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Original Research Article

Study of variants of papillary carcinoma of Thyroid with a special emphasis on NIFTP (Non-invasive Follicular Thyroid Neoplasm with Papillary like nuclear features)

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ABSTRACT

Introduction: Rapid advances have taken place in the classification of papillary thyroid neoplasms with reclassification and addition of new variants. One such change is the addition of a new entity called NIFTP (Non-invasive Follicular Thyroid Neoplasm with Papillary like nuclear features). So called recognising its non-malignant potential.
Study Design: The present study is a retrospective observational cohort study on thyroidectomy specimens collected between Jan 2018 to June 2021 focussing on variants of papillary carcinoma with special emphasis on recognising NIFTP – which has got good prognosis and is considered non-malignant.
Results: Out of the 40 cases of papillary neoplasms 36 were PTC and 4 were NIFTP. Among the PTC cases 27 were classic PTC, 4 were FVPTC (Follicular Variant of Papillary Thyroid Carcinoma) 3 were papillary microcarcinoma, 1 was Warthin like Variant of PTC and 1 was Encapsulated PTC.
Conclusion: The Study concludes that special vigilance is required in strictly adhering to the criteria proposed by new 2017 WHO classification of Papillary tumours. Recognising NIFTP as it is a non-malignant entity should be given due importance.

1. Introduction

A rapid increase in the incidence of Thyroid cancer especially Papillary thyroid carcinoma (PTC) has been observed the past decade which points to the improved diagnostic technology.[1] PTC is a malignant epitheial neoplasm with follicular cell differentiation and with distinct nuclear features.[2] The new 2017 WHO classification of thyroid tumours has made several modifications by emphasizing the risk stratification for both Papillary thyroid carcinoma(PTC) and Follicular thyroid carcinoma FTC, new histologic variants of PTC and adding up a new borderline category in order to avoid overdiagnosis and over treatment of low risk thyroid neoplasms.[3] The present study is aimed at the clinicopathological behavior of different variants of PTC that are reported from a single center experience and also to emphasize the histopathological patterns, diagnostic pitfalls observed in a newly added borderline entity named Non Invasive Thyroid neoplasm of PTC like nuclear features (NIFTP) that were been reported.

2. Materials and Methods

All the archived data related to the patients who underwent thyroidectomy on the basis of clinical diagnosis as PTC and suspicious of follicular neoplasm have been retreived. These thyroidectomies were conducted in our surgical department at ESIC Medical college, Sanath nagar, between the time period of January 2018 to June 2021.

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A total of 70 cases were collected out of which 36 were diagnosed as PTC, 23 as Follicular adenoma, 7 as Follicular thyroid carcinoma, 4 as NIFTP. The Follicular adenomas and FTCs were excluded from the study.

This is a retrospective observational cohort study focused on the different histological variants of PTC we have come across during the study period and also focusing on the clinicopathological characteristics of NIFTP.

2.1. Definitions

All the H & E slides from the surgical specimens of 40 diagnosed cases included in the study were reviewed according to the new 2017 WHO classification of tumours of endocrine organs, 4^{th} edition. Tumours with epithelial differentiation and a distinctive set of nuclear features i,e nuclear enlargement, overcrowding, nuclear grooves, inclusions and psammomma bodies are categorized as papillary carcinoma. And these PTC cases were further classified according to WHO classification. Our study showed the following histological variants: FVPTC, Microcarcinoma, Encapsulated variant, Warthin like variant.

When two or more foci of PTC either microcarcinoma (<0.1cm) or larger tumour in a single lobe or involving both the lobes is categorized as multifocal PTC. In all the variants of PTC extrathyroid extension is looked for. TNM staging was done for all the thyroidectomy specimens received depending on the lymph node involvement according to CAP guidelines. The histopathology of the adjacent thyroid parenchyma is also observed and reported accordingly either as simple nodular hyperplasia, Hashimotos thyroiditis or as normal thyroid. Considering the tumour size those which are not more than 1cm in the largest diameter are categorized as Papillary Microcarcinoma (PMC). Rest of the other variants are classified according to the respective differentiation patterns.

Besides these we had 4 cases of Non Invasive Thyroid neoplasm with Follicular growth pattern and with nuclear features of Papillary thyroid carcinoma (NIFTP). We strictly adhered to diagnostic criteria proposed by the new WHO classification of thyroid tumours, 2017, 4^{th} edition. to categorize this newly added entity.

This project was approved by the Ethics Committee of our institution.

3. Results

3.1. Demographic & Clinicopathological characteristics

A total of 40 cases were enrolled in this retrospective study conducted for the period of January 2018 to June 2021 at our institution. This included 36 (90%) of Papilllary thyroid carcinoma (PTC) and 4 (10%) cases of Non Invasive Follicular Thyroid neoplasm with Papillary like nuclear features (NIFTP). The average age at the time of diagnosis was (40.1) years spread across an age range of 15-71 yrs, with a female predominance (92.5%) i,e 37 out of 40 cases.

The tumour size has a range of (0.5-5.0cm) across the various histological patterns with a median of (2.0cm) and the pattern distribution as listed in Table 1. Out of the 36 diagnosed cases of PTC 27 were of Classic type, 4 were of Follicular Variant of Papillary Thyroid Carcinoma (FVPTC), 3 were Papillary microcarcinoma (PMC), one case each of Encapsulated PTC and Warthin like variant (WLPTC). The median tumour size for the respective variants as listed in Table 2. for the classic type (2.5cm), FVPTC (2.0cm), Microcarcinoma (0.8cm), Encapsulated (1.2cm), Warthin like variant (2.0cm), NIFTP (2.3cm).

Multifocality was observed in 3/27 (11.1%) cases of Classic PTC and all the 3 showed evidence of metastatic deposits in the respective Central compartment Lymph Node dissections. It was also observed that the adjacent thyroid parenchyma showed changes of Hashimotos Thyroiditis in 12/36 (33.3%) cases of total PTC and Nodular Hyperplasia in 7/36 (19.4%) while the remaining 17/36 (47.2%) cases were unremarkable. None of these showed evidence of Extra thyroid extension. A total of 5/36 (13.8%) cases of PTC showed lymph node deposits in the central compartment.

4 lobectomy specimens were diagnosed as FVPTC with exclusive follicular growth pattern of infiltrative type and nuclear features that of conventional PTC. There is no evidence of Intra tumoral fibrosis, Extra thyroid extension in the specimens examined. Keeping in view of the expected clinical outcome and lymphatic spread similar to that of conventional PTC, the respective patients underwent completion thyroidectomy and neck dissection. However there is no evidence of lymphnode spread in these patients.

Papillary Microcarcinoma (PMC) was detected in 3/36 cases of PTC with a mean tumour size of 0.7cm. All the 3 cases were encapsulated, with papillary histologic pattern in 2 cases and the other one showed micro follicular pattern with nuclear enlargement, overcrowding, grooves and inclusions. With regard to the enlarging tumour size on active surveillance from the time of initial diagnosis i,e >0.3cm, total thyroidectomy with lymph node dissection was performed for all these 3 cases but none has shown the evidence of lymph node spread or extra thyroid extension. Thus reducing the risk of recurrence.

One case of Warthin like variant of PTC has been reported in our study, with typical histopathological features of papillae lined by oncocytic neoplastic epithelial cells with nuclear clearing, grooves and inclusions. Lymphocytic aggregates and germinal centers are observed in the fibrovascular cores of the papillae with the adjacent thyroid parenchyma showing features of Hashimotos thyroiditis.

One case of Encapsulated variant of PTC was also reported with a tumour size of 1.2cm, thick capsule,

papillary growth pattern, but with no evidence of capsular or vascular invasion, nor lymphnode metastasis.

Taking into consideration of the diagnostic criteria proposed for NIFTP in IV WHO classification of thyroid tumours- 2017, 4 cases have been reported in our study. These were cytologically diagnosed under category-III (Follicular Lesion of Undetermined Significance) for one case and the other 3 as Category- IV (Suspicious of Follicular Neoplasm) according to TBSRTC. On histopathological examination of these lobectomy specimens the mean tumour size is 2.5cm. and 3/4 are encapsulated, the remaining one is well demarcated, showing follicular growth pattern, distinct nuclear features of PTC with an average nuclear scoring of 2. Sprinkling sign is noted in 2 out of 4 cases. There is no evidence of capsular or vascular invasion, neither intra tumoral necrosis nor mitotic figures. None of these showed evidence of lymph node metastasis. The background parenchyma showed nodular hyperplasia.

4. Discussion

In the current study we reviewed the clinicopathological behavior of different histological variants of PTC namely classic, FVPTC, PMC, Encapsulated and Warthin like variant of PTC (WLPTC) in addition NIFTP a newly added borderline thyroid neoplasm. There is no significant statistical difference in age and sex of the patients in this study.

Conventional PTC being the most prevalent type as in other studies showed similar prevalence in our study. All the cases showing multifocality in the current study are associated with lymph node deposits especially to central compartment (level VI), which is in concordane with the study conducted by Afif. et al which highlighted the presence of multifocality in PTC as an indicator of disease aggressiveness and higher tendency for recurrence, lymphatic spread and death.[4] A significant association (33.3%) of PTC and Hashimotos Thyroiditis (HT) was found in our study, however there is equal distribution of nodular and diffuse variants of HT. Study by Graceffa et al has underlined the frequent coexistence of these two pathologies in 28.6% of their cases.[5,6] Our study is in total agreement with this observation and highlights the definite link between these two pathologies. However the prognostic effect of peri tumoral lymphocytic infiltration was not studied in our cohort due to lack of follow up.

Some variants of PTC like PMC, Encapsulated and Warthin like variant are known to have more favourable prognosis. PMC is the only variant that is based on macroscopic dimensions and not on histologic patterns, either encapsulated or non- encapsulated. Despite the relatively known good prognosis of PMC, risk stratification plays an important role in taking appropriate therapeutic strategies.[7,8] Taking these into consideration the 3 cases of PMC diagnosed in our study are subjected for total thyroidectomy and lymph node dissection. The combined histological and molecular status of PMC will be a better prognostic predictor. However our study couldn't include the molecular status.

Encapsulated PTC though known for indolent course and better prognosis it must be looked out for lymph node spread, extra thyroid extension and treatment follow-up.[9] Studies by A.Pisanu, D.Deplano, I.Reccia et al reported lymph node involvement at the time of diagnosis in (5.7%), extra thyroid extension in (1.9%) of their cases.[10] However the one case reported in our study showed none of these charecteristics.

In the previous WHO classification WLPTC is considered along with oncocytic variant. Recently with the approved prognosis of the former similar to that of conventional PTC, it is now regarded as a distinct variant of PTC in the new 2017, WHO classification of Thyroid tumours.[2,3] It is a well known observation that WLPTC is associated with Hashimotos Thyroiditis in the surrounding non- neoplastic tissue as reported in several case series by Apel etal, Ludvikova et al. Our current study reported one case and it is in concordance with their studies in terms of age at presentation i,e usually a decade earlier than that of classic PTC, association with HT and lesser rates of lymph node metastasis.[11,12] The categorization of FVPTC into encapsulated and non-encapsulated in the previous WHO classification is now further refined by considering capsular and vascular invasion in the encapsulated category and thus a new borderline entity with diffuse follicular growth pattern, distinct nuclear features which is encapsulated and with no evidence of capsular or vascular invasion, otherwise named as NIFTP has been introduced in the new 2017, WHO classification of thyroid tumours. Nikiforov et al in their retrospective study proposed a consensus diagnostic criteria for EFVPTC and NIFTP. The diagnosis of NIFTP in our study showed a female predominance and the prior FNA diagnosis was either TIR-3 or TIR-4 which goes in line with the study by canini et al. Thus in general agreement that it is difficult to diagnose NIFTP on FNAs. The histpathological feature 'sprinkling sign' also supports this statement as the nuclear features are not diffuse in all NIFTP cases. However the diagnosis of NIFTP can occur only on histopathological sections as the scrupulous tumour capsule evaluation is a mandate to rule out its invasion.[13]

5. Conclusion

The new 2017 WHO classification of thyroid tumours has made notable changes with regard to clinicopathological behavior of different entities. The current study from a single center showed the clinicopathological behavior of few of the variants of PTC and also made an emphasis on the newly added entity named NIFTP. The features of tumour aggressiveness like lymph node metastasis, extra

Table 1: Age % sex distribution of variants of PTC and NIFTP.

S.No	Histologic type PTC (36)	Age <40yrs	Age >40yrs	Male	Female
1	Classic (27)	12	15	02	25
2	FVPTC (4)	03	01	01	03
3	PMC (3)	03	-	-	03
4	WLPTC (1)	01	-	-	01
5	EPTC (1)	-	01	-	01
6	NIFTP (4)	02	02	-	04

Table 2: Descripstive analysis of clinicopathological features of variants of PTC and NIFTP included in the study.

Histologic variant	Tumour size (cm)	Multifocality	Coexistent HT	MNG	Normal thyroid	Lymph Node deposits
Classic (27)	(1.1-5.0)	03/27	7+	6	14	05/27
FVPTC (4)	(1.5-3.0)	-	-	1	03	-
PMC (3)	(0.5-0.8)	-	3+	-	-	-
EPTC (1)	(1.2)	-	+	-	-	-
WLPTC (1)	(2.0)	-	+	-	-	-
NIFTP (1)	(1.5-4.6)	-	-	1	03	-

thyroid extension, features of invasion have to be looked out for in all the cases of PTC. Strict adherence to the new criteria proposed for diagnosis of NIFTP in association with extensive tumour capsule examination is necessary in order to avoid over diagnosis of the disease and further over treatment with radiation, reduce the apprehension to the patient.

6. Conflict of Interest

There is no potential conflict of interests related to the exclusive nature of this paper.

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