Follicular Variant of Papillary Thyroid Carcinoma: Accuracy of FNA Diagnosis and Implications for Patient Management

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ABSTRACT

Background: Follicular Variant of Papillary thyroid carcinoma (FVPTC) has created a continuous diagnostic dilemma among pathologists because of the paucity of nuclear changes of papillary carcinoma and overlapping features with benign and other neoplastic follicular lesions. Current guidelines for the management of thyroid nodules recommend surgery for confirmed PTC, suspicious and follicular neoplasm cases, while further immediate diagnostic studies or treatment are not routinely required if the nodule is benign on cytology. This study is designed to determine the accuracy of cytology in the diagnosis of FVPTC, based on the Bethesda classification system and determine the implications for patient management based on the current recommendation.

Design: Based on a retrospective review of cytologic diagnosis between January 2008 and December 2010, thyroid FNA cytology specimens with subsequent surgical intervention and a final diagnosis of FVPTC were selected from our files. The cytologic diagnoses were compared with the final diagnoses and the percentage of cases contributing to the final diagnosis of FVPTC was calculated for each diagnostic category. Triage efficiency and diagnostic accuracy were calculated.

Results: One hundred and fifty two cases with histologic confirmation of FVPTC were identified (representing 128 patients – 100 females, 28 males). All patients had undergone either lobectomy with completion thyroidectomy or total thyroidectomy. The cytologic diagnosis of "positive for malignancy" accounted for only 26% of the final histologic diagnosis of FVPTC while suspicious for carcinoma, follicular neoplasm, follicular lesion of undetermined significance and benign accounted for 11%, 22%, 22%, 15% of the final diagnosis of FVPTC, respectively. Non-diagnostic cytologic cases accounted for the remaining 4%. Only 18% of the 55 cases tested were positive for BRAF mutation.

Conclusion: The subtle nuclear features of FVPTC pose challenges for an accurate diagnosis. Therefore a better approach is to triage these cases for surgical intervention and/or further evaluation of the particular nodule. Our triage efficacy for FVPTC was 84%, however the diagnostic accuracy of PTC was 38%. Up to 15% of cases may have no further immediate diagnostic studies or treatment. BRAF mutation analysis has no effect on diagnostic accuracy.

BACKGROUND

Papillary thyroid carcinoma (PTC) is the most common malignant tumor of the thyroid gland, representing 70% to 80% of the cases. Thyroid carcinoma usually presents in a thyroid nodule, but only a small percentage of such thyroid nodules (approximately 5%) are malignant. Numerous subtypes of PTC have been described in the literature such as oxyphilic, tall cell, columnar cell, diffuse sclerosing and follicular variant.

The follicular variant of PTC (FVPTC) consists of 10 to 15 % of all PTCs. Current standard of care for triaging thyroid nodules is an initial ultrasound evaluation, followed by ultrasound-guided fine-needle aspiration (FNA). This technique is highly sensitive for detecting conventional PTC. However, numerous studies have reported a very low sensitivity with FNA for the identification of FVPTC. Although the cytologic diagnostic criteria for FVPTC are similar to those of the conventional PTC, cytologic diagnosis of FVPTC is challenging and poses a diagnostic problem, since nuclear features of PTC are less obvious and focal, coupled with the absence of papillary groups and presence of follicles with a variable colloid component. In a recent large study with a long term follow-up, FVPTC was concluded to have more favorable clinicopathologic features and a better tumor risk group profile. However, long term outcome was similar to conventional PTC patients. This current study was designed to determine the accuracy of cytology in the diagnosis of FVPTC, based on the Bethesda classification system and determine the implications for patient management based on the current recommendation for intervention.

DESIGN

Based on a retrospective review of cytologic diagnosis, using the 2007 NCI/Bethesda reporting guidelines, and the surgical outcomes at Yale New Haven Hospital (YNHH), 128 patients (152 FNA samples) underwent thyroid excision and received pathological diagnosis of FVPTC between 2008 and 2010. The corresponding cytologic diagnoses were reviewed and compared with the final surgical diagnoses. Triage efficiency (either trigger surgical intervention or repeat FNA biopsy of the particular nodule) and diagnostic accuracy (cytologic diagnosis of suspicious for papillary thyroid carcinoma and positive for papillary thyroid carcinoma) were calculated.

RESULTS

One hundred and twenty eight patients (152 FNA samples) underwent thyroid resection and received pathological diagnosis of FVPTC between 2008 and 2010. All patients had undergone either lobectomy with completion thyroidectomy or total thyroidectomy. Selected specimens were evaluated by intraoperative frozen section.

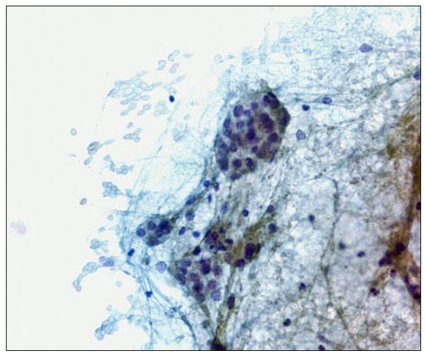

Figure 1: FVPTC case interpreted as negative on cytology

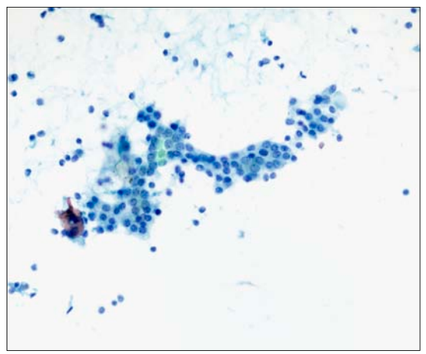

Figure 2: FVPTC case interpreted as indeterminate on cytology

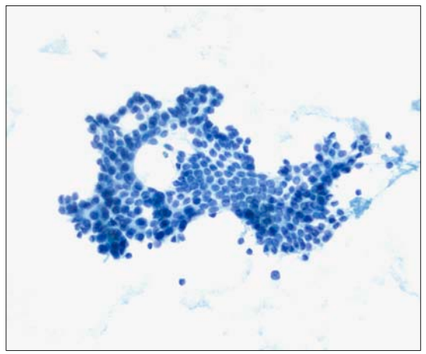

Figure 3: FVPTC case interpreted as positive on cytology

TABLE 1 Distribution of the Cytologic Diagnosis

Cytologic Diagnosis	Sub Diagnosis	No. of Cases
Positive	PTC	**39 (26%)**
Suspicious	PTC	**16 (11%)**
Follicular Neoplasm		**33 (22%)**
	Hurthle Cell Neoplasm	10 (7%)
	Microfollicular Patterned Neoplasm	11 (7%)
	FVPTC	12 (8%)
Indeterminate		**33 (22%)**
	Nuclear Atypia	31 (21%)
	Microfollicular Pattern	2 (1%)
Negative		**23 (15%)**
	Goiter	19 (13%)
	Lymphocytic Thyroiditis	4 (2%)
Non Diagnostic	Insufficient cellularity	**8 (4%)**
All Cases		**152 (100%)**

TABLE 2 Triage Efficacy (potential for triggering intervention)

Cytologic Diagnosis	No. of Cases	Current Intervention
Positive	39 (27%)	Total Thyroidectomy
Suspicious	16 (11%)	Lobectomy
Follicular Neoplasm	33 (23%)	Lobectomy
Indeterminate	33 (23%)	Repeat FNA
Negative	23 (16%)	No intervention
All Cases ex-Non Diagnostic	144 (100%)	

The 152 FNA samples, using the 2007 NCI/Bethesda reporting guidelines, resulted in the following distribution of cytologic diagnoses: Positive for PTC – 39 (26%); Suspicious for PTC – 16 (11%); Follicular neoplasm – 33 (22%); Indeterminate – 33 (22%); Negative – 23 (16%); Non-diagnostic – 8 (5%). At our institution, the term "Indeterminate", corresponds to the NCI 2007 guidelines category "Follicular cells of undetermined significance" (**Table 1**). Negative cytology diagnosis was predominantly rendered as hyperplastic nodule (19/23). Majority of the cases interpreted as indeterminate were due to the presence of nuclear atypia (31/33). Follicular neoplasm was reported under three sub-categories, with the following distribution: Hurthle cell neoplasm (10/33), microfollicular patterned neoplasm (11/33), Follicular lesion with some features suggestive but not diagnostic for papillary thyroid carcinoma follicular variant (12/33). The triage efficacy (potential for triggering intervention) was 84% (**Table 2**). Of the 55 cases tested for the BRAF mutation, 10 (18%) harbored the mutation.

CONCLUSIONS

- The subtle nuclear features of FVPTC pose challenges for an accurate diagnosis. Although several studies have looked at immunohistochemical and molecular markers to distinguish FVPTC from other follicular lesions, at present, the application of these techniques are not helpful in a routine practice. Therefore a better approach is to triage these cases for surgical intervention and/or further evaluation of the particular nodule.

- Our institutional data suggests that efficient triage of FVPTC will improve the clinical management. Our triage efficacy in cases with the FVPTC, by using the modified Bethesda reporting guidelines, was 84% (PTC, suspicious for PTC, follicular neoplasm and indeterminate). Diagnostic accuracy of PTC was at 38% (PTC and suspicious for PTC). Diagnostic accuracy may be slightly increased by routine BRAF mutation testing on all indeterminate cases.

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