Undifferentiated (Anaplastic) Carcinoma and Squamous Cell Carcinoma of the Thyroid

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Gregg A. Staerkel, Justin A. Bishop, Vinod B. Shidham, and Matthew A. Zarka

Background

Undifferentiated (anaplastic) thyroid carcinoma (UTC), also called "giant- and spindle-cell carcinoma," is an extremely aggressive thyroid malignancy. Accounting for less than 5% of thyroid cancers [1–3], it carries the poorest prognosis of all, significantly worse than well-differentiated and poorly differentiated thyroid carcinomas [4]. Most patients succumb to their disease within 6 months to 1 year of the initial diagnosis, typically as a result of tumor involvement of vital structures within the neck [2, 5]. Characteristic clinical features are associated with UTCs. These tumors are rarely seen in individuals below the age of 50 (<10% of cases) [3, 5, 6]. There is a female predominance (2–4:1) [3–7]. Patients present with a hard, nodular thyroid gland, and most have a rapidly growing mass. Neck enlargement is due to marked tumor growth, with or without reactive fibrosis, which infiltrates into surrounding extrathyroidal soft tissues, e.g., muscle, trachea, esophagus, and adjacent skin, cartilage, and bone [5]. Half of the patients with UTC report significant neck

G.A. Staerkel (✉)
Department of Pathology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 53, Houston, TX 77030, USA
e-mail: gstaerke@mdanderson.org

J.A. Bishop
Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

V.B. Shidham
Department of Pathology, Wayne State University School of Medicine, Karmanos Cancer Center & Detroit Medical Center, Detroit, MI, USA

M.A. Zarka
Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona, Scottsdale, AZ, USA

S.Z. Ali, E.S. Cibas (eds.), *The Bethesda System for Reporting Thyroid Cytopathology*, DOI 10.1007/978-3-319-60570-8_11

compression that can result in dyspnea, dysphagia, hoarseness, and/or pain [2, 5]. One-quarter to one-half of patients present with lymphadenopathy and/or distant metastases, most commonly to the lungs [2, 4, 6]. A history of long-standing goiter [2, 4, 6] and thyroid function tests indicating euthyroidism (despite extensive thyroid gland destruction) [2, 6] are common.

Definition

UTC is a high-grade, pleomorphic, epithelial-derived malignancy with epithelioid and/or spindle-cell features.

Criteria

Aspirates show variable cellularity but are usually moderately to markedly cellular.
Neoplastic cells are arranged as isolated cells and/or in variably sized groups.
Cells are epithelioid (round to polygonal) and/or spindle-shaped and range in size from small- to giant-sized. "Plasmacytoid" and "rhabdoid" cell shapes are seen.
Nuclei show enlargement, irregularity, extreme pleomorphism, clumping of chromatin with parachromatin clearing, prominent irregular nucleoli, intranuclear pseudoinclusions, eccentric nuclear placement, and multinucleation.
Necrosis, extensive inflammation (predominantly neutrophils, "abscess-like"), and/or fibrous connective tissue may be present.
Neutrophilic infiltration of tumor cell cytoplasm can be seen.
Mitotic figures are often numerous and abnormal.
Osteoclast-like giant cells (nonneoplastic) are conspicuous in some cases.
Tumors have the following immunocytochemical and molecular profile:

- Pan-keratins, PAX 8, and vimentin are often positive but can be focal.
- TTF-1 and thyroglobulin are usually negative.
- TP53, CTNNB1 (β-catenin), RAS (i.e., HRAS, KRAS, and NRAS), and BRAF V600E mutations are seen in up to 80%, 70%, 50%, and 30% of cases, respectively.

Explanatory Notes

Cellularity is variable. Some aspirates are sparsely cellular, due in part to the marked fibrosis and hyalinization seen in some tumors [7–9]. When fibrosis predominates, the resulting low cellularity can hamper interpretation (Fig 11.1). In other cases, widespread tumor necrosis yields a sparsely cellular sample with few viable malignant cells [7] (Fig. 11.2). Due to rapid infiltrative tumor growth, aspirations can result in the acquisition of tumor cells admixed with extrathyroidal tissue such as skeletal muscle (Fig. 11.3).

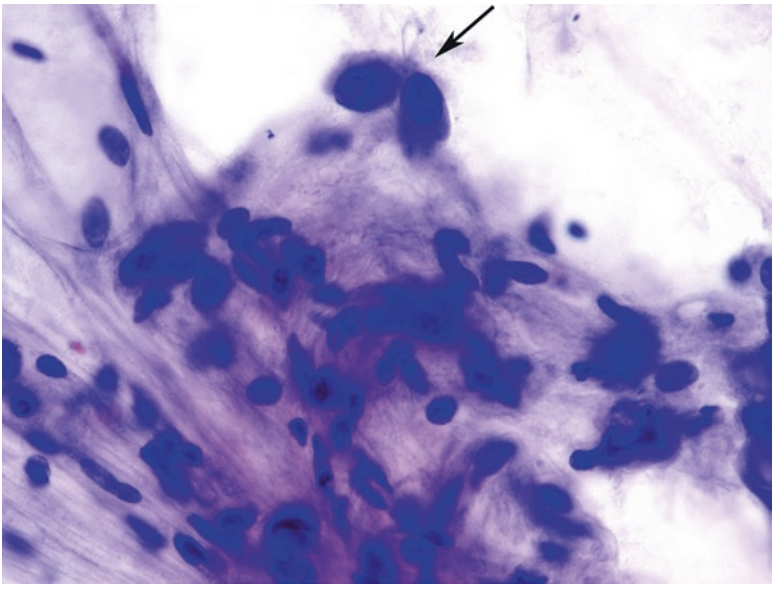

Fig. 11.1 Undifferentiated (anaplastic) thyroid carcinoma. Aspiration of tumors with abundant fibrosis can yield low cellularity. If cells lack marked nuclear atypia (*arrow*), rendering a definitive diagnosis can be difficult. Clinical correlation is important (smear, Papanicolaou stain).

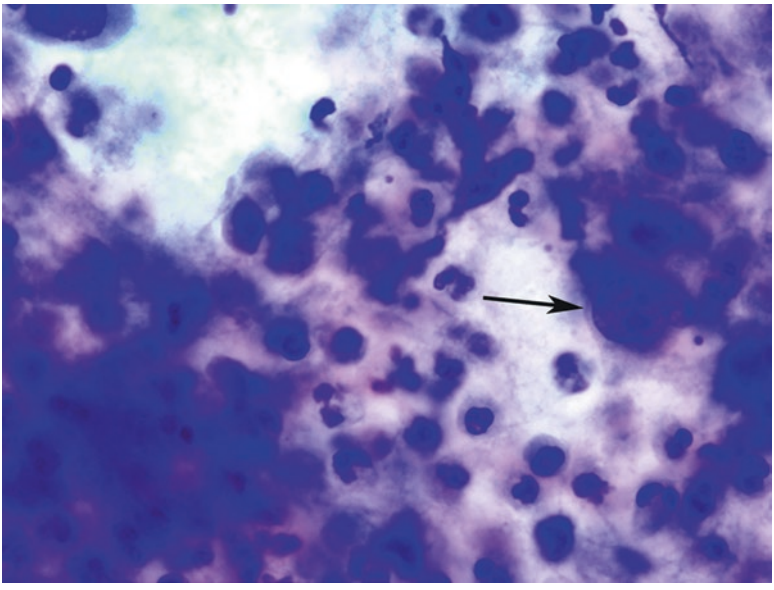

Fig. 11.2 Undifferentiated (anaplastic) thyroid carcinoma. Widespread tumor necrosis and associated inflammation can hinder diagnosis because well-preserved malignant cells are few and far between (*arrow*) (smear, Papanicolaou stain).

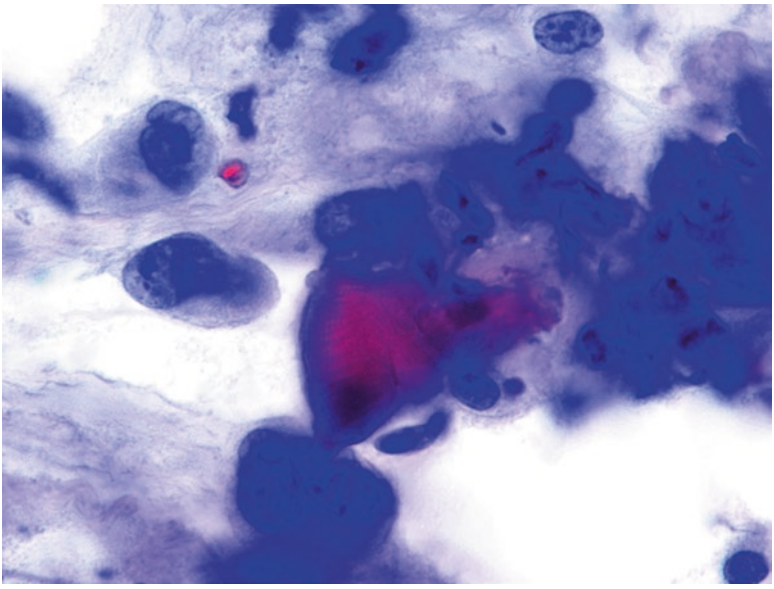

Fig. 11.3 Undifferentiated (anaplastic) thyroid carcinoma. Rapid tumor growth and invasion of extrathyroidal tissues is common. Aspiration samples can contain skeletal muscle fragments (*center*) as well as anaplastic tumor cells (smear, Papanicolaou stain).

Isolated cells and small- to medium-sized cell groups can be found in most cases (Figs. 11.4, 11.5, 11.6, and 11.7). In spindle-cell predominant UTCs, larger tumor tissue fragments can reveal a storiform-like pattern [6] (Fig. 11.8). Follicles, papillae, and trabecular/nested cell groups are not features of UTC.

Small to gigantic malignant cells may be epithelioid (round to polygonal) or spindle-shaped [7, 10, 11] (Figs. 11.4, 11.5, 11.6, and 11.7). A given tumor often displays a mixture of cell shapes and sizes (Figs. 11.4 and 11.9). Nuclear pleomorphism can be striking, with giant, bizarre, hyperchromatic forms [7, 10, 11] (Figs. 11.10 and 11.11). Nuclei may be variably positioned within the cells, but can be uniformly eccentric, resulting in a plasmacytoid morphology [7] (Fig. 11.12). Intranuclear cytoplasmic pseudoinclusions (Fig. 11.13), prominent nucleoli (Fig. 11.14), coarse chromatin (Fig. 11.6), and parachromatin clearing (Fig. 11.14) may be identified [7, 10, 11]. Neutrophilic infiltration of tumor cells (Fig. 11.15), osteoclast-like giant cells (Fig. 11.16), necrosis, fibrotic tissue fragments, and mitotic figures (Fig. 11.5) may be present in variable proportions [7–11].

Some UTCs have a focus of coexisting well-differentiated and/or poorly differentiated thyroid carcinoma, most often papillary thyroid carcinoma [5, 6, 9–11], but sometimes follicular carcinoma [5, 6, 12], Hürthle cell carcinoma [5, 6], insular carcinoma [4, 10] and other types of poorly differentiated carcinomas, or medullary thyroid carcinoma. Consequently, on occasion several components are observed in an aspirate. Hence, thorough sampling and attention to the possibility of multiple components are imperative so that the identification of the most significant

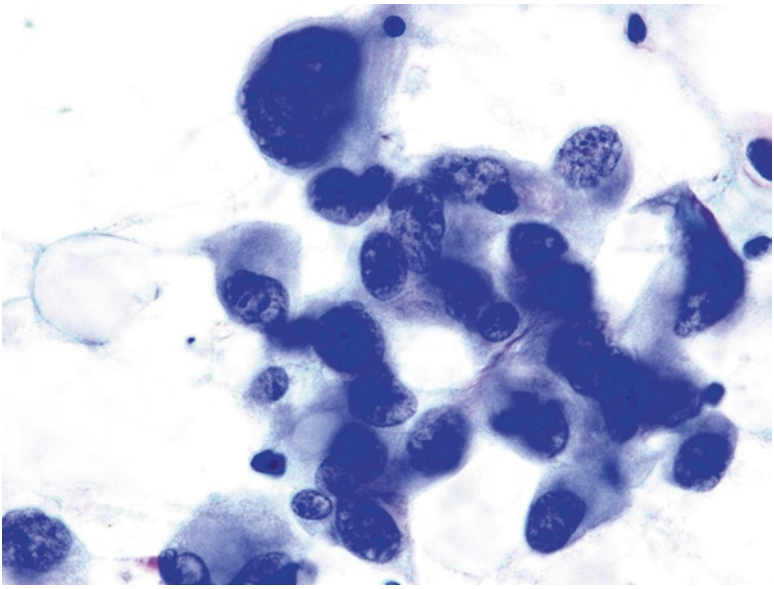

Fig. 11.4 Undifferentiated (anaplastic) thyroid carcinoma. Cells are epithelioid (polygonal) in appearance. Variation in cell and nuclear size is evident. Parachromatin clearing and nuclear contour irregularity are prominent (smear, Papanicolaou stain).

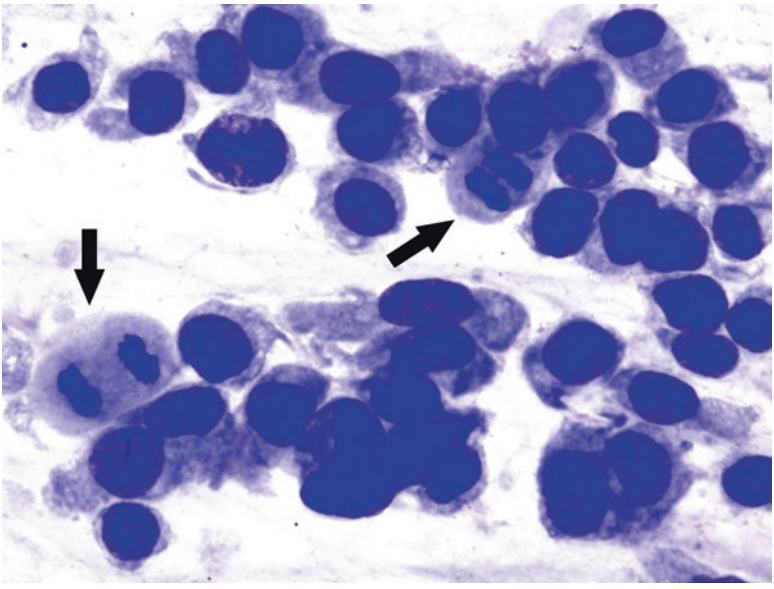

Fig. 11.5 Undifferentiated (anaplastic) thyroid carcinoma. The neoplastic cells are mostly round, with scant to moderate cytoplasm. There is less pleomorphism of nuclear size and shape than in most cases of UTC, but mitotic figures (*arrows*) are easily found (smear, Diff-Quik stain).

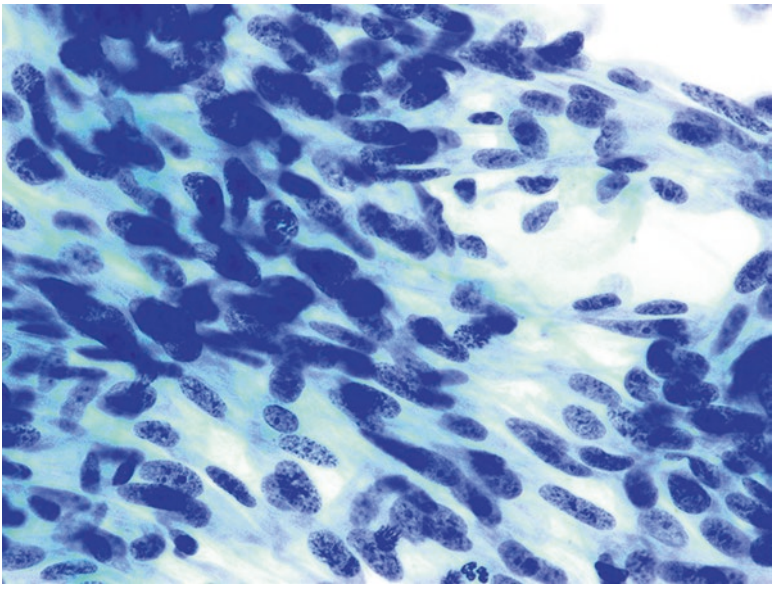

Fig. 11.6 Undifferentiated (anaplastic) thyroid carcinoma. All neoplastic cells are strikingly spindle-shaped, resembling the cells of a sarcoma. Although chromatin is coarse, parachromatin clearing, prominent nucleoli, and nuclear irregularity are not apparent (smear, Papanicolaou stain).

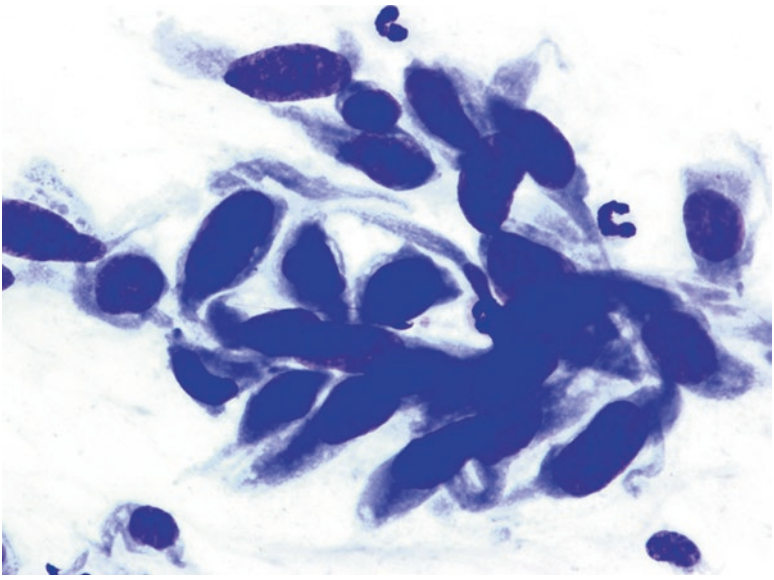

Fig. 11.7 Undifferentiated (anaplastic) thyroid carcinoma. Tumor cells are notably spindle-shaped, with long, tapering cytoplasmic processes (smear, Diff-Quik stain).

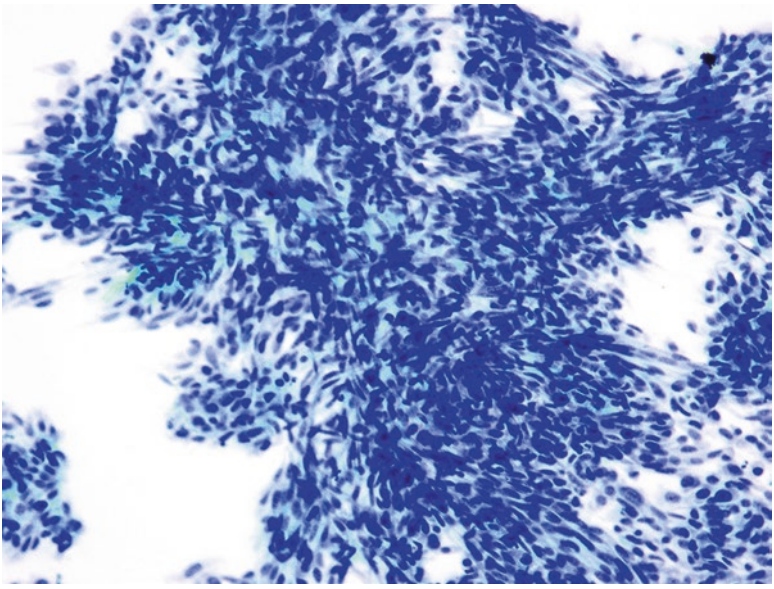

Fig. 11.8 Undifferentiated (anaplastic) thyroid carcinoma. Tumors with a predominantly spindle-cell morphology can appear as microbiopsy fragments. A storiform pattern can be appreciated (smear, Papanicolaou stain).

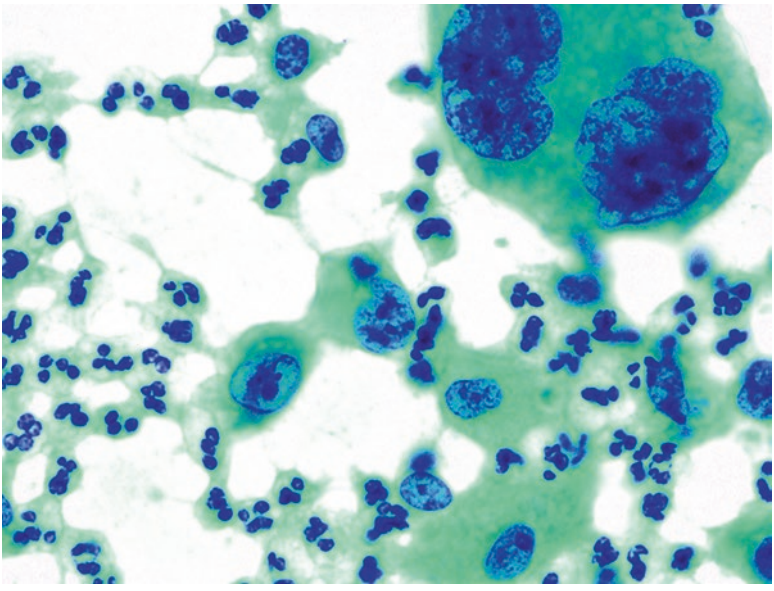

Fig. 11.9 Undifferentiated (anaplastic) thyroid carcinoma. These tumors can be associated with abundant inflammatory cells, typically neutrophils. A multinucleated tumor giant cell with bizarre nuclear features and smaller, isolated, less anaplastic malignant cells are readily identifiable (smear, Papanicolaou stain).

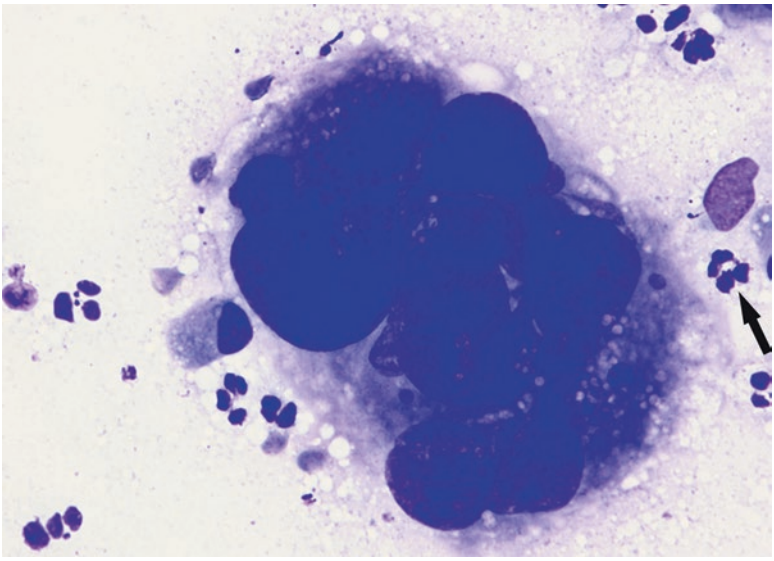

Fig. 11.10 Undifferentiated (anaplastic) thyroid carcinoma. Bizarre multinucleated tumor giant cells are found in some aspirations. The size of this tumor giant cell can be fully appreciated when compared to the adjacent neutrophils (*arrow*) (smear, Diff-Quik stain).

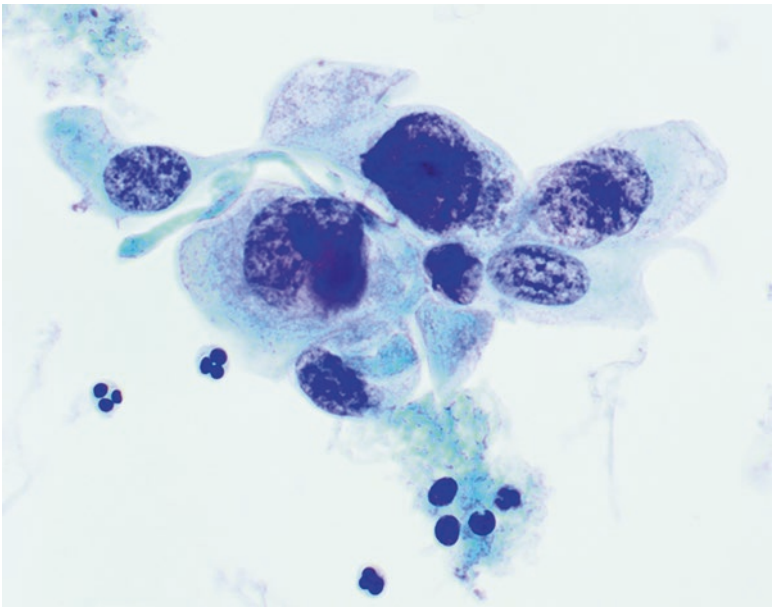

Fig. 11.11 Undifferentiated (anaplastic) thyroid carcinoma. Variably pleomorphic tumor giant cells with coarse chromatin are seen in a loosely cohesive cell group (ThinPrep, Papanicolaou stain).

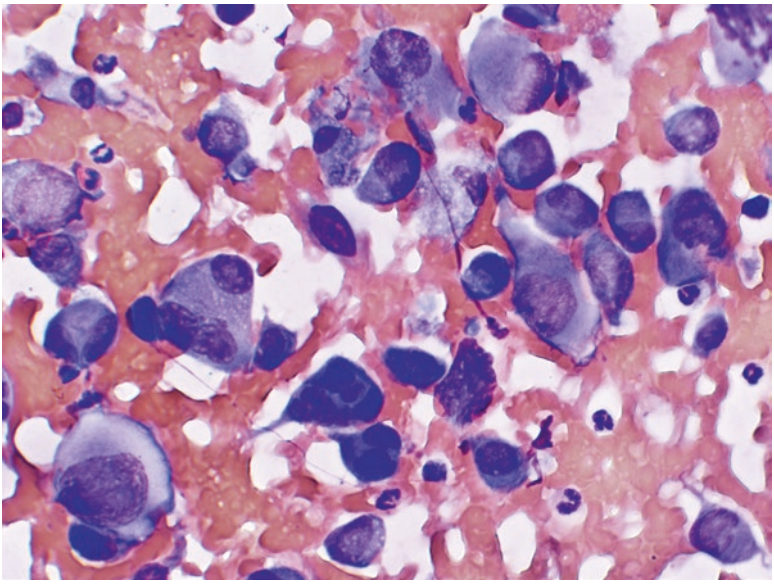

Fig. 11.12 Undifferentiated (anaplastic) thyroid carcinoma. In some cases, the epithelioid tumor cells have a conspicuously plasmacytoid appearance (smear, Diff-Quik stain).

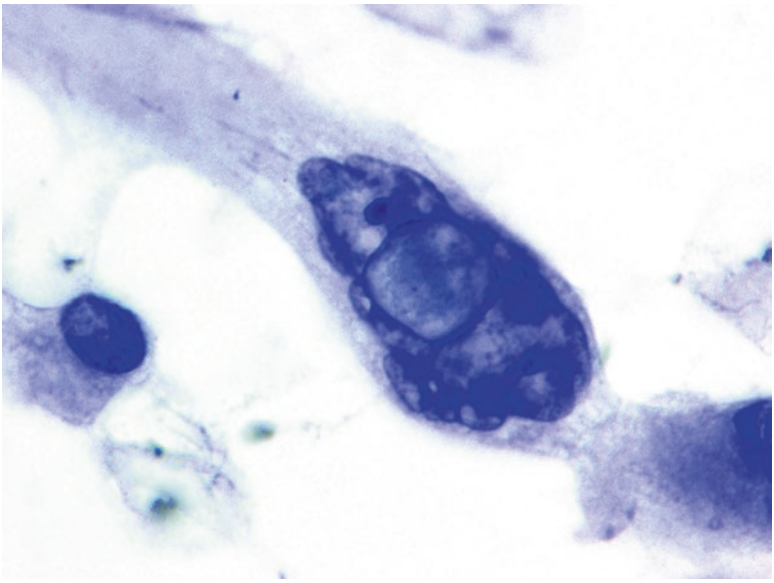

Fig. 11.13 Undifferentiated (anaplastic) thyroid carcinoma. A giant spindle-shaped tumor cell has a massive intranuclear cytoplasmic pseudoinclusion. Other nuclear features include enlargement, contour irregularity, and a prominent nucleolus (smear, Papanicolaou stain).

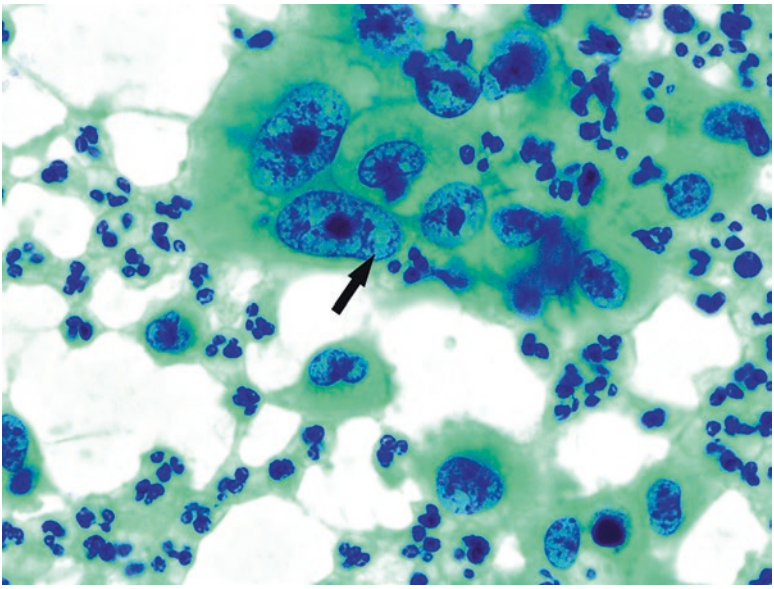

Fig. 11.14 Undifferentiated (anaplastic) thyroid carcinoma. Epithelioid tumor cells display size variation, mononucleated and binucleated forms, macronucleoli, and clumped chromatin with parachromatin clearing (*arrow*). Acute inflammatory cells are present in the background (smear, Papanicolaou stain).

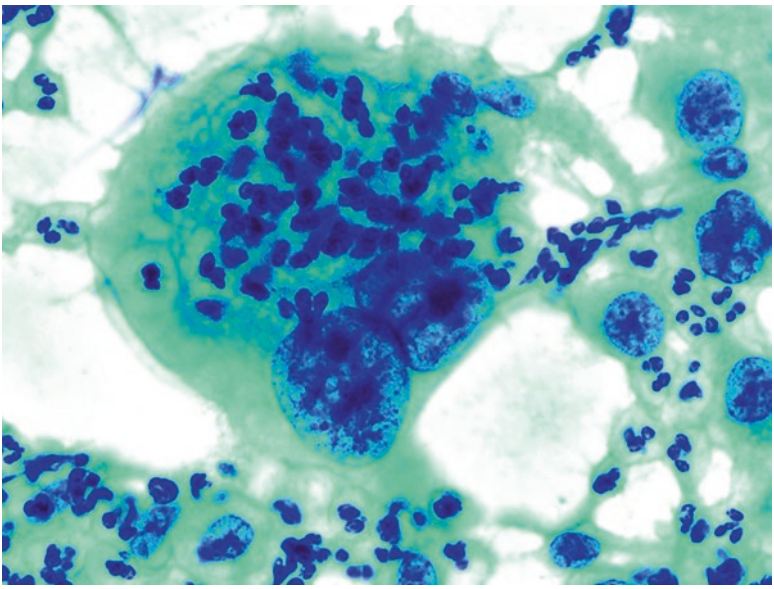

Fig. 11.15 Undifferentiated (anaplastic) thyroid carcinoma. There is conspicuous infiltration of a multinucleated tumor giant cell by neutrophils (smear, Papanicolaou stain).

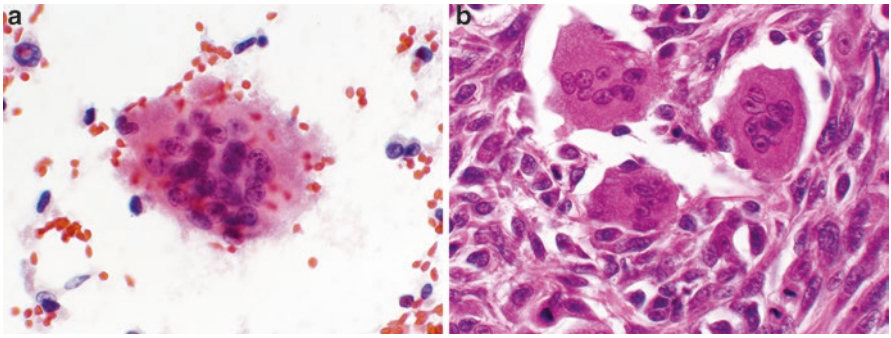

Fig. 11.16 Undifferentiated (anaplastic) thyroid carcinoma. (**a**) Some UTCs contain numerous nonneoplastic, osteoclast-like giant cells (smear, Papanicolaou stain). (**b**) The osteoclast-like giant cells are scattered among the malignant cells (thyroidectomy, hematoxylin and eosin stain).

(i.e., least differentiated) cellular pattern is made. The frequent coexistence of a nidus of well-differentiated thyroid cancers within a UTC suggests that UTC represents dedifferentiation of a well-differentiated thyroid cancer through a multistep process of carcinogenesis [2, 12]. This is supported by the occasional observation of UTC in metastatic foci from patients whose primary thyroid carcinomas were well differentiated [5, 12].

The most reliable immunostains yielding a positive result in UTCs are as follows: pan-keratins, with rates of expression ranging from 50% to 100% of cases [6, 13]; PAX8 (the most specific immunostain indicative of UTC's thyroid gland origin), seen in 76–79% of cases [14–16] (Fig. 11.17); and vimentin, present in 50–100% of cases, especially in the spindle-cell tumor component [6, 14]. Because thyroglobulin and TTF-1 are usually negative [6, 13] and PAX8 is negative in a quarter of cases, challenges occur with sparsely cellular samples or aspirates of spindle-cell tumors that are negative for keratins. In these cases, an erroneous diagnosis of sarcoma might be entertained, but primary sarcomas of the thyroid are rare. Therefore, determining that the tumor is centered in the thyroid gland based on imaging findings can help resolve this concern. Other entities in the differential diagnosis of UTC include insular thyroid carcinoma, medullary thyroid carcinoma, lymphoma, and a metastasis. Compared to UTC, insular carcinoma has a lesser degree of nuclear atypia (lacking prominent nucleoli), a strikingly monotonous appearance with a trabecular/nested architecture, and lacks spindle-shaped cells and osteoclast-like giant cells. Medullary thyroid carcinoma, overall, is usually less pleomorphic than UTC, has finely stippled chromatin, and usually contains amyloid. Osteoclast-like giant cells and necrosis are absent in medullary carcinoma. If doubt remains after morphologic assessment, immmunochemistry can be helpful, inasmuch as medullary carcinomas are reactive for calcitonin and chromogranin, and UTCs are negative. The most difficult mimic to exclude is often a metastasis (e.g., melanoma, sarcomatoid renal cell carcinoma, squamous cell or large cell

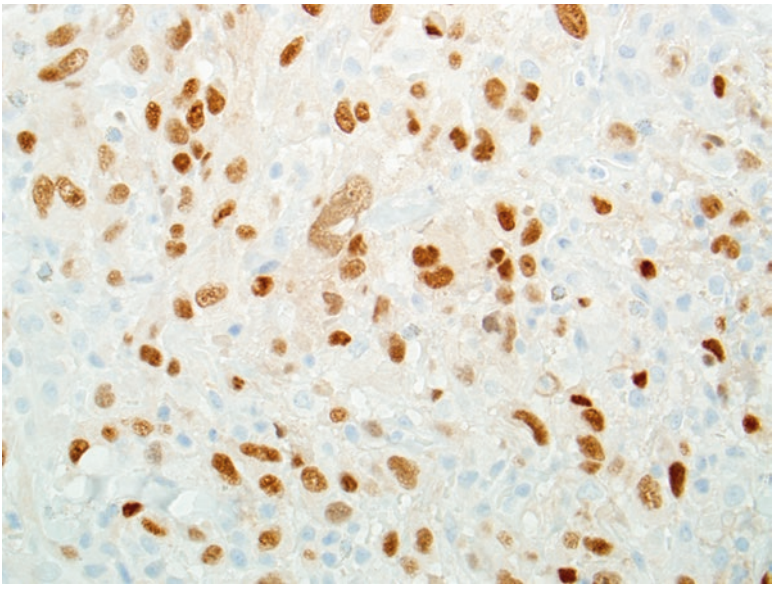

Fig. 11.17 Undifferentiated (anaplastic) thyroid carcinoma. PAX8, one of the most useful immunomarkers in this setting, displays crisp nuclear positivity (cell block, PAX8 immunostain).

carcinoma of the lung). Ruling out a thyroid metastasis requires knowledge of the patient's prior cancer history, clinical correlation (e.g., the size and the anatomic distribution of other extrathyroidal tumor masses), and selective immunostaining.

In paucicellular aspirates due to necrosis and/or fibrosis, an underappreciation of rare malignant cells can lead to a misdiagnosis of a reactive process (e.g., Riedel thyroiditis) [8].

Molecular alterations that are seen with some frequency include the early thyroid carcinogenesis mutations of RAS and BRAF (up to 50% and 30% of cases, respectively) and the late carcinogenesis mutations of TP53 and CTNNB1 (β-catenin) which lead to progressive loss in thyroid differentiation (up to 80% and 70% of cases, respectively) [14, 17].

Management

The overall survival of patients with UTC has not changed significantly in over 20 years. One-fifth of patients require tracheostomy due to airway obstruction during the course of their disease [18].

Complete surgical resection, with or without preoperative hyperfractionated radiotherapy and/or chemotherapy to enhance resectability through tumor shrinkage, is the optimal treatment strategy [1, 18]. Suppression with radioactive iodine is

largely ineffective for the treatment of UTC [1, 5, 18]. In cases where potential cure cannot be achieved, reducing the tumor burden through surgery facilitates the efficacy of postoperative radiation and/or chemotherapy [18]. In patients fit enough to tolerate these regimens, length of survival is improved [6, 18]. Not surprisingly, younger patients (<45 years old) and individuals with smaller tumors without extensive extrathyroidal extension or metastases have the best outcome [3, 5, 6]. The advent of novel therapies such as molecular targeted treatments holds promise; to date, they are largely directed at the BRAF mutation [19]. Other mutation targets are found in much lower frequencies than BRAF, which in turn suggests a more limited potential role for other targeted therapies. One patient with such a mutation in the mTOR pathway showed a dramatic 18 month response to the mTOR inhibitor Everolimus until resistance developed [20].

Squamous Cell Carcinoma of the Thyroid

Squamous cell carcinoma (SQC) of the thyroid accounts for less than 1% of thyroid cancers. Like UTC, it occurs in the elderly and has a similar (dismal) prognosis.

Definition

Squamous cell carcinoma of the thyroid is a malignant tumor that shows exclusively squamous differentiation.

Criteria

Cytologic samples are composed almost exclusively of large, pleomorphic keratinized cells.
Necrosis may be present.

Explanatory Notes and Management

Most squamous cell carcinomas of the thyroid are poorly differentiated. The differential diagnosis includes UTC and metastatic SQC. Primary squamous cell carcinomas of the thyroid are morphologically and immunochemically indistinguishable from squamous cell carcinomas of other organs (Fig. 11.18). For this reason, correlation with clinical and imaging findings is essential for excluding a metastasis. The behavior of squamous cell carcinomas of the thyroid is similar to that of UTC, as is the clinical management. In fact, given that squamous cell carcinoma sometimes coexists with UTC and is frequently PAX8 positive, it may simply represent a form of UTC.

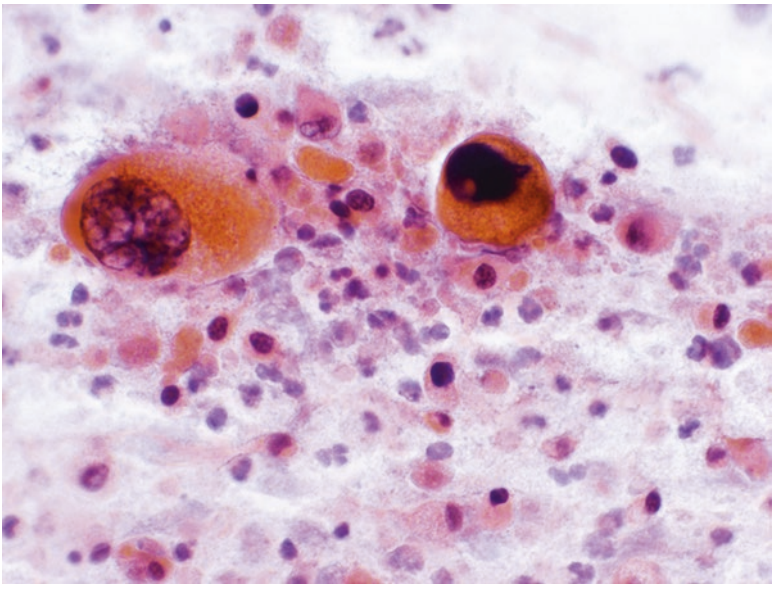

Fig. 11.18 Squamous cell carcinoma of the thyroid. The sample is composed of large pleomorphic cells with conspicuous dense orangeophilia of the cytoplasm. There is abundant necrosis, and nuclei show degenerative changes (i.e., dark, smudged, and/or marginated chromatin) (smear, Papanicolaou stain).

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.
Undifferentiated (anaplastic) thyroid carcinoma.

Note: Immunocytochemistry shows that the malignant cells are focally immunoreactive for pan-cytokeratins AE1/3 and PAX8 and negative for thyroglobulin and TTF-1.

Example 2
MALIGNANT.
High-grade carcinoma, consistent with undifferentiated (anaplastic) thyroid carcinoma.

Note: Immunocytochemistry shows that the malignant cells are focally immunoreactive for cytokeratins AE1/3, PAX8, and vimentin and negative for thyroglobulin, TTF-1, HMB-45, and S-100 protein. The prior clinical history of malignant melanoma is noted.

Example 3
MALIGNANT.
Consistent with squamous cell carcinoma of the thyroid.

Note: The distinction between a primary squamous cell carcinoma of the thyroid and a metastasis to the thyroid from a primary elsewhere is not possible by cytomorphology or immunochemistry. Correlation with clinical and imaging findings is advised.

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