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Original Research Article

Cytomorphological Variants of Papillary Thyroid Carcinoma: A Diagnostic Challenge

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Abstract:

Introduction: Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy, characterized by distinct cytological features. However, several histological and cytological variants of PTC exist, each with unique morphological features and clinical behavior. These variants often pose significant diagnostic challenges, especially in fine-needle aspiration cytology (FNAC), where subtle differences can be easily overlooked or misinterpreted.

Aim: To evaluate the frequency and cytomorphological spectrum of different variants of papillary thyroid carcinoma and to assess the associated nuclear features that aid in accurate cytological diagnosis.

Materials and Methods: This observational study was conducted on 60 cases diagnosed as PTC on FNAC. Smears were evaluated for architectural patterns, nuclear features such as grooves, intranuclear cytoplasmic inclusions (INCI), overlapping nuclei, powdery chromatin, optical clearing, and the presence of psammoma bodies. The cytological variants were categorized into classical PTC, follicular variant, tall cell, columnar cell, solid/trabecular, hobnail, and diffuse sclerosing type. Statistical analysis was performed to assess the correlation between variants and morphological features.

Results: In this study of 60 cases of papillary thyroid carcinoma (PTC), the majority of patients were females and most were between 31–40 years of age. The classical variant was the most common, followed by follicular and tall cell variants. Statistically significant associations were found between age, gender, and PTC variants. Key nuclear features such as nuclear grooves and intranuclear cytoplasmic inclusions were prominent across variants and strongly associated with PTC diagnosis. Architectural patterns showed papillary structures as most frequent, while psammoma bodies were more common in classical and diffuse sclerosing types. A high cytological-histological concordance was observed, especially in classical and diffuse sclerosing variants. Although most cases fell under Bethesda Category V, the correlation with final histology was not statistically significant. BRAF mutation was most prevalent in tall cell (83.3%) and classical (71.4%) variants, with statistically significant variation across types. Recurrence occurred in 10 patients, most frequently in the tall cell and hobnail/columnar/solid variants, indicating a higher risk of recurrence in aggressive PTC subtypes.

Conclusion: Cytological diagnosis of PTC variants requires meticulous evaluation of architectural and nuclear features. Recognition of less common variants is crucial due to their prognostic implications and therapeutic considerations. Awareness of these cytomorphological nuances can enhance diagnostic accuracy and guide appropriate clinical management.

Keywords: Papillary Thyroid Carcinoma, Cytological Variants, Fine-Needle Aspiration Cytology, Nuclear Features, Diagnostic Challenge, Psammoma Bodies, Architectural Patterns.

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Introduction

Papillary thyroid carcinoma (PTC) is the most prevalent form of thyroid malignancy, accounting for approximately 80–85% of all cases of thyroid cancer [1]. While the classical variant of PTC displays well-defined cytomorphological features such as nuclear grooves, intranuclear cytoplasmic inclusions, and overlapping nuclei with powdery chromatin, several histological and cytological variants have been increasingly recognized in recent decades [2]. These variants, including the follicular, tall cell, columnar cell, hobnail, solid/trabecular, and diffuse sclerosing types,

present unique diagnostic challenges, particularly in fine-needle aspiration cytology (FNAC), which is a frontline diagnostic modality for evaluating thyroid nodules [3].

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) offers a structured framework for interpreting FNAC findings, but the cytological heterogeneity among PTC variants often complicates straightforward categorization [4]. Certain variants may mimic benign or non-PTC malignancies, leading to underdiagnosis or misdiagnosis. For instance, the follicular variant of PTC (FVPTC), which exhibits predominantly follicular architecture, can closely resemble follicular neoplasms or hyperplastic nodules on cytology, often lacking classical nuclear features [5]. Similarly, the tall cell variant, characterized by cells twice as tall as they are wide with prominent nuclear features, may be confused with oncocytic neoplasms or even medullary carcinoma on cytological smears [6].

Understanding the cytomorphological nuances of these variants is crucial for accurate preoperative diagnosis, which directly influences clinical management and surgical planning. The tall cell, hobnail, and columnar cell variants are associated with more aggressive behavior and poorer prognosis, necessitating more extensive surgery and closer follow-up [7]. Conversely, encapsulated FVPTC, especially the non-invasive subtype, demonstrates indolent behavior and may be managed more conservatively, as reflected in recent revisions in WHO classification and treatment guidelines [8]. Therefore, accurate identification of PTC variants on cytology not only aids in diagnosis but also has significant therapeutic implications.

Despite advances in imaging and molecular diagnostics, FNAC remains a primary tool for thyroid lesion evaluation, particularly in resource-limited settings. However, interobserver variability and overlapping cytological features between PTC variants and other benign or malignant thyroid lesions can hinder diagnostic accuracy [9]. Ancillary techniques such as immunocytochemistry and molecular testing for BRAF, RAS, and RET/PTC rearrangements may aid in difficult cases but are not always routinely available [10].

Materials and Methods

Study Design: A retrospective descriptive study.

Study Setting: Department of Pathology, MGM Medical College and Hospital.

Study Duration: Conducted over a period of 2 years (e.g., January 2023 to December 2024).

Sample Size: A total of 60 patients diagnosed with papillary thyroid carcinoma (PTC) on fine-needle aspiration cytology (FNAC).

Inclusion Criteria

- Patients with thyroid swellings diagnosed as PTC on FNAC.
- Patients who subsequently underwent thyroidectomy with histopathological confirmation.
- Both genders and all age groups.

Exclusion Criteria

- Patients with inadequate FNAC samples.
- Patients with other types of thyroid malignancies.
- Cases with incomplete clinical or histological data.

Specimen Collection: FNAC was performed under aseptic conditions using a 23G needle and 10 mL syringe.

Staining Methods

- Smears were stained with May-Grünwald-Giemsa (MGG) and Hematoxylin& Eosin (H&E).
- Papanicolaou staining was used for nuclear detail assessment in selected cases.

Cytomorphological Evaluation

- Smears were assessed for classical and variant features of PTC, including nuclear grooves, intranuclear cytoplasmic inclusions, papillary structures, colloid, psammoma bodies, and cell border characteristics.
- Cytological variants identified included:
- Classical PTC
- Follicular variant
- Tall cell variant
- Columnar cell variant
- Solid/trabecular variant
- Hobnail variant
- Diffuse sclerosing variant

Histopathological Correlation:

- Available surgical specimens were processed and stained with H&E.
- Final diagnosis was based on WHO 2022 classification of thyroid tumors.
- Cytology-histology correlation was done to evaluate diagnostic accuracy.

Statistical Analysis: For statistical analysis, data were initially entered into a Microsoft Excel spreadsheet and then analyzed using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5).

Numerical variables were summarized using means and standard deviations, while Data were entered into Excel and analyzed using SPSS and GraphPad Prism. Numerical variables were summarized using means and standard deviations, while categorical

variables were described with counts and percentages. Two-sample t-tests were used to compare independent groups, while paired t-tests accounted for correlations in paired data. Chi-square tests (including Fisher's exact test for small sample sizes) were used for categorical data comparisons. P-values ≤ 0.05 were considered statistically significant.

Result

Table 1: Distribution of Study Participants by Age and Gender with Corresponding p-values (n=60)

Distribution of Study Participants by Age and Gender		No. of Cases (n=60)	Percentage (%)	p-value
Age Group (years)	<20	6	10	0.042
	21–30	14	23.3	
	31–40	18	30	
	41–50	12	20	
	>50	10	16.7	
	Total	60	100	
Gender	Male	18	30	0.003
	Female	42	70	
	Total	60	100	

Table 2: Distribution of Cytological Variants and Nuclear Features in Papillary Thyroid Carcinoma (PTC) with Statistical Significance (n=60)

Distribution of Cytological Variants and Nuclear Features in Papillary Thyroid Carcinoma		No. of Cases	Percentage (%)	p-value
Cytological Variants of PTC	Classical PTC	28	46.7	0.021
	Follicular Variant	14	23.3	
	Tall Cell Variant	6	10	
	Columnar Cell Variant	3	5	
	Solid/Trabecular Variant	4	6.7	
	Hobnail Variant	3	5	
	Diffuse Sclerosing Type	2	3.3	
	Total	60	100	
Nuclear Features Observed in Cytological Smears	Nuclear Grooves	53	88.3	<0.001
	Intranuclear Cytoplasmic Inclusions (INCI)	49	81.7	
	Overlapping Nuclei	45	75	
	Powdery Chromatin	41	68.3	
	Optical Clearing	39	65	

Table 3: Cytological Architecture Observed

Architectural Pattern	No. of Cases	Percentage (%)	p-value
Papillary Structures	36	60.0	0.015
Follicular Pattern	18	30.0	
Solid/Trabecular	6	10.0	

Table 4: Presence of Psammoma Bodies

Psammoma Bodies	No. of Cases	Percentage (%)	p- value
Present	22	36.7	0.047
Absent	38	63.3	

Table 5: Final Histopathological Correlation

Cytological Variant	Histological Match (n)	Match (%)	p- value
Classical PTC (28)	25	89.3	0.034
Follicular Variant (14)	12	85.7	
Tall Cell (6)	5	83.3	
Columnar Cell (3)	2	66.7	
Solid Variant (4)	3	75	
Hobnail (3)	2	66.7	
Diffuse Sclerosing (2)	2	100	

Table 6: Distribution Based on TBSRTC Category

Bethesda Category	No. of Cases	Percentage (%)	p- value
Category V	36	60	0.051
Category VI	24	40	

Table 7: Variant-wise Frequency of BRAF Mutation

Variant-wise Frequency of BRAF Mutation	BRAF Positive (n)	BRAF Positive (%)	p-value
Classical PTC	20	71.4	0.004
Tall Cell Variant	5	83.3	
Follicular Variant	4	28.6	
Others (combined)	2	22.2	

Table 8: Recurrence Risk Based on Variant Type (Follow-up Cases Only)

Recurrence Risk Based on Variant Type	Recurrence (n=10)	Percentage of Recurrence (%)	p-value
Classical PTC	3	10.7	0.016
Tall Cell Variant	3	50	
Follicular Variant	2	14.3	
Hobnail/Columnar/Solid	2	33.3	

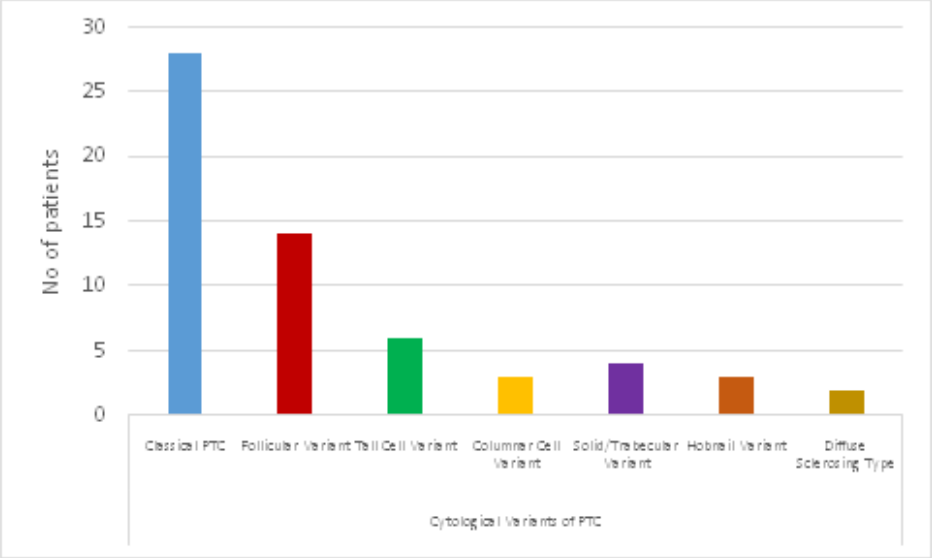

Figure 1: Cytological Variants of PTC

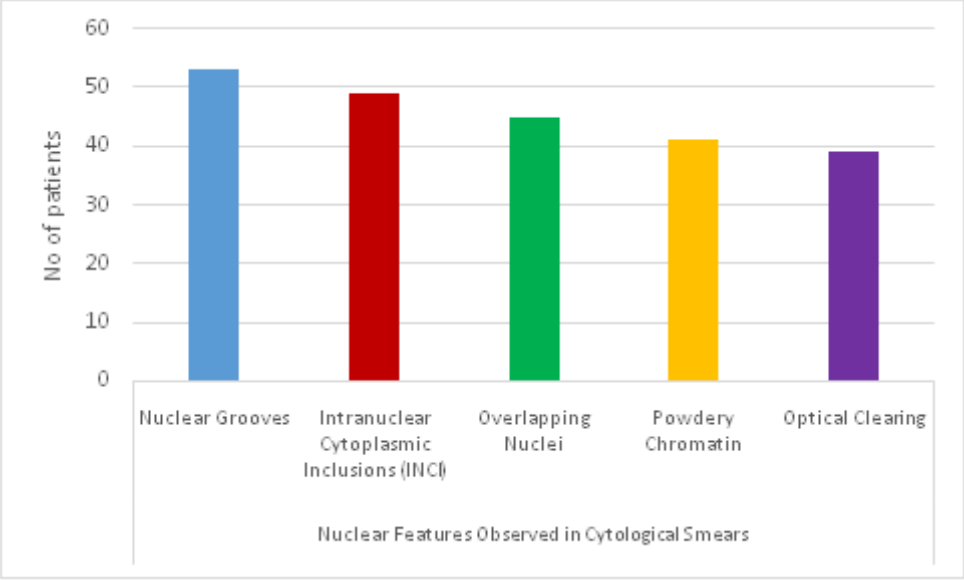

Figure 2: Nuclear Features Observed in Cytological Smears

Out of the 60 patients included in the study, the majority were in the age group of 31–40 years (30%), followed by 21–30 years (23.3%), 41–50 years (20%), >50 years (16.7%), and <20 years (10%). The association between age group and papillary thyroid carcinoma (PTC) variants was found to be statistically significant ($p = 0.042$). Regarding gender distribution, females constituted the majority with 42 cases (70%), while males accounted for 18 cases (30%). The gender difference showed a statistically significant correlation with PTC variants ($p = 0.003$).

Among the 60 cases of papillary thyroid carcinoma (PTC) evaluated, the classical variant was the most frequently observed, accounting for 28 cases (46.7%), followed by the follicular variant in 14 cases (23.3%), tall cell variant in 6 cases (10%), solid/trabecular variant in 4 cases (6.7%), columnar cell variant and hobnail variant in 3 cases each (5%), and the diffuse sclerosing type in 2 cases (3.3%). The distribution of cytological variants showed a statistically significant correlation ($p = 0.021$). With respect to nuclear features observed in cytological smears, nuclear grooves were the most common finding, present in 53 cases (88.3%), followed by intranuclear cytoplasmic inclusions (INCI) in 49 cases (81.7%), overlapping nuclei in 45 cases (75%), powdery chromatin in 41 cases (68.3%), and optical clearing in 39 cases (65%). These nuclear features demonstrated a highly significant association with the diagnosis of PTC ($p < 0.001$).

Analysis of architectural patterns in cytological smears revealed that papillary structures were the most common, observed in 36 cases (60%), followed by a follicular pattern in 18 cases (30%) and solid/trabecular architecture in 6 cases (10%). A statistically significant correlation was found between architectural pattern and the cytological variant of papillary thyroid carcinoma ($p = 0.015$).

Psammoma bodies were identified in 22 out of 60 cases (36.7%), while they were absent in 38 cases (63.3%). The presence of psammoma bodies showed a statistically significant association with specific variants of papillary thyroid carcinoma, particularly the classical and diffuse sclerosing types ($p = 0.047$). Correlation between cytological and histological diagnoses showed a high degree of concordance across most variants of papillary thyroid carcinoma (PTC). The classical variant demonstrated the highest cytological-histological match with 25 out of 28 cases (89.3%), followed by the follicular variant with 12 of 14 cases (85.7%), and the tall cell variant with 5 of 6 cases (83.3%). Solid variant showed a match in 3 of 4 cases (75%), while columnar cell and hobnail variants each had a match in 2 of 3 cases (66.7%). The diffuse sclerosing variant showed a perfect match in all 2 cases (100%). The correlation between cytological variants and their corresponding histological diagnoses was statistically significant ($p = 0.034$).

In this study, 36 out of 60 cases (60%) were categorized under Bethesda Category V (suspicious for malignancy), while 24 cases (40%) were classified as Bethesda Category VI (malignant). Although a higher number of cases were reported in Category V, the association between Bethesda category and final histological diagnosis approached but did not reach statistical significance ($p = 0.051$).

Analysis of BRAF mutation status across different cytological variants of papillary thyroid carcinoma (PTC) revealed the highest mutation frequency in the tall cell variant, with 5 out of 6 cases (83.3%) testing positive. The classical variant showed BRAF positivity in 20 of 28 cases (71.4%), while the follicular variant had a significantly lower frequency with 4 of 14 cases (28.6%). Among the remaining variants combined (including columnar cell, hobnail, solid, and diffuse sclerosing types), only 2 of 9 cases (22.2%) were BRAF-positive. The variant-wise distribution of BRAF mutation was found to be statistically significant ($p = 0.004$).

Out of the 60 cases studied, 10 patients experienced recurrence. The recurrence was most frequent in the tall cell variant, with 3 out of 6 cases (50%) showing recurrence. The hobnail, columnar, and solid variants collectively accounted for 2 recurrences out of 6 cases (33.3%). The follicular variant showed recurrence in 2 of 14 cases (14.3%), while the classical variant had the lowest recurrence rate, with 3 of 28 cases (10.7%). The association between cytological variant type and recurrence risk was statistically significant ($p = 0.016$), indicating a higher recurrence tendency in aggressive variants like tall cell and hobnail.

Discussion

This study highlights important cytomorphological and molecular distinctions among papillary thyroid carcinoma (PTC) variants, with several findings aligning with existing literature but also presenting novel insights. We observed a notably high BRAF mutation rate in variants such as classical (71.4%) and tall cell (83.3%) PTC, corroborating findings by Silver et al., who reported a strong association between BRAF V600E mutations and aggressive features even in microcarcinomas (≤1.5 cm) [11]. Furthermore, our recurrence analysis—50% recurrence in tall cell PTC—mirrors Longheu et al.'s observation of significantly increased local recurrence in tall cell variants compared to classical PTC [12]. This is supported by Liu et al.'s meta-analysis, which concluded that tall cell PTCs exhibit more aggressive behavior, including higher rates of extrathyroidal extension and lymphovascular invasion [13]. The frequent

presence of psammoma bodies in the classical and diffuse sclerosing variants in our study aligns with the variant-specific features outlined by Karger et al., who emphasized the diagnostic utility of these structures in variant identification [14]. Additionally, the high concordance between cytological and histological diagnoses across PTC variants in our study (e.g., 89.3% in classical and 83.3% in tall cell) is consistent with Korean studies, which showed similar agreement when comparing classic PTC with tall cell features [15]. Nuclear features such as grooves (88.3%) and intranuclear cytoplasmic inclusions (81.7%) reinforce the diagnostic criteria established in previous reviews, where these features were highlighted as hallmark identifiers of PTC, particularly in distinguishing among its variants [16]. Importantly, recurrence patterns noted in our study, particularly among tall cell and hobnail variants, are in agreement with Bongers et al., who demonstrated that even focal tall cell change (<10%) is associated with recurrence risks similar to that of full tall cell variants [17]. Moreover, a study by Kim et al. emphasized that classical PTC with tall cell features should not be underestimated, as it shares comparable oncologic outcomes with tall cell variant PTC [18]. Liquid-based cytology has been shown to improve diagnostic sensitivity in detecting tall cell features, as demonstrated by Lee et al., suggesting that technical advancements may enhance preoperative recognition of aggressive variants [19]. Fonseca et al. also identified distinct cytologic patterns in rare variants like the Warthin-like subtype, highlighting the continuous need for variant awareness in cytological evaluation [20]. Lastly, while our study showed a significant association between BRAF mutation and aggressive behavior, Wang et al. argued that tall cell histology alone may not independently predict recurrence, suggesting a multifactorial interplay of molecular and histological characteristics in disease progression.

Conclusion

This study underscores the diagnostic complexity and clinical significance of identifying cytological variants of papillary thyroid carcinoma (PTC) on fine-needle aspiration cytology (FNAC). The classical variant was the most prevalent, but aggressive subtypes such as the tall cell and hobnail variants were associated with higher BRAF mutation rates and increased recurrence risk.

Distinct nuclear features—such as grooves, intranuclear cytoplasmic inclusions, and powdery chromatin—proved highly reliable for cytological diagnosis. A strong concordance was observed between cytological and histological findings, reinforcing the diagnostic value of FNAC. Recognition of variant-specific patterns, along with ancillary molecular testing, can aid in accurate preoperative risk stratification and guide optimal clinical management.

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