Recognizing the Limitations and Pitfalls of Cytology for Anaplastic Carcinoma within Hürthle Cell (Oncocytic) Carcinomas

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Introduction

Comprising roughly 4% of all thyroid cancers, Hürthle cell follicular carcinoma (HCFC) is a well-differentiated malignant tumor of the thyroid gland composed of mitochondrial-rich oncocytes. Although most authors continue to consider it a variant of follicular cell carcinoma, HCFC has somewhat more aggressive behavior with an increased incidence of invasion and a higher predilection for lymphatic invasion [1]. Cytologic evaluation shows an abundance of oncocytic cells characterized by abundant polygonal cytoplasm, distinct cell borders, large nucleoli and large nuclei with occasional pleomorphism and atypia [1]. Hürthle cell neoplasms are typically well-encapsulated and considered malignant only when capsular invasion or lymphovascular invasion is noted [2]. While still showing some level of positivity in many cases, there appears to be decreased levels of TTF-1, TG and BCL-2 in Hürthle cell adenomas and carcinomas compared with the surrounding thyroid tissue [3] and low levels of cyclin D1 positivity [4].

Unlike HCFC, the diagnosis of undifferentiated or anaplastic thyroid carcinoma (ATC) is based on cytologic features with necrosis rather than evaluation of a capsule. ATC is one of the most aggressive and swiftly fatal tumors. Accounting for 5% of thyroid cancers, it typically arises from a background of well-differentiated thyroid carcinomas [5,6] and has been documented to rarely arise from a Hürthle cell neoplasm [7,8]. Hunt et al. describes a high rate of allelic loss in Hürthle cell carcinomas, which would require less additional mutations to transform to ATC when compared to papillary thyroid carcinomas [9]. The clinical presentation of ATC is typically a rapidly enlarging tumor with invasion into surrounding thyroid tissue and adjacent neck structures. Histologically, it is very pleomorphic with striking atypia, multinucleated giant cells, spindled or squamoid cells, mitotic figures and necrosis [10]. ATC has a very high proliferative rate, in some studies surpassing 30% by MIB-1 staining, as well as an increased level of p53 staining as compared to well-differentiated thyroid tumors. In addition, these anaplastic neoplasms are often TTF-1 and thyroglobulin (TG) negative [11,12] and cyclin D1 positive [13] which could possibly aid in distinguishing them from follicular carcinoma variants.

We discuss the role of FNA in the diagnostic process of thyroid lesions alongside clinical, radiographic and histological findings; as well as the potential pitfalls of this modality in the context of these two case reports.
Case Report

Case 1

The patient, a 44 year old female, noticed a painless rapidly enlarging right neck mass that had been present for the past 1.5 months. She stated that there was a feeling of pressure on her throat and with swallowing, but no stridor or difficulty breathing. On physical exam, there was a single right thyroid mass measuring approximately 6.0 cm; without any palpable lymphadenopathy.

A neck CT scan at an outside institution indicated a 5.0 x 4.0 cm complex solid mass in the right thyroid producing tracheal deviation, which appeared encapsulated and contained within the thyroid. A follow-up PET scan showed an intense hypermetabolic mass in the right thyroid deemed consistent with malignancy; although no invasion or metastasis was seen. Neither of these radiographic studies showed evidence of lymph node involvement.

Within days of the initial CT scan, an ultrasound-guided fine needle aspiration (FNA) was performed at an outside hospital. FNA smears from this study demonstrated a significantly pleomorphic population of cells with marked nuclear atypia including prominent hyperchromatic macronucleoli and finely vacuolated to squamoid cytoplasm. The cells were arranged as dispersed isolated cells, as well as small cohesive cell clusters with occasional multinucleated giant cells within a background devoid of colloid or necrosis (Figs. 1A-B). The case was signed out as an undifferentiated (anaplastic) thyroid carcinoma.

Based on these preliminary findings the patient was scheduled for a total thyroidectomy with possible tracheal resection, as well as post-thyroidectomy thyroid ablation with Iodine-131 and Synthroid hormonal replacement. During surgery it was found that the mass did not extend outside of the right thyroid lobe and was not adherent to the trachea or esophagus. Intraoperatively, the surgeon noted the thyroid was soft, with the semblance of a multinodular goiter. Both thyroid lobes, as well as the isthmus were successfully dissected from the surrounding structures and sent for pathologic evaluation. Bilateral recurrent laryngeal nerves and the inferior left parathyroid were identified and unaffected by tumor.

On gross examination, multiple adhesions were noted along the capsule with the right thyroid lobe contained a single, tan multinodular mass measuring 5.2 cm x 4.3 cm x 3.5 cm; which was submitted in its entirety. This Hürthle cell neoplasm was microscopically circumscribed and encapsulated with pushing invasion. There was likely vascular invasion on CD31 immunohistochemical staining (not shown); although this could not be unequivocally demonstrated. Histologically, the tumor was composed of trabeculae and small follicles of polygonal oncocytic (Figure 1C) with some areas containing large, atypical pleomorphic nuclei, prominent nucleoli and multinucleation (Figure 1D) without necrosis. On immunostaining, the clonal areas of pleomorphic cells were TTF-1 negative (Figure 3A), BCL-2 negative (Figure 3B), and cyclin D1 negative (Figure 3C) in comparison to the background HCFC; which stained positive for all three stains. The HCFC had p53 positivity and a 5-10% proliferative rate as demonstrated by MIB-1 staining (not shown). This specimen was sent to The University of Pennsylvania for consultation, confirming the diagnosis of an oncocyctic (Hürthle) follicular carcinoma with high levels of nuclear pleomorphism and likely lymphovascular infiltration. The final pathologic stage was pT3N0Mx.

Case 2

An 81 year old female who has subclinical hypothyroidism presented with acute onset neck swelling thought to be a left-sided goiter. Ultrasound-imaging showed a 3.5 cm nodule, which was aspirated. The cytologic specimen showed numerous follicular cells, both scattered singly and in sheet-like clus-
Anaplastic thyroid cancer is usually a straightforward diagnosis on FNA, as it shows frankly malignant features, including necrosis, striking nuclear pleomorphism/atypia, pleomorphic multinucleated giant cells, very large cells and frequent single non-cohesive cells; cumulative features that are uncommon of more differentiated thyroid tumors [14]. The distinction between ATC and well-differentiated tumors, such as HCFC, can occasionally be difficult. ATC and poorly differentiated thyroid carcinoma can have a similar oncocytic appearance at first glance; and therefore may be mistaken for follicular cell thyroid carcinoma variants [15]. This distinction may be challenging, since ATC can arise from Hürthle cell neoplasms [7,8]. In addition, Hürthle cell neoplasms can display a high level of nuclear pleomorphism and atypia (Figures 1B,1D) and high N/C ratio without being considered malignant [16]. Recent studies however, have shown that 83.5% of Hürthle cell neoplasms are placed in the correct category based solely on FNA [17].

Immunohistochemical staining can be helpful in differentiating ATC from Hürthle cell neoplasms in these questionable cases. Hürthle cell tumors are often positive for TTF-1 and BCL-2 while these markers are typically negative in ATC [5,6]. This is demonstrated in the background positive staining of the oncocytic cells in both cases, with negative staining in the atypical cells (Figures 3A,3B) and ATC (Figure 3D,3E). Hoos
et al. describes down-regulation of BCL-2 expression associated with widely invasive Hürthle cell carcinomas; whereas BCL-2 expression in Hürthle cell carcinomas is associated with relapse-free and disease-specific survival [18].

An additional marker that could provide a distinction between the two tumors is cyclin D1 [4,13]. Authors have shown that a very low percentage of Hürthle cell neoplasms stain positive for cyclin D1 (1.7% and 18% in Hürthle cell adenomas and carcinomas, respectively), whereas the majority of ATC cases are positive for this marker (77%). In our Case 1, cyclin D1 was negative in the atypical cells and positive in the background oncocytic carcinoma (Figure 3C). A reversed pattern was noted in case 2, since the positive staining is limited to the anaplastic cells and only scattered cells within the background HCFC (Figure 3F).

Unfortunately, in the first case, stains could not be applied to the cell block produced at an outside hospital, as it did not contain tumor cells (not shown). The lack of tumor cells in the cell block, a fairly common occurrence with FNA sampling, prevented the application of immunostains for differentiation between an anaplastic thyroid tumor in favor of a follicular neoplasm. Given the somewhat variable expression levels of cyclin D1 in both Hürthle cell neoplasms and ATC [4,13], it would be unwise to base an FNA diagnosis of malignancy on this marker alone. However, in combination with morphology and other markers as well as the proliferative index, cyclin D1 could prove to be a valuable tool in favoring a benign versus malignant process in cases that are difficult to classify based on FNA alone [11,12].

Fine needle aspiration is the most common first step in diagnosing a thyroid tumor, in order to determine next clinical step. For follicular cell neoplasms in particular, cytology cannot distinguish between benign and malignant, as this requires demonstration of capsular or vascular invasion [16]. In our first case, the combination of rapidly progressing clinical symptoms and marked cellular atypia suggested poorly differentiated/undifferentiated tumor but was actually a HCFC with atypia. Whereas, the second case shows a non-aggressive clinical presentation and bland oncocytic cytologic aspiration, that missed the significant underlying anaplastic carcinoma arising within HCFC. In these cases, we highlight the sampling limitations of FNA and susceptibility of clinical bias in formulating an accurate diagnosis. These cases reiterate the need to excise “gray-zone” lesions (i.e. HCFC and follicular neoplasms) for full pathologic evaluation, since ATC commonly develops from within well-differentiated carcinomas. Overall, in the setting of thyroid cytology, it is essential not only to correlate cytologic findings with clinical-radiographic findings; but to also recognize the limitations; which may require further excisional evaluation to obtain an accurate final diagnosis and treatment plan.

Declaration of Interest
The authors declare no conflict of interest.

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