Atypia in Follicular Neoplasm: Making a Case for Follicular Variant of Papillary Thyroid Carcinoma

Berrin Ustun, David Chhieng, Constantine Theoharis, Manju Prasad, Adebowale J. Adeniran

Department of Pathology, Yale School of Medicine, New Haven, CT, USA

ABSTRACT

Background: The Bethesda thyroid classification describes follicular neoplasm (FN) as a cellular lesion showing microfollicular architecture with scant or absent colloid. Fine-needle aspiration (FNA) diagnosis of FN is a screening test that does not differentiate between a benign and malignant tumor. The majority of thyroid nodules (up to 80%) diagnosed as FN are benign upon histologic examination. This study is designed to determine the predictive value of cytologic diagnosis in a subset of FN and offer a practical guide for thyroid physicians by identifying significant risk factors for malignancy based on cytologic atypia.

Design: Based on a retrospective review of cytologic diagnosis between January 2008 and December 2011, all thyroid FNA cases with the diagnosis of FN were reviewed. A subset with cytologic atypia – some features suggestive but not diagnostic for Papillary thyroid carcinoma follicular variant (FVPTC) – was identified. The PPV of the cytologic interpretation of FN with atypia for neoplasia (including adenoma and carcinoma) and that for malignancy were calculated.

Results: A total of 38 cases of thyroid FNA (29 female and 9 male) with the cytologic diagnosis of FN with atypia (and with surgical follow-up) were identified (representing 12% of the total number of cases diagnosed as FN with surgical follow-up over this time period). All patients had undergone either lobectomy with completion thyroidectomy or total thyroidectomy. The 38 FNA samples resulted in the following distribution of final histological diagnosis: Neoplastic – 30/38 (out of which 26 were malignant), Benign – 8/38. The positive predictive value for neoplasia and malignancy were 78% and 68% respectively. The malignant cases were predominantly FVPTC (19/26). Others included classic PTC (5/26) and follicular carcinoma (2/26).

Conclusions: The reported incidence of malignancy in FN is 10%-30%. FN with subtle atypical features has a much higher rate of malignancy (68%). The main diagnostic challenge is to differentiate FVPTC from other follicular lesions. Subclassifying FN based on presence of atypia has implications for management. This subset of patients will benefit from a more aggressive follow-up including immediate referral for lobectomy.

BACKGROUND

FNA of the thyroid is one of the most successful screening tests; it has resulted in a tremendous decrease in unnecessary thyroid surgery. Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma, accounting for 70–90% of all thyroid malignancies. FNA technique is highly sensitive for detecting PTC (ranging between 60% to > 90%), especially for conventional PTC. However, FNA of the solitary thyroid nodule is a screening test for the selection of cases that may require excision.

The majority of thyroid nodules (up to 80%) diagnosed as “follicular neoplasm” (FN) end up being benign after histologic examination. As of now, diagnosis of follicular neoplasm on FNA remains a gray area, because of overlapping cytological features between benign and malignant follicular lesions. The differential diagnoses of follicular neoplasm on FNA include follicular variant of papillary carcinoma (FVPTC), follicular adenoma, follicular carcinoma, and a benign solitary cellular nodule associated with goiter.

Some studies have looked into either cytologic features or biologic markers that could distinguish between benign and malignant follicular patterned lesions in the thyroid; however, none of these cytologic criteria or markers were found to be of reproducible diagnostic value. More than half of the malignant diagnoses were FVPTC on histologic follow-up. Many studies concluded that the main diagnostic challenge is to differentiate FVPTC from other follicular lesions.

This study was designed to determine the predictive value of cytologic diagnosis in a subset of FN and offer a practical guide for thyroid physicians by identifying significant risk factors for malignancy based on cytologic atypia.

DESIGN

Based on a retrospective review of the cytopathology database at Yale-New Haven Hospital between January 2008 and December 2011. All thyroid FNA cases with the diagnosis of FN were reviewed. At our institution, the 2007 NCI/Bethesda reporting guidelines is used to classify thyroid FNAs. Thirty-eight cases were identified with the diagnosis of FN with atypia with subsequent thyroid excision.

Follicular neoplasm with cytologic atypia refers to “some features suggestive but not diagnostic for papillary thyroid carcinoma follicular variant (FVPTC)”. Follow-up histology reports were obtained from our laboratory information system. Histologic diagnoses were used as the gold standard for the correlation with cytologic interpretations. The positive predictive value of cytologic interpretation of FN with atypia for neoplasia (including adenoma and carcinoma) and malignancy were calculated.

RESULTS

Figure 1. Follicular lesion with some features (i.e. slight mem-brane irregularity, nuclear groves) suggestive of but not diagnostic for papillary carcinoma follicular variant (FL)

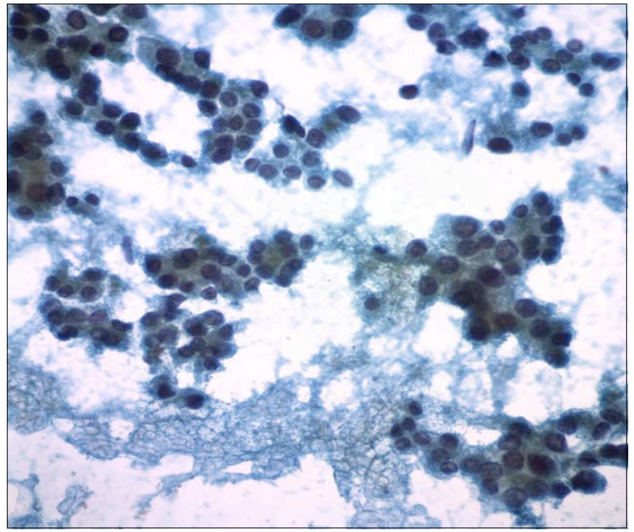

TABLE 1.
Distribution of the Final Histologic Diagnosis

Diagnosis	Sub Diagnosis	Number of Cases
Neoplastic		**30 (79%)**
Malignant		*26 (68%)*
	FVPTC	19 (50%)
	PTC	5 (13%)
	FC	2 (5%)
Non-malignant		
	Adenoma	4 (11%)
Benign		**8 (21%)**
	Goiter	7 (18%)
	Thyroiditis	1 (3%)
All Cases		**38 (100%)**

RESULTS

Thirty-eight cases of thyroid FNA (29 female and 9 male) with cytologic diagnosis of FN with atypia (and with surgical follow-up) were identified (representing 12% of the total number of cases diagnosed as FN with surgical follow-up over the study period). The size of the nodules ranged between 0.3cm and 11.3cm. There was no repeat FNA on any of the nodules. All patients had undergone either lobectomy with completion thyroidectomy or total thyroidectomy. Selected specimens were evaluated by intraoperative frozen section.

The distribution of the final histologic diagnosis is summarized in **Table 1.** The 38 FNA samples resulted in the following distribution of final histological diagnosis: Neoplastic – 30/38 (out of which 26 were malignant), Benign – 8/38. The positive predictive value for neoplasia and malignancy were 78% and 68% respectively.

CONCLUSIONS

Not uncommonly, many cases of FVPTC are misdiagnosed on cytologic samples as benign, or underdiagnosed as follicular neoplasms due to its overlapping features with other follicular-derived lesions. The reported incidence of malignancy in FN is 10%-30%.

Here we have presented our experience with cases diagnosed by FNA as FN with atypia. The predominant feature in these cases is the presence of follicular architecture.

On closer look those cases have very focal and subtle nuclear atypia commonly seen in PTC. The positive predictive value for neoplasia and malignancy were 78% and 68%, respectively.

Our institutional data suggests that FN cases should have a comment regarding the presence or absence of nuclear atypia, as subclassifying FN based on presence of atypia has implications for management. This subset of patients will benefit from a more aggressive follow-up including immediate referral for lobectomy.

REFERENCES

1. Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of “follicular neoplasm”: a grey zone in thyroid fine-needle aspiration cytology. *Diagn Cytopathol*. 2002;26:41– 44.
2. Kapur U, Wojcik EM. Follicular Neoplasm of theThyroid—Vanishing Cytologic Diagnosis? Diagn Cytopathol. 2007;35:174-178.
3. Goldstein RE, Netterville JL, Burkey B, et al. Implications of follicular neoplasms, atypia, and lesions suspicious for malignancy diagnosed by fine-needle aspiration of thyroid nodules. Ann Surg 2002;235:656–664.