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ORIGINAL ARTICLE

STUDY OF FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA AND ITS SUBTYPES

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ABSTRACT: BACKGROUND: Follicular variant of papillary thyroid carcinoma is relatively common variant of papillary thyroid carcinoma. Fine needle aspiration cytology (FNAC) is an important investigation in preoperative diagnosis of thyroid lesions. The diagnosis of follicular variant of papillary thyroid carcinoma in FNAC is usually missed and is challenging compared to classic papillary thyroid carcinoma. **OBJECTIVES:** To assess the clinical and histopathological features of subtypes of follicular variant of papillary thyroid carcinoma and to document the features that would improve the sensitivity of FNAC in the preoperative diagnosis. **METHODS:** Retrospective study of histologically confirmed follicular variant of papillary thyroid carcinoma in our institution over 5 years from 2009 to 2013.**RESULTS:** Of 26 cases of FVPTC, 21 cases were encapsulated and 5 cases were non-encapsulated, with male: female ratio was 1:18. The median age was 33.5 years. The most frequent microscopic pattern on FNA was micro follicular (23 cases). The p value for monolayered sheets, papillary fronds, nuclear grooves, pseudo inclusions, nucleomegaly and irregular nuclear membrane were found to be significant. Non-encapsulated variant had significantly higher rate of intra tumoral fibrosis (80% vs. 14% compared to encapsulated variant), extra thyroidal extension (60% vs. 5% respectively), positive margins (60% vs. 5% respectively) and lymph node metastases (60% vs. 9% respectively). **CONCLUSION:** FVPTC appeared to be a heterogeneous disease composed of 2 distinct groups: an infiltrative/diffuse (non-encapsulated) subvariant, which resembles classic papillary carcinoma in its metastatic lymph node pattern and invasive growth, and an encapsulated form, which behaves more like FTA/FTC. The sensitivity of FNA in preoperative diagnosis of FVPTC can be increased by carefully looking for specific features like nuclear grooving and nuclear pseudo inclusions in suspected smears. Further studies with large sample size and long term follow up in required to document the prognosis of FVPTC.

KEYWORDS: Follicular variant, fine needle aspiration, papillary thyroid carcinoma.

INTRODUCTION: Based on the predominant histological features well differentiated carcinoma of thyroid gland has been traditionally classified has papillary thyroid carcinoma(PTC) or follicular thyroid carcinoma (FTC).[1] Papillary thyroid carcinoma is the most frequent type constitutes 85.3% of thyroid malignancies in whites and 72.3% in blacks.[2,3] It often is multifocal, non-encapsulated, and spreads through the lymph nodes. DeLellis defined papillary carcinoma as a well differentiated malignant epithelial tumour characterized by formation of papillary structures, psammoma bodies and a set of distinct nuclear features such as grooves, pseudo inclusions and ground glass appearance.[4] Papillary thyroid carcinoma has many variants such as oncocytic, tall cell, diffuse sclerosing, encapsulated and follicular variant which is the most frequent variant. The follicular variant of papillary thyroid carcinoma (FVPTC) constitutes 9% to 22.5% of the cases.[5-7] This variant is composed entirely or almost completely of follicles, which are lined by cells that have the nuclear

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features of papillary carcinoma. FVPTC. When non-encapsulated, FVPTC infiltrates the surrounding thyroid parenchyma or diffusely involves the thyroid, the diagnosis of carcinoma usually poses no problem.[8,9] Encapsulated FVPTC without invasion of the surrounding thyroid parenchyma, the diagnosis of malignancy depends solely on the presence of nuclear features of PTC (E.g. nuclear clearing, grooves, pseudo inclusions), which often may be borderline. This diagnostic dilemma has important therapeutic implication. If an FVPTC measures more than 1.5 cm, then many physicians will recommend completion thyroidectomy followed by radioactive iodine therapy (RAI). Some authors believe that only lobectomy is sufficient in encapsulated FVPTC since this subtype has excellent. Prognosis. There has been few studies in which tumour behaviour was analysed according the histologic ''sub variants'' of FVPTC. (i.e., non-encapsulated [Infiltrative/diffuse] vs. encapsulated) that can serve as the basis for a conservative treatment approach of encapsulated, non-invasive FVPTC. Further, FNAC is the important investigation in the preoperative diagnosis of thyroid lesion.[10] Follicular variant of papillary thyroid carcinoma is a well-defined entity in histopathology, but its diagnosis in FNAC is challenging and is usually missed.[11] This study also aims to study the cytological features to improve the sensitivity of FNAC in the preoperative diagnosis of this specific variant.

MATERIALS AND METHODS:

Patients: The histopathological records of all patients who underwent thyroidectomy in our institution between 2009 to 2013 with final histopathological report as follicular variant of papillary thyroid carcinoma were included. FVPTC was considered if the tumour composed completely or almost entirely (99% of the tumour) of follicles lined by cells that had nuclear features of PTC.[12] Many cases of papillary carcinoma, cases of poorly differentiated carcinoma, tumours with undifferentiated zone, cases without description of the size of the largest nodule, cases with medullary neoplasia associated with thyroid carcinoma were excluded from the study.

All cases underwent clinical examination and preoperative ultrasound and fine needle aspiration (FNA) of the swelling. The following parameters were noted: age, gender, FNA of thyroid nodule, preoperative ultrasound neck, surgical procedure, associated lymph node dissection, concomitant Hashimoto's thyroiditis, and detailed histopathological description with information on predominant nodule diameter, capsular invasion, vascular invasion, multifocality, extrathyroidal extension, T and N staging.

Definition and Pathology Review: Twenty six cases with histologically confirmed diagnosis of FVPTC with FNA slides in our institution for a period of 5 years between 2009 – 2013 were included in the study. Smears stained with hematoxylin & eosin (H&E) and papanicolaou were examined by two independent pathologists in our institution. Papanicolaou smear were examined because it increase the sensitivity of detecting nuclear features of PTC.[13] Cytomorphological features were analyzed for a minimum of two representative smears. Aspirate is considered adequate if there is presence of 5-6 groups of well-preserved follicular cells, with each group containing 10 or more cells on at least two slides on different passes.[14]

The features analyzed included cellularity, microscopic pattern (Monolayered sheets, syncytial clusters, microfollicular pattern, papillary fronds and single cell distribution), nuclear features (Anisonucleosis, nucleomegaly, fine powdery chromatin, grooves, intranuclear cytoplasmic inclusions, irregular nuclear membrane and nucleoli), colloid characteristics (Thick or thin) and

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psammoma bodies. These features were graded as absent (0), occasional (1), frequently seen (2), prominent finding (3).

Follicular variants were sub-divided into the following histologic subvariants: 1) encapsulated when the tumour is totally surrounded by capsule with or without capsular/vascular invasion. 2) un encapsulated subvariant included infiltraive and diffuse variant, infiltrative if there was absent or incomplete encapsulation with invasive tongues of tumor infiltrating non neoplastic thyroid parenchyma, almost always with prominent fibrosis; diffuse if 1 lobe or an entire thyroid was involved by a non-encapsulated, diffuse, or multinodular tumor without desmoplasia and with pushing borders or absence of a clear cut delineation between the tumor and the adjacent parenchyma. Tumor size was measured as the greatest dimension of the resected tumor specimen. Mitotic rate was determined by counting 10 high-power fields (X 400 magnification) in the areas of greatest concentrations of mitotic figures. Vascular and capsular invasion were identified according to the criteria outlined in the last Armed Forces Institute of Pathology fascicle on thyroid tumors.[12] Capsular invasion was defined as complete penetration of the entire thickness of the tumour capsule. Vascular invasion was defined as invasion of a vessel located within or outside the tumour capsule.

The degree of intratumoral fibrosis was recorded as absent, mild, or marked. The presence or absence of tumour extension into the extra thyroid soft tissue stroma as well as the presence of extrathyroid vascular invasion were documented. Finally, microscopic resection margins were categorized as either positive (Tumour at the inked margin) or negative (No tumour at the inked margin).

STATISTICAL ANALYSIS: Descriptive statistics were used to summarize study data. Associations between categorical variables were evaluated by using the Fisher exact test or the chi-square test, as appropriate. In all statistical analysis, a 2-tailed P value <.05 was considered statistically significant. Follow-up was calculated from the time of surgery to date of last follow-up.

RESULTS: Histopathological examination showed FVPTC in 26 cases in our institution for 5 years between 2009 – 2013 were included in the study. Table 1 shows the descriptive analysis of clinicopathological traits of cases included in the study.

Clinical Parameters: Table 2 lists the clinical and pathological features according to histologic sub variant of FVPTC of 26 cases that were included in the study. The median age for 26 cases included in the study was 33.5 years. Twenty two of 26 patients (84%) were females, male: female ratio was 1:18. 17 patients underwent total thyroidectomy, 5 patients underwent hemithyroidectomy, and remaining 4 patients underwent Dunhill's procedure. two patients underwent central compartment neck dissection and four patients underwent unilateral modified radical neck dissection which included central compartment. Following surgery all patients received radioactive iodine therapy. The lymph node metastasis rate was significantly higher in patients of non-encapsulated variety (3 out of 5; 60%) compared with encapsulated variety (2 out of 21; 10%; $p < 0.03$) which was significant. None of the patients in either subvariant had distant metastases.

Pathological Parameters: In preoperative FNA diagnosis, 15 cases were diagnosed as adenomatous goitre, 5 as follicular adenoma, 3 as classical PTC, 2 cases as FVPTC and 1 case suspicious of PTC. After

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review of smears 8 cases were diagnosed as FVPTC, 13 as adenomatous goitre, 3 as classical PTC, 1 case as follicular adenoma and 1 suspicious of PTC. 20 cases with moderate to high cellularity, 6 cases with low cellularity. Multiple microscopic patterns were observed in some cases, however the most frequent microscopic pattern was micro follicular (23 cases) followed by syncytial clusters (21 cases). Nuclear grooves and pseudo inclusions were seen in 20 and 11 cases respectively. Fine powdery chromatin, anisonucleosis and nucleomegaly was seen in all cases. Psammoma bodies were not seen in any case. The p value for monolayered sheets, papillary fronds, nuclear grooves, pseudo inclusions, nucleomegaly and irregular nuclear membrane were found to be significant.

The median tumour size of the tumour in our study was 5cm in capsulated variant and 3 cm in non-encapsulated variant, 14 of 26 cases (54%) of FVPTC exceeded more than 4 cm. 21 of 26 cases (81%) were encapsulated variant, 5 of 26 cases (19%) were non-encapsulated variant which invaded into the surrounding thyroid parenchyma in diffuse (1 case) or infiltrative (4 cases) pattern. There was no statistically significant difference between capsulated and non-capsulated sub variant in tumour size, vascular invasion, capsular invasion, mitosis, oncocytic cytoplasm. The nuclear features of papillary thyroid carcinoma was found diffusely in 19 of 21 (90%) and multifocal in 2 of 21 cases (10%) in encapsulated variant. Assessment of nuclear features in non-encapsulated variant was not required because the diagnosis of tumour is confirmed by its invasive characteristics. However non-encapsulated variant had significantly higher rate of intratumoral fibrosis (80% vs. 14% compared to encapsulated variant), extra thyroidal extension (60% vs. 5% respectively), positive margins (60% vs. 5% respectively) and lymph node metastases (60% vs. 9% respectively).

DISCUSSION: Crile and Hazard first described FVPTC they named it as alveolar variant of PTC.[15] This was later confirmed by Lindsay who observed that the tumour had follicular architecture but the nuclear features of classical PTC and named it as FVPTC. Chen and Rosai showed that the FVPTC behaved similar to classical PTC and stressed the importance of nuclear features than architecture in making diagnosis of FVPTC.[16]

In a study by Lin HS et al.,[4] sensitivity of FNAC for the diagnosis of FVPTC was only 25% compared to 74% for the classic PTC. The reason for low sensitivity was the FVPTC has features in common with the benign and neoplastic follicular lesion due to the presence of follicular architecture and mono layered sheets in the follicular cells and FVPTC has nuclear features of classical PTC. This led to misdiagnosis as follicular neoplasm and adenomatous goitre leading to inadequate surgical treatment in the form of hemi thyroidectomy. This emphasizes the importance of increasing the sensitivity of FNA in preoperative diagnosis of FVPTC.

Aron et al.,[17] in their study stressed that syncytial clusters, micro follicular pattern, chromatin clearing and nuclear grooves were significant features to the diagnosis of FVPTC. Nucleomegaly was seen in all of their cases. In our study micro follicular and syncitial clusters were the predominant pattern. Fine powdery chromatin, anisonucleosis and nucleomegaly was seen in all cases though it did not reach statistical significance.

According to Powari et al.,[18] FVPTC should be considered in the diagnosis if the smears show high cellularity, syncytial clusters and follicular arrangement and thick colloid. Shih SR et al.,[19] concluded in their study that it was difficult to differentiate FVPTC from classic PTC in FNAC and when follicular structures were seen in smears, careful search for nuclear features should be done.

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To avoid misdiagnosis and choose correct modality of treatment, the smears with features like micro follicular pattern, syncytial clusters, fine powdery chromatin, anisonucleosis, nucleomegaly should lead the pathologist to look more carefully for specific features like nuclear grooves and nuclear pseudo inclusions.

The median age in our study was 33.5 years with a female predominance (84%) were in keeping with the previous studies of papillary carcinomas that included FVPTC.[12,20] in our study encapsulated variant outnumbered the non-encapsulated variant (21 vs. 5 respectively, this rarity seems to be in concordant with the first detailed study of FVPTC by Chem and Rosai.[21] In their 1977 article, all their cases were infiltrative with an apparently very low incidence since they found only 6 cases of infiltrative FVPTC out of all thyroid carcinoma cases diagnosed at the University of Minnesota Hospitals up to the year 1975.

In our study patients with infiltraive/diffuse FVPTC had significantly greater frequency of ($p < 0.001$) intratumoral fibrosis, extra thyroidal extension, positive margins and greater lymph node metastasis than patients who had encapsulated FVPTC. There was no significant difference in capsular/vascular invasion, mitosis between the two variants. It has been difficult to document the clinical behaviour in our study due to small sample size and lack of long term follow-up. Many published series evaluating clinico pathologic features and

Outcome of this tumour lack a clear definition of this condition. Many authorities believe FVPTC has same prognosis as classical PTC.[20,22] FVPTC presents with large tumour size and at younger age.[20] In some reports it was found to mimic pathological and clinical behaviour of follicular neoplasm.[20,23] some encapsulated variant can have distant metastasis in the absence of lymph node metastasis mimicking follicular carcinoma.[20] Some cases demonstrated significantly higher prevalence of capsular and vascular invasion, distant metastasis and poorly differentiated areas.[24] FVPTC has significantly lower rates of lymph node metastases, is more often encapsulated and shows extra-thyroidal invasion less often than conventional PTC.[20,22]

In a recent study that involved more than 500 thyroid cancer patients and with more than 15 years of follow-up, FVPTC was concluded to have more favourable clinicopathological features and a better tumour risk group profile. However, long term outcome was similar to conventional PTC patients.[25] In recent years; advances in molecular biology have shed some light on the diagnosis and prognosis of thyroid cancer. The controversial issues related to the follicular variant of PTC could be explained by molecular biology.

To conclude, FVPTC is a relatively common subtype of PTC. FVPTC appeared to be a heterogeneous disease composed of 2 distinct groups: an infiltrative/diffuse (non-encapsulated) subvariant, which resembles classic papillary carcinoma in its metastatic lymph node pattern and invasive growth, and an encapsulated form, which behaves more like FTA/FTC. The sensitivity of FNA in preoperative diagnosis of FVPTC can be increased by carefully looking for specific features like nuclear grooving and nuclear pseudo inclusions in suspected smears. Further studies with large sample size and long term follow up in required to document the prognosis of FVPTC.

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SL. No.	Age/ gender	FNAC	PROCEDURE	VARIANT	NODULE DIAMETER	HASHIMOTOS THYROIDITIS	MULTI FOCALIY	LYMPH/ VASCULAR/ NEURAL INVASION	GLAND/ CAPSULAR INVASION	EXTRA GLANDULAR SPILL	T	N
1	65/M	PAPILLARY NEOPLASM	TOTAL THYROIDECTOMY + RT MRND	CAPSULATED	5	A	A	A	A	A	T3	N0
2	30/F	FOLLICULAR NEOPLASM	TOTAL THYROIDECTOMY	UNCAPSULATED	5	A	P	P	P	P	T3	N1b
3	60/F	FOLLICULAR NEOPLASM	TOTAL THYROIDECTOMY + CENTRAL NECK DISSECTION	CAPSULATED	4	A	A	A	A	A	T2	N0
4	25/F	FOLLICULAR NEOPLASM	TOTAL THYROIDECTOMY	CAPSULATED	5	A	A	A	A	A	T3	N0
5	42/M	COLLOID GOITRE	LEFT HEMITHYROIDECTOMY	CAPSULATED	3	A	A	P	A	A	T2	N0
6	37/F	COLLOID GOITRE	LEFT HEMITHYROIDECTOMY	CAPSULATED	4.4	A	A	A	A	A	T3	N0
7	24/F	COLLOID GOITRE	LEFT HEMITHYROIDECTOMY	CAPSULATED	5.5	A	A	A	A	A	T3	N0
8	43/M	COLLOID GOITRE	TOTAL THYROIDECTOMY + RT MRND	CAPSULATED	8	A	A	A	A	A	T3	N0
9	57/M	COLLOID GOITRE	LEFT HEMITHYROIDECTOMY	UNCAPSULATED	4	A	A	A	A	A	T2	N1a
10	25/F	SUSPICIOUS PAPILLARY NEOPLASM	TOTAL THYROIDECTOMY	CAPSULATED	6	A	A	A	A	A	T3	N0
11	55/F	MNG +HURTLE CELL HYPERPLASIA	TOTAL THYROIDECTOMY	CAPSULATED	15	A	A	P	P	A	T3	N1b
12	40/F	NODULAR GOITRE	TOTAL THYROIDECTOMY	CAPSULATED	12	A	A	A	A	A	T3	N0
13	20/F	NODULAR GOITRE	TOTAL THYROIDECTOMY	CAPSULATED	2	A	A	A	A	A	T1	N0
14	32/F	FVPTC	TOTAL THYROIDECTOMY	CAPSULATED	6	A	A	A	A	A	T3	N0
15	30/F	FOLLICULAR NEOPLASM	TOTAL THYROIDECTOMY	CAPSULATED	3	A	A	A	A	A	T2	N0
16	35/F	COLLIOD GOITRE	TOTAL THYROIDECTOMY	CAPSULATED	5	A	A	A	A	A	T3	N0
17	25/F	COLLOID GOITRE	DUNHILL PROCEDURE	CAPSULATED	6	A	A	A	P	A	T3	N1b
18	18/F	PAPILLARY CARCINOMA	TOTAL THYROIDECTOMY + CENTRAL NECK DISSECTION	CAPSULATED	5	A	A	A	A	A	T3	N0
19	28/F	NODULAR GOITRE	LEFT HEMITHYROIDECTOMY	CAPSULATED	4	A	A	A	A	A	T2	N0
20	30/F	COLLOID GOITRE	DUNHILLS PROCEDURE	CAPSULATED	3	A	A	A	A	A	T2	N0
21	35/F	FVPTC	TOTAL THYROIDECTOMY	UNCAPSULATED	3	A	A	A	A	P	T2	N0
22	32/F	FOLLICULAR NEOPLASM	DUNHILLS PROCEDURE	CAPSULATED	6	A	P	A	P	P	T3	N0
23	21/F	COLLOID GOITRE	TOTAL THYROIDECTOMY	CAPSULATED	2	A	A	A	A	A	T1	N0
24	52/F	COLLOID GOITRE	TOTAL THYROIDECTOMY	CAPSULATED	4	A	A	A	A	A	T2	N0
25	40/F	PAPILLARY NEOPLASM	TOTAL THYROIDECTOMY + LT MRND	UNCAPSULATED	3	A	A	A	P	P	T2	N0
26	50/F	NODULAR GOITRE	DUNHILLS PROCEDURE	UNCAPSULATED	4	A	A	A	A	A	T2	N1a

Table 1: Descriptive analysis of clinicopathological traits of FVPTC included in the study

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Characteristics	No. of patients (%)		P value
	Encapsulated FVPTC (n= 21 cases)	Non-encapsulated FVPTC (n=5 cases)	
Age, y (median, 33.5 years)			
< 45	17	3	0.25
>45	3	2	
Gender			
Male	18	4	1
Female	3	1	
Tumour size, cm			
Median	5	3	0.14
< 4	8	4	
>4	13	1	
Vascular invasion			
Absent	19	4	0.48
Present	2	1	
Capsular invasion			
Absent	18	3	0.23
Present	3	2	
PTC nuclei in tumour			
Multifocal	2	NA	NA
Diffuse	19	NA	
Mitosis			
Absent	19	5	1
Present	2	0	
Oncocytic cytoplasm			
Absent	20	5	1
Present	1	0	
Intratumoral fibrosis			
Absent/mild	18	1	0.01
Marked	3	4	
Extrathyroidal extension			
Absent	20	2	0.01
Present	1	3	
Margins			
positive	1	3	0.01
Negative	20	2	
Thyroid surgery			
Less than total thyroidectomy	7	2	1
Total thyroidectomy	14	3	
Lymph node metastasis			
Present	2	3	0.03
Absent	19	2	
Distant metastasis			
Present	0	0	1
Absent	21	5	

TABLE 2: Clinical and pathological features according to histologic sub variant of follicular variant of papillary thyroid carcinoma

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ABBREVIATIONS:

FTA – follicular thyroid adenoma.
FTC – follicular thyroid carcinoma.
FNAC – fine needle aspiration cytology.
FVPTC – follicular variant papillary thyroid carcinoma.

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