Review

Recent Advances in Follicular Variant of Papillary Thyroid Carcinoma

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The follicular variant of papillary thyroid carcinoma (FVPTC) constitutes a distinct class of papillary thyroid carcinoma (PTC), presenting unique challenges to the clinician and pathologist regarding its diagnosis, prognosis and treatment. Fifty years since its identification as a unique class of thyroid neoplasms, controversies still exist with respect to the histologic diagnosis and categorization of FVPTC. While agreement exists among experts as to its generic place within PTC, FVPTC exhibits biologic and molecular properties that distinguish it from conventional PTC. Many studies and proposals utilizing histopathologic criteria, immunohistochemical and molecular techniques have been brought to bear on the problems posed by these set of tumors with varying degrees of success. Here we examine the clinical and pathologic features of FVPTC, highlighting diagnostic controversies and recent molecular findings that attempt to provide clues to the proper classification of this unique group of thyroid tumors.
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Key Words: *papillary thyroid carcinoma, follicular variant, thyroid cancer, RET/PTC, BRAF*

INTRODUCTION

The papillary thyroid carcinoma (PTC) constitutes 85.3% of thyroid malignancies in whites and 72.3% in blacks.[1,2] Classic PTC is characterized histologically by the presence of clear, irregularly shaped, overlapping nuclei with grooves and/or pseudoinclusions. Cell arrangement is variable and consists of a mixture of papillae and follicles. The follicular variant of papillary thyroid carcinoma (FVPTC) is defined by the presence of tumor cells arranged almost entirely in a follicular pattern with the nuclear features identical to that of PTC. The actual incidence of FVPTC is not certain because this subclass of tumor may be over-diagnosed by pathologists.[3,4]

CLINICAL PRESENTATIONS OF FVPTC

The median age of FVPTC is 44 years, similar to that of PTC which is 43 years.[5] The female to male ratio is 6:1.[6] Both FVPTC and PTC are presented as thyroid masses. At the time of diagnosis, the rates of extensive extra thyroidal local spread, bilateral lesions, and vascular invasion were higher in FVPTC than those in PTC.[6] However, the risk for regional lymph node metastasis is lower than the classic PTC.[5,6] Although FVPTC appears not to be dissimilar from the classic PTC prognostically,[5] One study showed that FVPTC may be more aggressive than previously considered.[6]

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Although typically arising within the thyroid gland, occurrence in other organ sites has been reported, including the ovaries in struma ovarii and lingual thyroid.[7,8] Unusual presentations such as collision tumors involving FVPTC and tumors from other organ sites have been reported, including cases involving metastasis of breast carcinoma and renal cell carcinoma to FVPTC within the thyroid. In these cases, immunohistochemical and molecular studies were useful in determining the component and source of the tumor complex.[9]

MORPHOLOGICAL AND IMMUNOHISTO-CHEMICAL FEATURES OF FVPTC

Ultrasound imaging and fine needle aspiration are useful diagnostic tools in the investigation of thyroid malignancies; however, studies have shown very low sensitivity for the diagnosis of FVPTC, making histologic examination the mainstay of diagnosis. As its name implies, FVPTC is defined histologically by the presence of follicular architecture throughout the tumor (**Figure 1**). The cellular features of FVPTC are identical to that of PTC and include clear nuclei, nuclear grooves, and pseudonuclear inclusions (**Figure 2**).[10] Psammoma bodies and a desmoplastic response at site of invasion are also frequent findings.[10] FVPTC tend to have fewer calcifications and less psammmoma body formation when compared to conventional PTC.[11]

A range of histologic patterns of FVPTC have been seen. The two main prognostically and morphologically distinct forms

are the diffuse variant and the encapsulated variant. The diffuse follicular variant shows diffuse replacement of the gland by the neoplasm. Compared to the encapsulated form, the diffuse variant of FVPTC carries a worse prognosis and demonstrates a higher rate of the BRAF V600E mutation, lymph node involvement and distant metastasis.[12-14] The encapsulated variant of FVPTC, defined by a complete peri-tumoral capsule, has an overall excellent prognosis.[10,15,16] Encapsulated FVPTC shows a distinctive tumor biology compared to conventional PTC.[17] While conventional PTC (encapsulated and nonencapsulated) has a greater propensity for lymph node metastasis (26% vs 3%) and an increased frequency of capsular invasion (65% vs 38%), encapsulated FVPTC has a higher rate of vascular invasion than conventional PTC (25% vs 5%). As vascular and capsular invasion are the most important indicators of metastatic potential, histopathologic evaluation of FVPTC must include a meticulous and thorough search for these features. The noninvasive variety of FVPTC can be managed like minimally invasive follicular carcinoma by lobectomy without radioactive iodine (RAI) therapy. On average, the overall clinical course of FVPTC with capsular invasion is noted to be quite indolent particularly if no distant metastasis is identified at presentation.

Rare histologic patterns of FVPTCs, such as mixed follicular and papillary pattern, adenoid cystic pattern, and macrofollicular pattern, have been reported in the literature. A reported case of FVPTC containing adenoid cystic areas exhibited prominent follicular clusters containing hyaline globules and areas with morula-like groups of neoplastic cells.[18] Immunohistochemical staining was positive for thyroglobulin in the follicular region but negative in the hyaline globules. This feature may be of importance to the cytopathologist when considering the possibility of adenoid cystic carcinoma metastatic to the thyroid.

Reported cases of mixed follicular and papillary patterns of PTC have shown molecular features suggesting that they best fit into the category of conventional PTC rather FVPTC.[19] BRAF mutation occurred with a frequency more consistent with conventional PTC. Furthermore, both follicular and papillary areas of these mixed tumors displayed the BRAF mutations.

Macrofollicular FVPTC is another unusual variant that can be confused with nodular goiter or follicular adenoma.[20] This variant of FVPTC, despite being described as having a good prognosis with a low incidence of metastases, can on occasion present as a highly aggressive tumor, making its detection and proper characterization of importance.

Common diagnostic difficulties posed by FVPTC include: (1) A high number of these tumors develop within a background of nodular goiter, resembling an adenoma or adenomatoid nodules which are mostly encapsulated and lack vascular or capsular invasion.[21] (2) Lesions can be multifocal, without a diffuse distribution of the typical nuclear features of PTC. In these cases, the presence of incomplete or focal characteristic nuclear features makes the distinction from follicular adenoma or follicular carcinoma difficult.[21] (3) Most encapsulated FVPTCs are solitary, with no evidence of invasion, and are confined to the thyroid.[10] These facts have practical importance in the management of these tumors because overdiagnosis results in excessive treatment, including total thyroidectomy with radioactive iodide therapy.

Significant inter-observer and intra-observer variation have been noted even among experts, with major inter-observer disagreements reported in up to 40% of cases. Ironically, intra-observer agreement was found to range from 17 - 100%.[21] A general consensus exists as to the most important diagnostic features, which include nuclear clearing, nuclear grooves, nuclear overlapping and crowding, nuclear membrane irregularity and nuclear enlargement.[21] Discrepancies arise due to the lack of agreement on the minimal criteria necessary for a definite diagnosis of FVPTC.[21]

The absence of a strict and uniform approach among expert pathologists, particularly in difficult cases, results in the use of terms such as “multifocal papillary thyroid carcinoma arising in a benign nodule”, “follicular tumor of uncertain malignant potential” or the consideration of an entire nodule showing only focal nuclear changes as a FVPTC. A range of proposals have been made to clarify this issue. LiVolsi and Baloch prefer a scheme in which a diagnosis of FVPTC is made on any encapsulated lesion that shows any area with the characteristic cytologic features of papillary thyroid carcinoma.[22] Chan suggests using stricter criteria including the evaluation of major and minor features.[3] The four major features proposed include: (1) oval rather than round nuclei, (2) crowding of nuclei with lack of polarity in the follicles, (3) clear or pale nuclear chromatin pattern throughout the entire lesion or prominent nuclear grooves, and (4) presence of psammoma bodies. When only a single one of these features is identified, the presence of all of the following subsidiary criteria is necessary to establish the diagnosis. These subsidiary criteria include: (1) presence of abortive papillae, (2) predominantly elongated or irregularly shaped follicles, (3) dark-staining colloid, (4) presence of rare nuclear pseudoinclusions, and (5) multinucleated histiocytes in the lumen of the follicles. A group of Chernobyl pathologists advocates the use of the terminology of “well-differentiated thyroid tumor of uncertain malignant potential (WDT-UMP)” when incomplete or equivocal features are present rather than an outright diagnosis of carcinoma.[4] This may obviate the fear of litigation that results in the overdiagnosis of malignancy and the excessively aggressive treatment of this group of tumors, which have been shown not to be associated with any significant risk of recurrence or metastasis by many authors.[3,4]

Many studies demonstrate the use of immunohistochemistry and molecular assays in separating FVPTC from other benign conditions.[23,24] A study of the immunomarkers, galectin-3, cytokeratin 19 (CK19), Ret oncoprotein (RET), and HBME-1 suggested a high utility of these markers in differentiating benign lesions from malignant tumors.[24] Saleh and collegues

have demonstrated galectin-3 expression in a large number of malignant tumors in contrast to benign lesions with a reported sensitivity and specificity of 92.6% and 77.3% respectively. In the same study, staining for HBME-1 was also pronounced in malignant lesions and showed a sensitivity and specificity of 88.9% and 72.7%. However, the use of these markers is limited by their expression in a smaller number of benign lesions (22.7% for galectin-3, 31% for Ret and 29.5% for CK19). The illustration of positive galectin-3 staining of FVPTC and positive CK19 staining are shown in **Figure 3** and **Figure 4**.

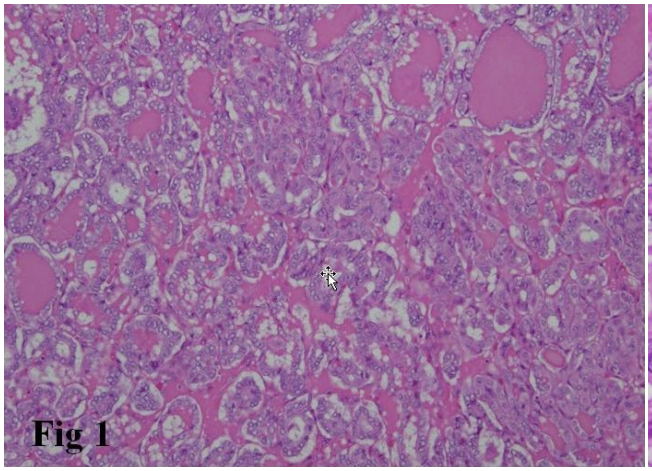

Figure 1. Low-power view of Follicular Variant of Papillary Thyroid Carcinoma. Tumor shows follicles of varying sizes with colloid. (Magnification 100x).

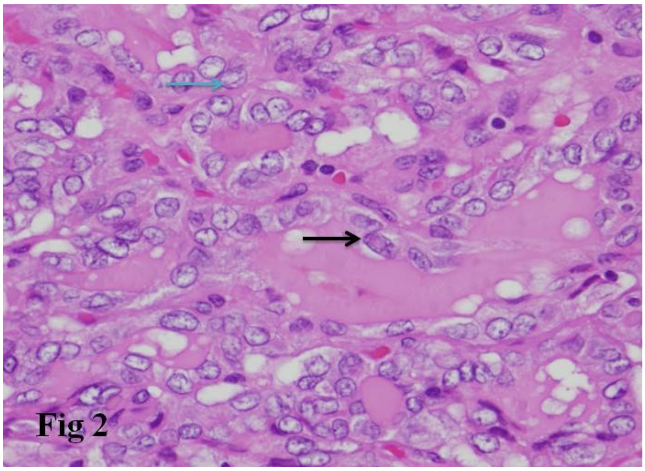

Figure 2. High-power view of Follicular Variant of Papillary Thyroid Carcinoma. Tumor shows follicles with nuclear features of papillary carcinoma. Blue arrow: Nucear grooves; Black arrow: pseudonuclear inclusion. (Magnification 400x).

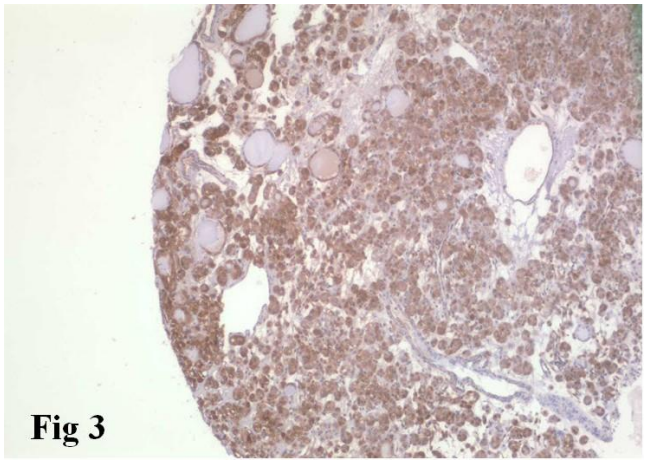

Figure 3. Follicular Variant of Papillary Thyroid Carcinoma is strongly positive for Galactin 3 (Magnification 100x).

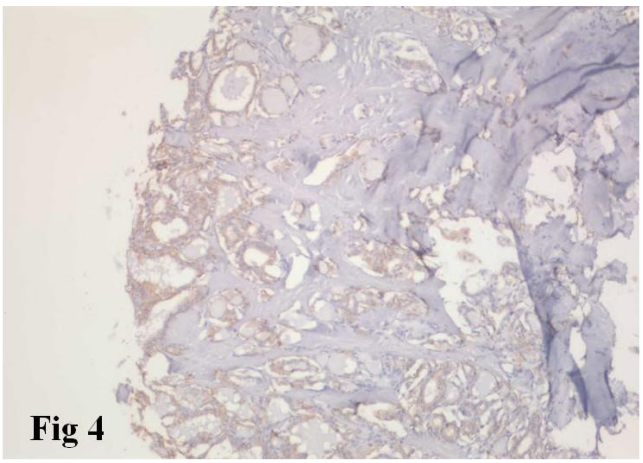

Figure 4. Follicular Variant of Papillary Thyroid Carcinoma is positive for CK19 (Magnification 100x).

MOLECULAR GENETICS OF FVPTC

Tumorigenesis of thyroid carcinomas involves in several oncogenes, including *RET*, *RAS*, and *BRAF*, etc.[25,26] *RET* gene encodes a membrane receptor tyrosine kinase involved in signaling via a ligand-coreceptor-RET protein complex. RET dimerization is triggered by ligand binding and complex formation, resulting in tyrosine residue autophosphorylation within its intracytoplasmic domain. Further tyrosine phosphorylation of downstream target proteins produces an activated signaling pathway. Target proteins include mitogen-activating protein kinase (MAPK), extracellular signal-regulated kinase (ERK)1/2, phosphatidylinositol 3-kinase, c-Jun N-terminal kinase, p38, ERK5 and cAMP responsive element-binding protein.[25]

FVPTC has a molecular identity intermediate between the two well differentiated thyroid carcinomas,,follicular carcinoma (FC) and PTC. FC is characterized by *RAS* mutations and *PAX8/PPARγ* rearrangement.[26-30] The gene fusion of *PAX8/PPARγ* rearrangement has been cytogenetically defined as translocation t(2:3)(q13;p25).[29] PTC has a genetic profile consisting of somatic rearrangements of the *RET* protooncogene[25,31] and *BRAF* mutations.[32,33] FVPTC has a high occurrence of *RAS* mutations and *PAX8/PPARγ* rearrangements[34] but a less common BRAF K601E form, which is present in about 7% of cases.[35] Other BRAF mutations reported in FVPTC include V600E, G474R and a novel gain of function T5991-VKSR(600-603) del.[36] These mutations with the exception of G474R share biological similarities in activating the MAPK pathway. The G474R mutation knocks down the enzymatic activity of BRAF, providing a first example of a knockdown mutation in FVPTC. The genetic profiling of thyroid tumors offers potential diagnostic and therapeutic targets in their management. Candidate compounds, many with tyrosine kinase inhibitor function, are presently in various phases of clinical trials.[37] The role of these mutations in prognosis remains controversial. Some studies suggest a correlation between RET/PTC and tumor aggressiveness[38] while others indicate that tumors harboring RET/PTC show slow growth and lower risk of progression to poorly differentiated and undifferentiated thyroid carcinoma.[25,31,39]

CLINICAL UTILITY OF MOLECULAR TESTING IN FVPTC

When using the Bethesda classification for the diagnosis of thyorid neoplasms, up to 3.6% of specimen will fall into the indeterminate category.[40] The risk of malignancy in this category may be up to 15-30%.[40] Molecular tests (especially assays for BRAF V600E and Kras mutations) have been shown to play an adjunct role to cytology samples in equivocal cases classified as follicular lesions of undetermined significance, improving diagnostic accuracy of malignancy and directing subsequent therapy.[41,42] Although these molecular techniques have not achieved widespread clinical usage, but they are gaining ground in reference laboratories. Their utility, nevertheless, is restricted to classical PTC due to the low incidence of BRAF mutations in FVPTC and the high occurrence of Kras mutations in benign follicular lesions.[35] Suitable clinical molecular biomarkers for FVPTC still await discovery.

CONCLUSION

Since its description fifty years ago, knowledge regarding FVPTC has expanded significantly. However, difficulty persists regarding the precise histopathologic calssification of those cases with less distinctive diagnostic features or with characteristics overlapping with that of FC or Follicular adenoma. The use of molecular techniques, while further elucidating tumor biology and indicating potential therapeutic targets, have not been completely successful in improving diagnostic sensitivity or specificity. Further research will be necessary to achieve this goal.

CONFLICT OF INTEREST
The authors have no conflict of interest to disclose.

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