(26–29). However, the cytological diagnosis of aggressive types of thyroid cancer, especially ATC, can be challenging (30) and is often associated with interobserver variability (31). The diagnostic yield of FNA is highly variable, but the diagnosis of ATC can be obtained in the majority of cases (>60%) (31,32), especially when the aspirate is highly cellular and immunohistochemistry (IHC) can be performed using a ''cell block'' using the IHC markers discussed below (33,34). In those cases in which the cellular yield is insufficient, core biopsy may be diagnostic (35). However, such biopsies may also be nondiagnostic due to sampling issues related to the presence of tumor necrosis and reactive and inflammatory changes; hence, ultrasound guidance is helpful to identify solid areas or nodal disease that may be more suitable for biopsy. FNA of the paucicellular variant of ATC has been technically infeasible due to the inability to obtain sufficient cells (36). Molecular analysis can be performed on FNA materials (37), but core biopsy often permits a broader range of genomic testing. Rarely, some cases of ATC are only diagnosed after surgical/open biopsy or surgical resection despite undergoing FNA and/or core biopsy.

Histopathology

The diagnosis of many thyroid tumors, especially ATC, includes clinical, biochemical, radiographic, and histomorphologic evaluations. While the diagnosis of ATC is often suspected in older patients with large, symptomatic, and rapidly growing neck masses, the diagnosis of ATC ultimately rests on tissue-based pathological assessment to confirm the diagnosis and exclude other treatable entities that may have significantly better prognoses and other treatments.

The WHO defines ATC as ''a highly aggressive thyroid malignancy composed of undifferentiated follicular thyroid cells'' (WHO Classification of Tumours of Endocrine Organs, IARC 2017, Lyon, France). Several synonyms are recognized, including undifferentiated thyroid carcinoma, plus several others that reflect specific morphological features (e.g., sarcomatoid carcinoma). The histopathological spectrum of ATC is highly variable (38,39), which creates diagnostic challenges and reflects the marked degree of underlying genetic and genomic complexity that has recently been illuminated. Despite this wide variation, several morphological subtypes have been recognized, including sarcomatoid or spindle cell, giant cell, and squamoid or epithelial (40,41). Many tumors display mixed morphologies with the combination of spindle cell and giant cell being a common presentation. Significant mixed chronic inflammation is usually present in ATCs (42,43). Rare subtypes have also been recognized, including the paucicellular variant (44), which is characterized by abundant hypocellular fibrous tissue, and the rhabdoid (45–47), angiomatoid (48,49), and lymphoepithelial variants. Recognizing the wide spectrum of histological variation is diagnostically useful, but is generally not prognostically nor otherwise clinically significant and can add confusion in diagnosis.

ATCs are highly invasive tumors characterized by tumor cell infiltration of adjacent thyroid and other tissues, as well as lymphatic and blood vessel invasion and of high potential for distant metastases. All ATCs are characterized by a high degree of cellular proliferation regardless of the specific morphological subtype observed. Accordingly, high mitotic rates (>1 mitoses per hpf) and high Ki-67 proliferation indices (generally >30% but usually higher) are expected (50,51), and the absence of proliferation suggests an alternative diagnosis. Atypical mitoses are also very common, which reflects ATC's underlying genomic instability. Confluent areas of tumor necrosis are common, best observed in resection specimens and large biopsies, and may confound the diagnostic process. Heterologous elements, such as malignant bone and cartilage, have been described; hence, the use of the term carcinosarcoma by some authors. ATCs uniformly represent high-grade undifferentiated neoplasms; accordingly there is no established grading scheme.

The diagnosis of ATC is straightforward when a coexistent differentiated carcinoma, commonly a tall cell variant or other high-grade variant of PTC (52), is identified and intimately admixed with an undifferentiated component (53). Thus, extensive tissue sampling of resection specimens is recommended to increase the likelihood of sampling the often minority differentiated component. Recent genomic studies of such mixed cases demonstrate common molecular alterations (24,25,54,55), reflecting their shared lineage and supporting a model in which ATC often arises from preexiting differentiated carcinomas.

Immunohistochemistry

The use of IHC is essential in the diagnostic evaluation of ATC, with the only possible exception being unequivocal cases that contain a form of coexistent differentiated carcinoma as mentioned above. As a general rule, thyroid-specific proteins such as thyroglobulin (TG) and thyroid-lineage markers such as thyroid-transcription factor 1 (TTF-1) are expected to be absent, reflecting the undifferentiated nature of ATC (41,50,56,57). Significant expression of TG or TTF-1 indicates higher levels of thyroid differentiation than predicted based on morphology alone and suggests other diagnoses may be more appropriate. However, expression of another thyroid-lineage marker, PAX8, is retained in 40–60% of ATCs, at least focally (50,58–60). Thus, immunohistochemical detection of PAX8 can provide essential affirmative evidence of follicular cell origin and supports a diagnosis of ATC in the proper morphological context of an otherwise undifferentiated high-grade neoplasm. However, PAX8 expression is not restricted to thyroid and occurs in the kidney and Müllerian system (61). Thus, renal cell and ovarian carcinomas must be entertained in the differential diagnosis, but neither prominently or commonly involve the thyroid gland. Furthermore, some PAX8 antibodies can cross-react with PAX5 (62,63), a B cell lineage marker that is expressed in some large B cell lymphomas (64). Thus, PAX8 IHC must be interpreted in the proper morphological context and as part of a broad panel of IHC markers.

IHC for cytokeratins can be useful in many cases, especially those in the epithelial nature of the neoplasm are not readily apparent by morphology, such as the spindle cell and giant cell variants (41,65,66). However, the complete absence of cytokeratin expression does not eliminate a diagnosis of ATC.

In some cases, especially where it may be difficult to assess proliferation by mitotic activity (e.g., small biopsies), cellular proliferation can be assessed by Ki-67 IHC. In general, ATCs