Diagnostic challenges in thyroid cytopathology

Christopher J VandenBussche
Syed Z Ali

Abstract

Fine needle aspiration (FNA) is a long-standing modality used to obtain diagnostic material from patients with thyroid nodules. However, some common and uncommon situations exist in which diagnostic categorization of an FNA specimen is not straightforward. Diagnostically challenging thyroid lesions are typically either benign entities with cytomorphology that mimics malignancy, or malignant entities with unusual cytomorphology that causes difficulty in classification. Awareness of such diagnostic challenges can help broaden one's differential diagnosis when encountering such lesions on FNA. However, in many instances a definitive diagnosis may not be possible and providing an indeterminate diagnosis is most appropriate.

Keywords fine needle aspiration; papillary thyroid carcinoma; the Bethesda System for Reporting Thyroid Cytopathology; thyroid

Introduction

Fine needle aspiration (FNA) is a long-standing modality used to obtain diagnostic material from patients with thyroid nodules. In most laboratories in the United States, a standardized diagnosis is given according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) and this diagnosis is used to guide further patient management. In most cases thyroid nodules represent common entities such as adenomatoid nodules or papillary thyroid carcinoma (PTC) which can be easily diagnosed when sufficient material is obtained by FNA. However, some common and uncommon situations exist in which categorization of a specimen is not straightforward. Generally speaking, diagnostically challenging thyroid lesions are either benign entities that contain cytomorphological changes which mimic malignancy, or are malignant entities that have unusual characteristics which make them appear benign, or difficult to classify. Awareness of such diagnostic challenges can help broaden one's differential diagnosis when encountering such lesions on FNA. In many instances there may be no solution leading to a definitive diagnosis, meaning that an indeterminate diagnosis is most appropriate.

Benign entities that mimic malignancy

Benign papillary hyperplasia

Benign papillary hyperplasia (PH) refers to the formation of non-neoplastic papillary-like structures within a thyroid nodule (Figure 1). The aspiration of such nodules results in tissue fragments which may architecturally mimic papillary fragments found in PTC. Furthermore, as these nodules contain proliferative follicular epithelium, the FNA material often appears hypercellular, further contributing to the impression of a neoplastic process. Rarely, focal nuclear atypia may also be present and can include nuclear grooves, nuclear enlargement, nuclear crowding, pale chromatin, and, in extremely rare circumstances, nuclear pseudoinclusions.[1] However, in most instances the extent of nuclear atypia is much more limited than what is seen in PTC. The presence of cytoplasmic pigment may suggest the presence of PH, but one study showed only approximately one-quarter of cases contained such pigment.[1]

Hurthle cell nodule

Proliferative benign nodules may contain focal or diffuse Hurthle cell change which results in hypercellular FNA specimens with an abundance of Hurthle cells. Hurthle cell adenomas are follicular adenomas in which more than 75% of follicular cells are oncocytes and lack lymphocytic thyroiditis. When such proliferations lack colloid, they may be diagnosed as *Suspicious for a Follicular Neoplasm* (SFN) with oncocytic features, resulting in unnecessary surgery. Unfortunately, Hurthle cell carcinoma is only rarely seen on follow up. Occasionally an oncocytic PTC or medullary thyroid carcinoma may give the appearance of a Hurthle cell neoplasm, especially if other diagnostic features of these entities are absent, such as pseudoinclusions or amyloid. If a limited sampling occurs, a small number of follicular cells containing only Hurthle cells may be diagnosed as *Atypia of Undetermined Significance* (AUS) which may result in unnecessarily surgery or a follow up FNA procedure.

The use of molecular analysis in determining malignant from benign Hurthle cell neoplasms is challenging. Molecular analysis of Hurthle cell neoplasms has shown that the *RET/PTC* oncogene can be activated in both Hurthle cell adenomas and carcinomas, but not in oncocytic hyperplastic lesions.[2] In one study of 13 Hurthle cell neoplasms with a suspicious Afirma classifier, 85% (11) were benign as compared to 47% (8/17) of non-oncocytic follicular neoplasms with a suspicious Afirma classifier.[3]

Graves' disease with nuclear atypia

Graves' disease affects 2% of women and <1% of men in the United States and results in a diffuse hyperplasia of thyroid follicular cells. FNA specimens may contain follicular cells with a "tall cell" appearance with granular cytoplasm and basally-located nuclei. In some instances, Graves' disease can result in nuclear atypia which may be mistaken for atypia seen in PTC. Furthermore, patients may undergo treatment with radioactive iodine which may cause additional cytologic atypia. It is thus important to know the patient's clinical history when examining such specimens.

PTC arising in a setting of Graves' disease is particularly challenging because one must distinguish background atypia from malignancy. Anderson et al. found that four features that were statistically significant in distinguishing PTC from benign Graves changes: prominent nuclear elongation, pale powdery chromatin, intranuclear grooves, and small eccentric nucleoli.[4] This and other studies have suggested the utility of CK19 and HBME-1 immunochemistry, with PTC being positive for these

Christopher J VandenBussche *MD PhD Assistant Professor of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA. Conflicts of interest: none declared.*

Syed Z Ali *MD FRCPath FIAC Professor of Pathology and Radiology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA. Conflicts of interest: none declared.*

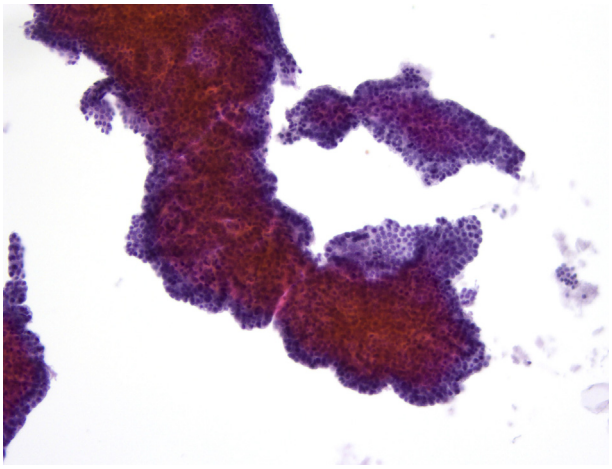

Figure 1 Benign papillary hyperplasia. The specimen is very cellular, forming papillary structures and areas with monolayer-like sheets. Such a specimen gives the impression of a neoplastic process. However, nuclear features of papillary thyroid carcinoma are rare in such lesions (Diff-Quick; low power).

markers as compared to benign hyperplastic processes.[5] However, some studies have shown that benign lesions can also be positive for these markers.

Hashimoto thyroiditis with nuclear atypia

Hashimoto thyroiditis can produce Hurthle cell change and deplete colloid, resulting in a cytomorphological pattern that may mimic a Hurthle cell neoplasm (Figure 2). Additionally, Hashimoto thyroiditis can also cause nuclear atypia that may be similar to that seen in PTC, in particular nuclear enlargement and overlap. As a result, the diagnostic threshold for PTC as well as other categories should be raised in the presence of Hashimoto thyroiditis. In instances where a specimen would otherwise be diagnostic of PTC, a diagnosis of *Suspicious for Malignancy* (SFM) may be most appropriate.

Baloch (2003) has noted that two populations of follicular cells may be present in cases of PTC arising from Hashimoto thyroiditis.[6] One group consists of carcinoma cells which lack associated lymphocytes and have features of PTC. The second are reactive Hurthle cell groups with infiltrating lymphocytes and some, but not all, features of PTC. Regardless, the distinction between PTC and reactive changes secondary to florid Hashimoto thyroiditis is not always possible.

Cyst lining cells

Adenomatous hyperplasia of the thyroid may produce abundant colloid, resulting in colloid nodules with compressed follicular cells at the periphery. When aspirated, colloid may be watery and difficult to discern in the background, leaving only the follicular cells lining the cystic colloid nodule, also known as "cyst lining cells". Cyst lining cells may appear as stretched cells, often in small fragments, and may have elongated nuclei. Atypical features seen in cyst lining cells include nuclear enlargement, nuclear grooves, and fine chromatin. Rarely pseudoinclusions may be seen (Figure 3). Specimens are not typically cellular enough to cause a diagnosis of PTC, but may be classified as AUS or even SFM when pseudoinclusions are present. In most cases, colloid can be easily identified and allow dismissal of the mild atypia seen in cyst lining cells. In cases where cyst contents are primarily cyst fluid without colloid, there may be concern for a cystic PTC.

Faquin et al. compared cyst lining cells from benign cystic thyroid lesions to those of cystic PTC, and found that benign cyst lining cells were well-spaced and had "windows" separating the cells.[7] In cystic PTC, the lining cells were crowded and overlapping. The authors recommend that when cells are arranged in flat sheets with an elongated shape, enlarged pale nucleus, and distinct cell borders with windows in a background of colloid and benign macrofollicles, they should be interpreted as cyst lining cells.

Hashimoto thyroiditis with benign monoclonal lymphoid population

An association between Hashimoto thyroiditis and an increased risk of lymphoma has been postulated, in particular primary

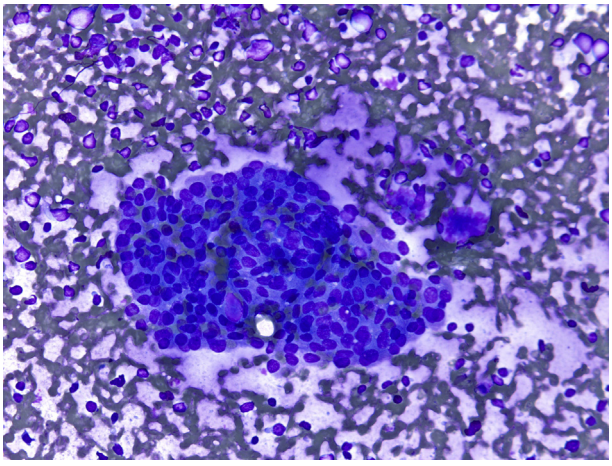

Figure 2 Nuclear atypia in Hashimoto thyroiditis. This fragment of follicular cells is surrounded by numerous lymphocytes. The follicular cells have enlarged and slightly elongated nuclei, many of which overlap. Colloid, a reassuring finding in benign thyroid nodules, may be depleted in thyroiditis (Diff-Quik; medium power).

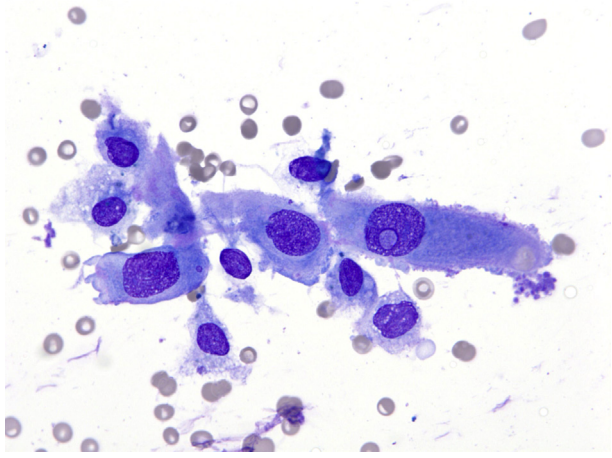

Figure 3 Cyst lining cells. The cells have elongated cytoplasm, perhaps the only suggestion that they line a large cystic space. In some instances these cells have nuclear features of papillary thyroid carcinoma; in this instance, an intranuclear pseudoinclusion can be seen (Diff-Quik; high power).