Update in Thyroid Fine Needle Aspiration

William C. Faquin · Massimo Bongiovanni · Peter M. Sadow

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Abstract Thyroid fine needle aspiration (FNA) is a safe, cost effective, and relatively accurate method for guiding the initial management of a thyroid nodule. The popularity of thyroid FNA is reflected in the fact that over 350,000 thyroid FNAs are performed each year in the USA. As we move into the next decade, several issues pertaining to thyroid FNA are being addressed including: how to better apply thyroid FNA as a differential test for follicular-patterned thyroid tumors, how to manage the atypical thyroid FNA, and how to use thyroid FNA in the evaluation of poorly differentiated thyroid carcinomas.

Keywords Thyroid · FNA · Cytology · Follicular-patterned lesions · Bethesda · Poorly differentiated carcinoma

Introduction

Over the past three decades, fine needle aspiration (FNA) has become the most accurate and cost-effective method for guiding the initial clinical management of patients with thyroid nodules [1–4]. Over 350,000 thyroid FNAs are performed each year in the USA, and approximately 60–70% of these are diagnosed as “benign,” avoiding the need for surgery in these patients [3]. In experienced hands, the mean reported accuracy of thyroid FNA is 76.8%, with a range from 53% to 95%; however, it is difficult to evaluate the accuracy for benign thyroid aspirates because these nodules are infrequently resected [3, 5–12]. Thyroid FNA specimens containing follicular cell-derived lesions are the most commonly encountered and include various forms of benign thyroid nodules (e.g., colloid nodules, adenomatous nodules, follicular adenomas), follicular carcinomas, papillary carcinomas and its many variants, poorly differentiated thyroid carcinomas, and undifferentiated carcinomas. Several challenges exist for thyroid cytology as we move through the next decade including (1) how to apply thyroid FNA more effectively as a differential test for follicular-patterned thyroid lesions, (2) how to diagnose and report the “atypical” thyroid FNA, and (3) how to recognize poorly differentiated carcinomas by thyroid FNA.

FNA as a Screening Test for Follicular-Patterned Thyroid Lesions

The large number of benign thyroid nodules relative to the small number of malignant ones creates a clinical dilemma—how to manage patients with a detectable thyroid enlargement that statistically is more likely to be benign? Thyroid FNA is used as a screening test for follicular and Hurthle cell carcinomas while it is often a diagnostic test for other follicular cell-derived cancers such as papillary carcinoma.

There are limitations of thyroid FNA as a screening test for follicular-patterned lesions. Once the decision to aspirate the thyroid nodule is made, there is a 20–40%
chance that the patient will undergo a partial or total thyroidectomy and, in a majority of these cases, the resected thyroid nodule will be benign [1, 2, 4, 13]. Ancillary molecular markers are in the early stages of being applied to thyroid FNA samples, but with recent advances, there are good prospects that thyroid FNA in the near future might be used as a diagnostic test for follicular and Hurthle cell tumors. Future molecular markers may take the form of a panel of “ATA recommended” markers or an expression profile [14–17].

Another limitation of thyroid FNA is that its use has been plagued by inconsistencies in reporting terminology between laboratories both within the USA and throughout the world. Until very recently, there has been no uniform, standardized, and internationally recognized system for reporting the results of thyroid FNA. Several classification schemes had been suggested by various authors and adopted by different societies, including the Papanicolaou Society of Cytopathology in 1997, the American Thyroid Association in 2006, the American Association of Clinical Endocrinologists and the Associazione Medici Endocrinologi in 2006, the Royal College of Physician-British Thyroid Association, and the Italian Society of Anatomic Pathology and Cytopathology.

The recently published, six-tiered Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) represents a major step towards standardization and reproducibility of thyroid FNA [18, 19]. The six diagnostic categories used in the Bethesda system are (Table 1): (1) non-diagnostic or unsatisfactory, (2) benign, (3) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance, (4) suspicious for a follicular neoplasm (±oncocytic features) or follicular neoplasm, (5) suspicious for malignancy, and (6) malignant. An important aspect of this system is that each diagnostic category is associated with a relative risk of malignancy that ranges from 0–3% in the benign category to nearly 100% for the malignant category. In addition, each diagnostic category can be linked to a clinical management algorithm. In this way, a major role of thyroid FNA is to provide a relative risk of malignancy upon which clinicians, endocrinologists, and surgeons can base their management decisions.

While the application of thyroid FNA as a screening test for follicular carcinoma is generally straightforward, one follicular-patterned thyroid lesion which can be particularly problematic is the follicular variant of papillary thyroid carcinoma (FVPTC). In FNA specimens, it can pose a diagnostic pitfall due to the abundance of microfollicles or monolayer tissue fragments mimicking a follicular neoplasm (Fig. 1a). In fact, among those FNAs diagnosed as “suspicious for a follicular neoplasm” that are malignant in histologic follow-up, over 30% are identified as the FVPTC [20–22].

In contrast to the hyperchromatic chromatin seen in follicular neoplasms, the classic FVPTC exhibits pale, powdery chromatin along with nuclear grooves and occasional intranuclear pseudoinclusions, but in a subset of cases, the nuclear findings will be subtle (Fig. 1b). The cells of the FVPTC tend to be round to oval and less pleomorphic than the conventional type of papillary carcinoma. Variable amounts of dense colloid are frequently seen in the FVPTC, and multinucleated giant cells may also be identified. The sometimes subtle nuclear features combined with the follicular cytomorphology results in the diagnosis of many of these tumors as “suspicious for a follicular neoplasm” or as “AUS/FLUS.”

Molecular tests for RET/PTC rearrangements or point mutations of the BRAF gene in routine thyroid FNA samples can be used to detect classical PTC, but are often less useful for the FVPTC since the latter is often characterized by RAS mutations rather than BRAF mutations or RET–PTC gene rearrangements [14–17]. In fact, a major obstacle to the application of molecular markers to thyroid FNA is the fact that currently available markers tend to work well with lesions that are readily diagnosed microscopically by thyroid FNA but are less useful for the difficult thyroid FNA lesions diagnosed as “AUS/FLUS,” “suspicious for a follicular neoplasm”, or suspicious for FVPTC.

Table 1 Six-tiered Bethesda System for Reporting of Thyroid Cytopathology*

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Management</th>
<th>Implied risk of malignancy (%)</th>
</tr>
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<tbody>
<tr>
<td>Non-diagnostic or unsatisfactory</td>
<td>Repeat FNA</td>
<td>1–4</td>
</tr>
<tr>
<td>Benign</td>
<td>Follow</td>
<td>0–3</td>
</tr>
<tr>
<td>Atypia of undetermined significance</td>
<td>Repeat FNA</td>
<td>~5–15</td>
</tr>
<tr>
<td>Suspicious for follicular neoplasm or follicular neoplasm (specify if oncocytic type)</td>
<td>Lobectomy</td>
<td>15–30</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>Lobectomy/total thyroid</td>
<td>60–75</td>
</tr>
<tr>
<td>Malignant</td>
<td>Total thyroidectomy</td>
<td>97–99</td>
</tr>
</tbody>
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*Modified from Cibas and Ali [18]
The Atypical Thyroid FNA

The reporting of borderline atypia in thyroid aspirates has historically been problematic. Approximately 10% of thyroid FNAs exhibit some form of atypia of uncertain significance which is often related to a variety of benign cellular changes, but in some cases, it reflects an underlying malignancy. TBSRTC has addressed the issue of the atypical thyroid FNA by introducing the AUS/FLUS category [18].

The AUS/FLUS category is the most controversial of TBSRTC diagnostic categories, and as further studies are performed, the category will continue to be better defined. According to TBSRTC, the AUS/FLUS category is reserved for aspirates that contain follicular, lymphoid, or other cell types with architectural and/or nuclear atypia that is more pronounced than that observed in benign reactive lesions yet not sufficient to be classified as suspicious for a follicular neoplasm, suspicious for malignancy, or malignant [18, 23]. As such, the AUS/FLUS category is a heterogeneous one, and because of the general nature of the AUS/FLUS category, it has the potential to be overused. TBSRTC recommends that the AUS/FLUS category should not exceed 7% of FNA thyroid diagnoses; however, in recent studies, the rates of AUS/FLUS have varied from 3% to 20% signaling that adjustments in the recommended rates of AUS/FLUS may be needed [24–29]. QA metrics applied to the AUS/FLUS category within individual labs may be useful to keep its rate within a reasonable level. The risk of malignancy associated with the AUS/FLUS category is estimated at 5% to 15%, and the suggested management algorithm based upon this diagnosis is a repeat FNA [21, 23, 27]. Based upon recent evidence in the literature, surgery should be considered for those patients who have a repeat thyroid FNA that is also AUS/FLUS [21, 23, 27].

TBSRTC defines eight different scenarios for the use of the AUS/FLUS category including a sparsely cellular aspirate with a predominance of microfollicles (Fig. 2a), cytologic atypia in the setting of preparation artifact, rare follicular cells with nuclear atypia in an otherwise benign-appearing aspirate. (Smears, Papainicoau stain)

Fig. 1 Follicular variant of papillary thyroid carcinoma. a A microfollicular architecture combined with oval pale, grooved nuclei can be seen in a majority of cases. b A subset of cases will have subtle nuclear features that can be difficult to recognize by thyroid FNA. (Smears, Papanicoloau stain)

Fig. 2 The AUS/FLUS category. a This hypocellular thyroid FNA lacked sufficient cells to meet adequacy criteria, but the few groups present were primarily microfollicles. b This thyroid FNA contained
oncocytic atypia, and focal atypia suggestive of papillary carcinoma in an otherwise predominantly benign-appearing sample (Fig. 2b). One of the most common scenarios is the presence of a compromised specimen due to scant cellularity, partial air-drying, or obscuring blood.

Already, since the publication of TBSRTC, there have been many studies published pertaining to the AUS/FLUS category. Some studies have suggested that the AUS/FLUS category might be further subdivided [25, 30], particularly with regard to the presence of focal cytologic features of papillary carcinoma. Such nuclear atypia has been shown to confer a higher risk of malignancy than other AUS patterns [25, 30], while architectural atypia alone is half as likely to be malignant as other patterns. As experience is gained with TBSRTC in general and with AUS/FLUS in particular, it is expected that the criteria for AUS/FLUS will be further refined. Furthermore, it is likely that some form of molecular testing will one day play an important role in triaging patients with an AUS/FLUS diagnosis.

FNA of Poorly Differentiated Thyroid Carcinoma

Poorly differentiated thyroid carcinoma (PDTC) is a rare thyroid cancer of follicular cell origin that has distinct clinical, histological, and biological characteristics that were further defined in 2007 by the Turin Proposal [31]. PDTC has an aggressive clinical behavior intermediate between that of WDTCs and undifferentiated (anaplastic) thyroid carcinomas [32–36]. While PDTC represents an extremely important clinical entity, few studies have examined its cytologic features, and aspirates of PDTC represent a diagnostic challenge for the cytopathologist. One of the first cytological descriptions of PDTCs was a report of 6 cases by Pietribiasi et al. in 1990, followed by 4 cases in 1992 by Sironi et al., 6 cases in 1999 by Guiter et al., 5 cases in 2001 by Nguyen et., and 40 cases by our group in 2009 [37–41]. In addition to these series, a limited number of published case reports are also available, but only a few FNAB cases have prospectively recognized the tumors as PDTC.

Aspirates of PDTC are typically cellular with severely crowded clusters and scant colloid although some cases can show single cells [37]. The insular type will often display a recognizable insular cyt架构ural pattern at low magnification (Fig. 3a). The malignant cells are small with scant delicate cytoplasm and a high nuclear/cytoplasmic ratio. Nuclei are generally round, mildly hyperchromatic, and cytologically uniform although some cases will exhibit nuclear grooves and prominent nucleoli, and occasionally cells are highly pleomorphic. Necrosis within the smear background and increased mitotic activity are cytologic features that help distinguish PDTC from the usual “follicular neoplasm” (Fig. 3b). While a cytologic diagnosis of malignancy can be made in a subset of cases, for many PDTC cases, the lesion will be diagnosed as “suspicious for a follicular neoplasm.” Using stepwise logistic regression analysis, a combination of insular, solid, or trabecular cyt架构ural patterns, single cells, high N/C ratio, and severe crowding have been shown to be the most useful in combination for predicting PDTC in FNA samples [37].

Currently, no specific immunohistochemical or molecular markers exclusively expressed in PDTCs have been identified to aid the cytologic diagnosis. High molecular weight cytokeratins, thyroglobulin, TTF-1, HBME-1, galectin-3, CD44v6, p3, PAX8-PPARγ1, and Bcl-2 have been identified in PDTCs, but these markers do not distinguish between WDTC and PDTC [42, 43]. The molecular biology of PDTCs is not well understood. A high prevalence of Ras mutations ranging from 18% to 63% has been found in PDTCs, but this is not a specific molecular feature [44, 45]. As more advances are made on

Fig. 3 Poorly differentiated thyroid carcinoma. a This aspirate is cellular and contains follicular cells with high N/C ratio in a crowded insular arrangement. b Background necrotic debris can be seen in a subset of PDTC cases. (Smears, Papanicoloau stain)
the molecular front using cohorts defined by the Turin Proposal, it may be possible to provide more objective diagnostic markers for cytologic specimens.

References


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