cellular with scant colloid [8–19]. The cells of PDTC have a monomorphic appearance at

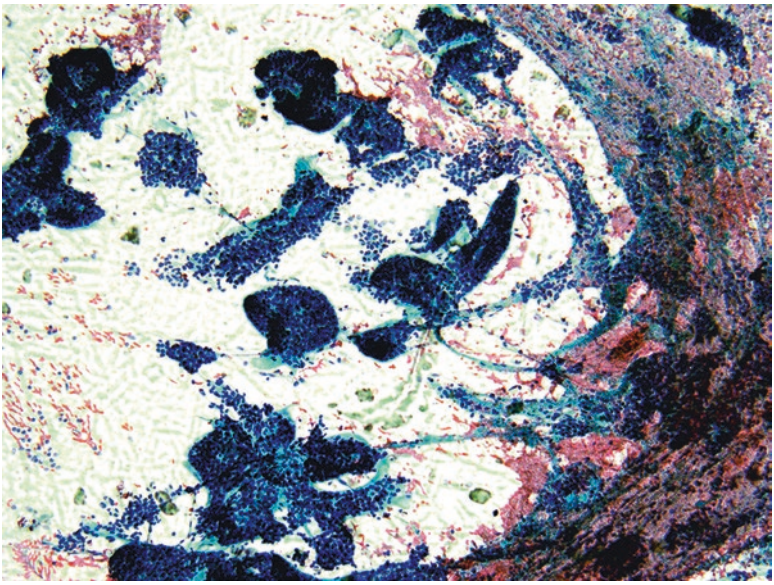

Fig. 10.1 Poorly differentiated thyroid carcinoma. A low magnification view reveals small follicular cells arranged in crowded insulae (smear, Papanicolaou stain).

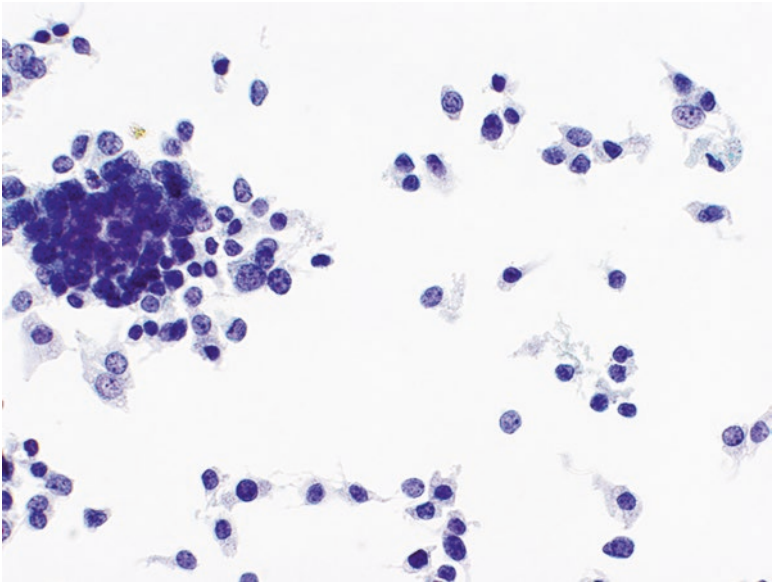

Fig. 10.2 Poorly differentiated thyroid carcinoma. The monomorphic cells are arranged in crowded three-dimensional groups and scattered as isolated cells (ThinPrep, Papanicolaou stain).

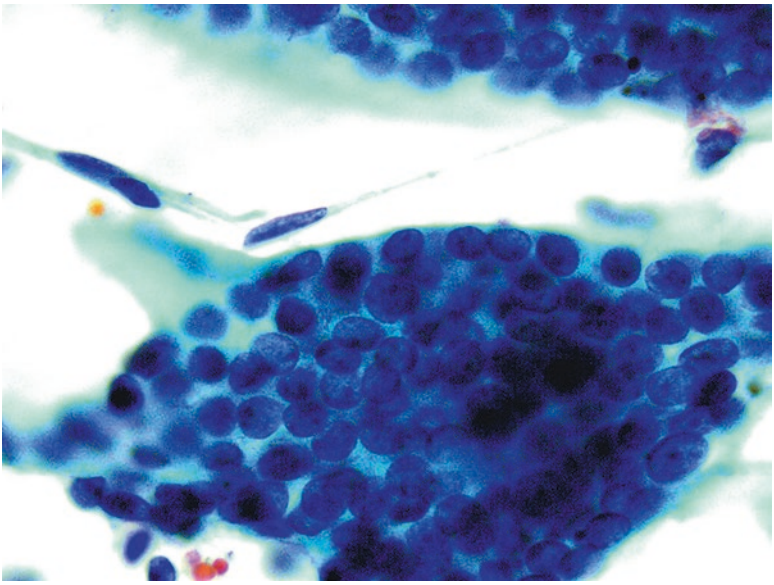

Fig. 10.3 Poorly differentiated thyroid carcinoma. Endothelium wrapping around cell groups can often be found highlighting the insular arrangements (smear, Papanicolaou stain).

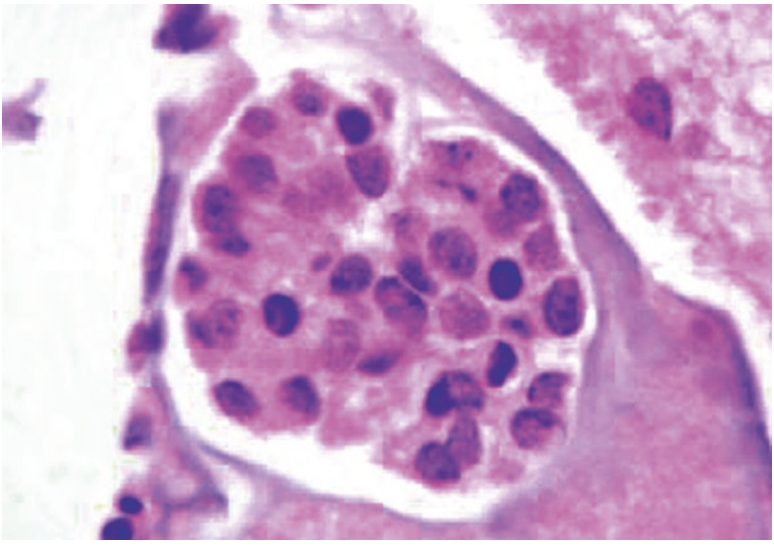

Fig. 10.4 Poorly differentiated thyroid carcinoma. This cell block demonstrates the arrangement of cells in insular groups (cell block, H&E stain).

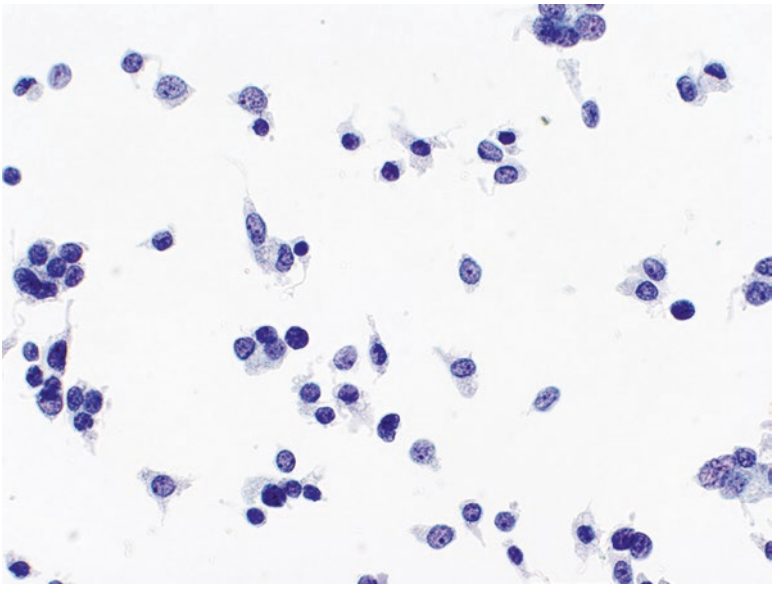

Fig. 10.5 Poorly differentiated thyroid carcinoma. In some cases, the malignant cells are arranged predominantly as isolated cells. They can have a plasmacytoid cytomorphology, as seen here (ThinPrep, Papanicolaou stain).

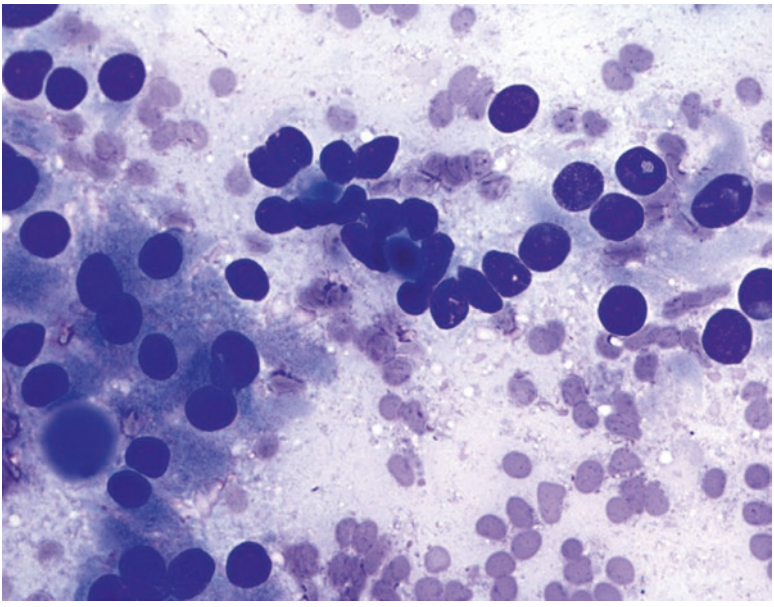

Fig. 10.6 Poorly differentiated thyroid carcinoma. In some cases, the cells have oncocytic cytoplasm. Some bare nuclei are also present (smear, Diff-Quik stain).

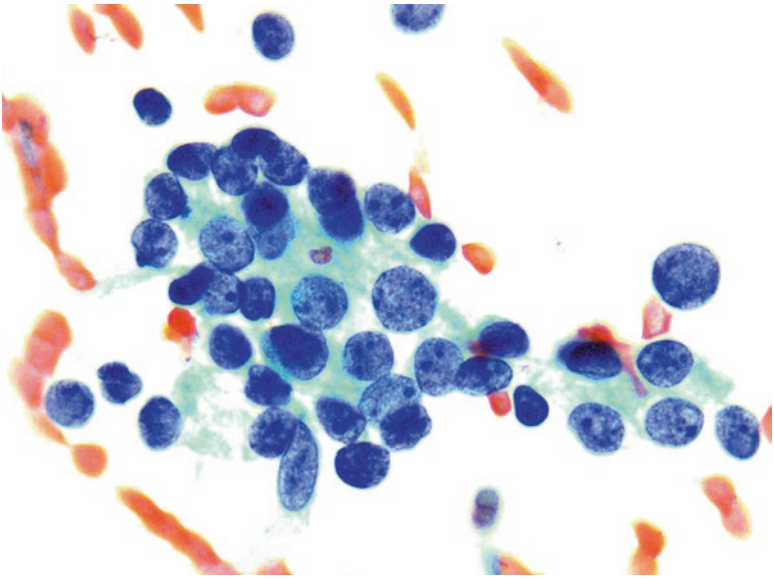

Fig. 10.7 Poorly differentiated thyroid carcinoma. Some tumors demonstrate only mild nuclear atypia, with small nucleoli and delicate chromatin (smear, Papanicolaou stain).

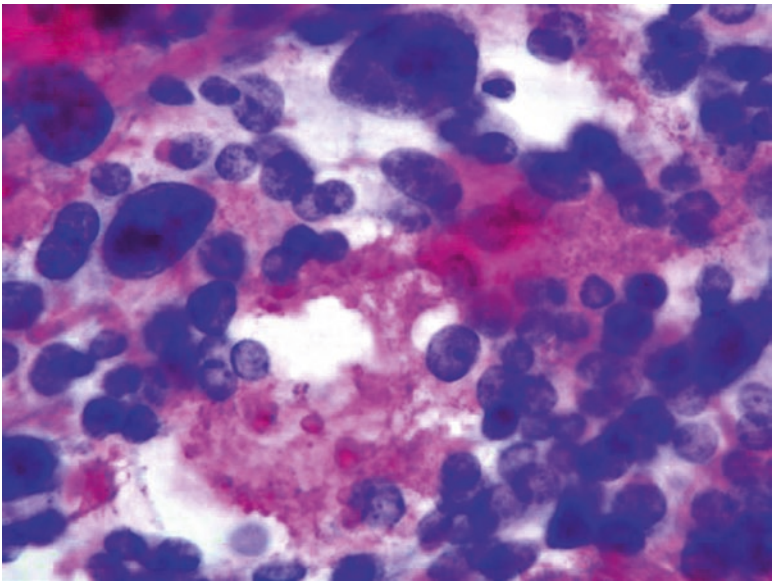

Fig. 10.8 Poorly differentiated thyroid carcinoma. Some aspirates exhibit marked nuclear atypia. In this example, there is impressive anisokaryosis (smear, Papanicolaou stain).

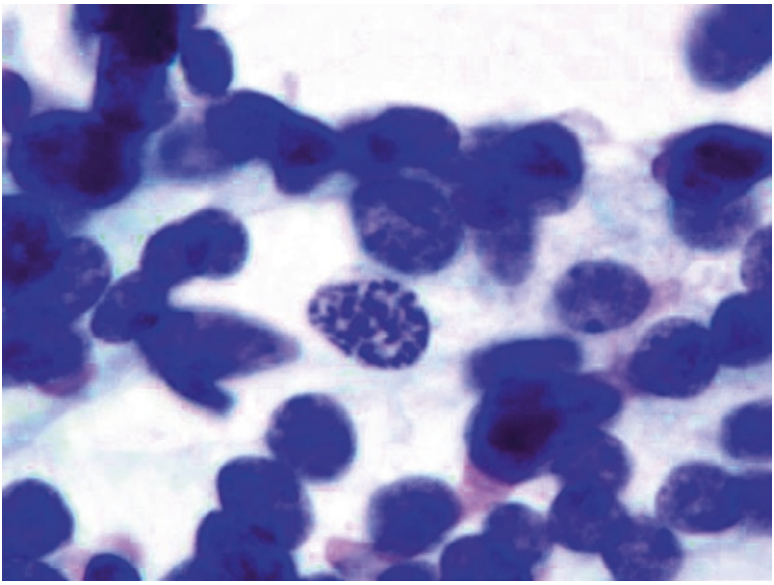

Fig. 10.9 Poorly differentiated thyroid carcinoma. Aspirates of poorly differentiated carcinomas often contain mitotically active cells (smear, Papanicolaou stain).

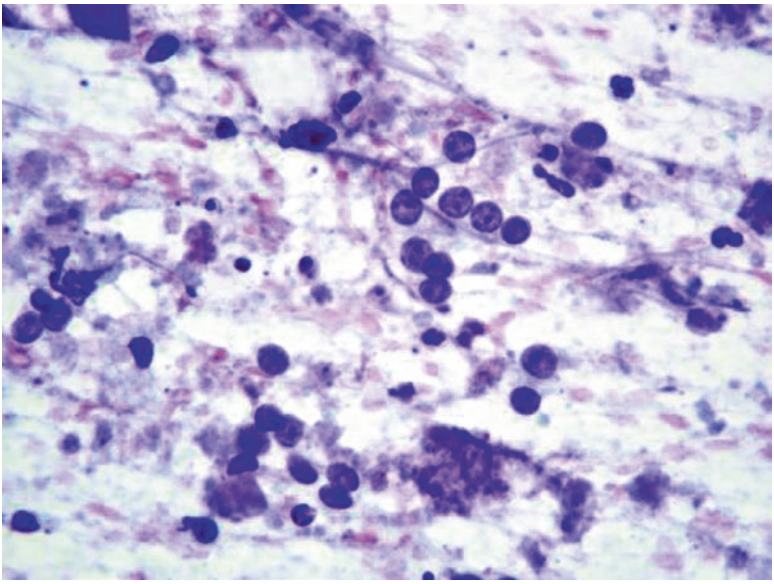

Fig. 10.10 Poorly differentiated thyroid carcinoma. Necrotic debris (cytoplasmic and nuclear fragments) is seen in some poorly differentiated carcinomas (smear, Papanicolaou stain).

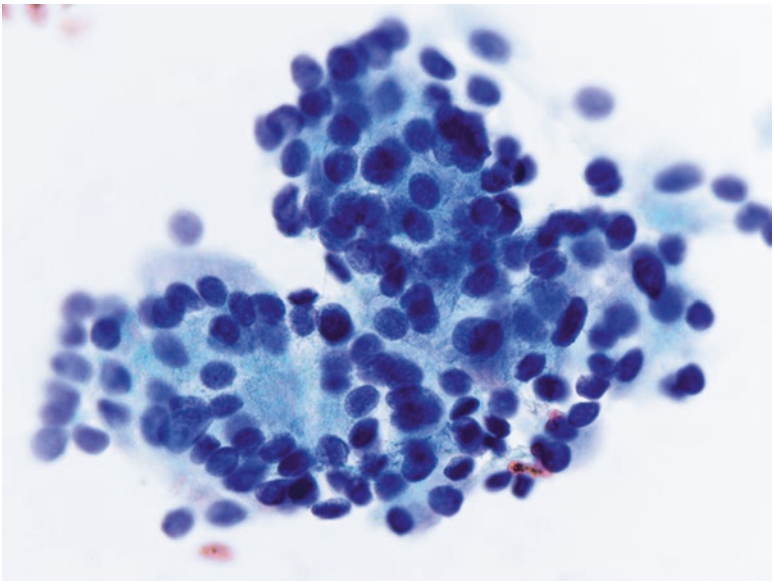

Fig. 10.11 Poorly differentiated thyroid carcinoma. The presence of microfollicles does not preclude the possibility of a poorly differentiated thyroid carcinoma (smear, Papanicolaou stain).

low magnification owing to their high N/C ratio and round nuclei, but at higher magnification variable degrees of atypia can be found along with abrupt nucleomegaly. Numerous isolated cells alternate with large solid fragments of mitotically active and apoptotic cells. The proportion of isolated cells versus fragments varies from case to case. Necrosis is often seen. The tumor cells are positive for keratins, thyroglobulin, thyroid transcription factor (TTF)-1, and PAX8 [20].

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. A similar pattern can be recognized in a subset of PDTC aspirates. Depending upon whether a well-differentiated component is also present, aspirates of PDTC can exhibit microfollicles (Fig. 10.11), nuclear grooves, and pseudoinclusions (Fig. 10.12). In the majority of cases, PDTCs are diagnosed cytologically as "suspicious for a follicular neoplasm." In two large series of PDTCs sampled by FNA, around 35% of cases were prospectively recognized as "poorly differentiated carcinoma" by FNA [17, 19]. 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, the features most predictive of PDTC were its characteristic cytoarchitecture (neither macrofollicular nor microfollicular), severe crowding, high N/C ratio, and isolated cells [19].

According to the authors of the WHO volume on *Pathology and Genetics of Tumours of Endocrine Organs*, "a definitive diagnosis of poorly differentiated carcinoma can be made only at the histological level" [3]. The combination of

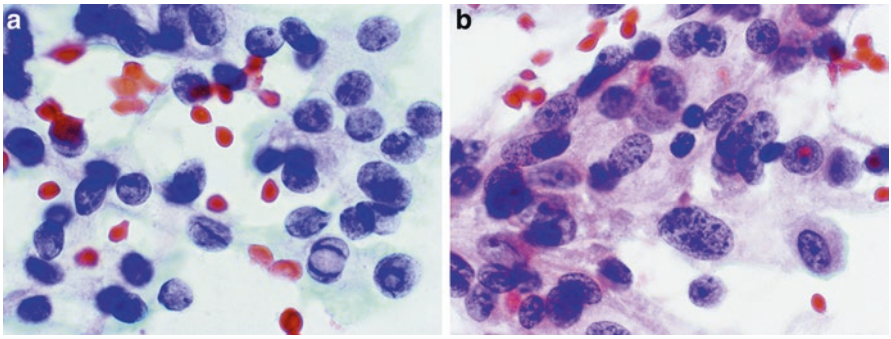

Fig. 10.12 Poorly differentiated thyroid carcinoma. (**a**) In some cases, tumors show features of papillary carcinoma, including nuclear grooves and pseudoinclusions. (**b**) There can be significant nuclear pleomorphism (**a**, **b**, smears, Papanicolaou stain).

cytomorphologic features described above, however, is suggestive of PDTC in FNA specimens. Clinical and ultrasonographic correlation is also helpful: PDTCs are usually large tumors with extrathyroidal extension.

Certain other primary thyroid tumors and metastatic malignancy 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 by immunocytochemistry. In contrast to medullary thyroid carcinoma, most PDTCs are strongly immunoreactive for thyroglobulin (Fig. 10.14) and negative for calcitonin and CEA. In addition, PDTCs are rarely immunoreactive for the neuroendocrine markers synaptophysin and chromogranin. TTF-1 is not useful for this distinction because both PDTC and medullary thyroid carcinoma are positive. Based purely on cytomorphology, a PDTC resembles a metastasis from an extrathyroidal primary tumor: both yield cellular specimens with nuclear atypia and necrosis and colloid is scant in both. The positive immunoreactivity of PDTCs for thyroglobulin, TTF-1 and PAX 8 [20] helps to exclude a metastasis. Undifferentiated (anaplastic) thyroid carcinomas are also characterized by unusual cytomorphologic patterns (see Chap. 11) together with necrosis and increased mitotic activity, but PDTCs lack the marked nuclear pleomorphism, high-grade atypia, and sarcomatoid features of undifferentiated carcinomas. 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). Recent studies have shown that immunohistochemical expression of p53 is often observed in PDTC [21].

Management

Because of their poor clinical prognosis, PDTCs are usually managed more aggressively than well-differentiated thyroid carcinomas, with consideration of postoperative ^{131}I therapy [22]. For stage T3 PDTCs without distant metastases, as

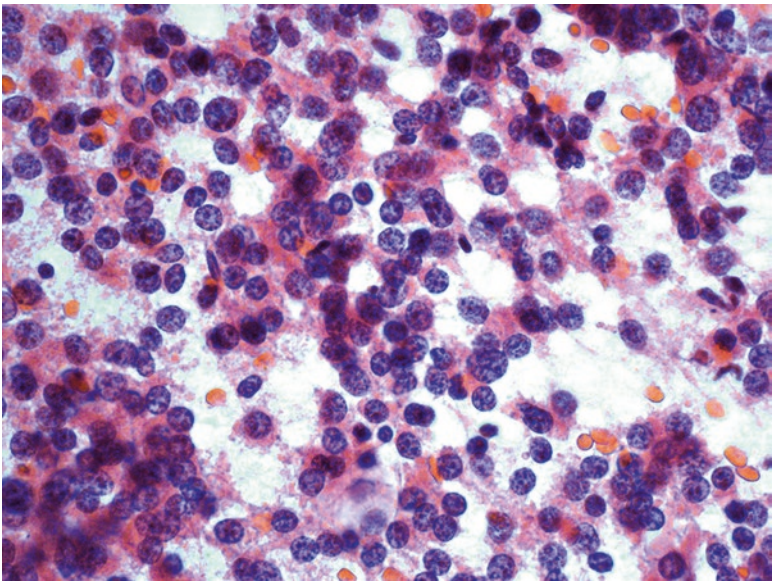

Fig. 10.13 Poorly differentiated thyroid carcinoma. Because some aspirates are comprised predominantly of isolated cells with granular chromatin, they mimic both medullary thyroid carcinoma and metastatic neoplasms (smear, Papanicolaou stain).

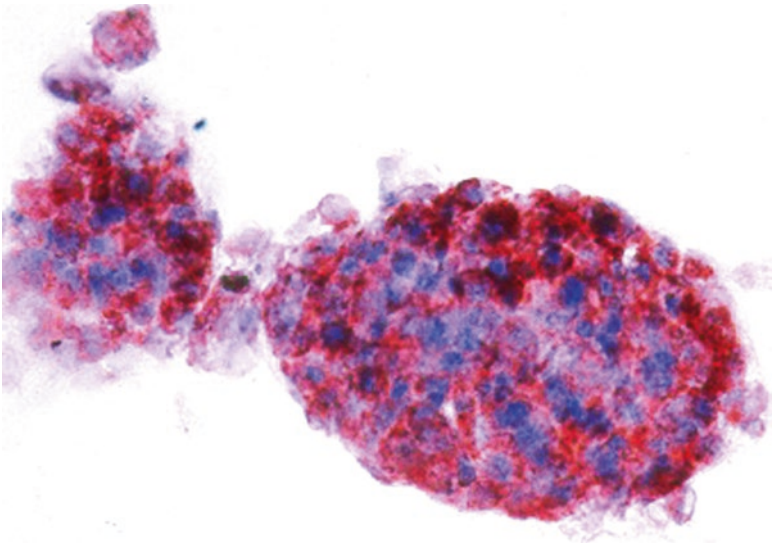

Fig. 10.14 Poorly differentiated thyroid carcinoma. Poorly differentiated thyroid carcinomas are positive for thyroglobulin, which helps to distinguish them from medullary thyroid carcinoma and metastatic tumors (ThinPrep, thyroglobulin immunoperoxidase reaction).

well as all T4 tumors and cases with regional lymph node involvement, patients benefit from external beam radiotherapy in addition to surgery.

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 "SUSPICIOUS FOR A FOLLICULAR NEOPLASM" (or "FOLLICULAR NEOPLASM").

Example 1
MALIGNANT.
Highly cellular aspirate with atypical follicular cells, necrosis, and scant colloid, most consistent with poorly differentiated thyroid carcinoma.

Example 2
MALIGNANT.
Papillary thyroid carcinoma with poorly differentiated features, suggestive of poorly differentiated thyroid carcinoma.

Example 3
SUSPICIOUS FOR A FOLLICULAR NEOPLASM.
Atypical follicular cells with a prominent isolated-cell component, focal necrosis, and mitotic activity.

Note: Immunostains on cell block sections show that the lesional cells are immunoreactive for thyroglobulin and TTF-1 and negative for calcitonin. The findings suggest the possibility of a poorly differentiated thyroid carcinoma.

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