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Clinicopathological Profile of Papillary Thyroid Carcinoma with Emphasis on Nuclear Features and Immunohistochemical Expression of CK19 and HBME-1.

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Abstract

Background: Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the thyroid and is characterized by distinctive histopathological and nuclear features. Immunohistochemical markers such as cytokeratin 19 (CK19) and Hector Battifora mesothelial-1 (HBME-1) may assist in diagnostically challenging cases. ***Methods:*** A descriptive study was conducted in the Department of Pathology, Karpaga Vinayaga Institute of Medical Sciences, Maduranthagam, over a period of two years from 2019 to 2021. A total of 33 histologically confirmed cases of PTC were included by consecutive sampling. Demographic and clinical characteristics, histopathological variants, nuclear features, and immunohistochemical expression of CK19 and HBME-1 were evaluated. Data were analyzed using SPSS version 20. ***Results:*** Of the 33 patients, 32 (97.0%) were female. Most patients were aged 21–50 years. The follicular variant was the most common histopathological subtype (42.4%), followed by classical papillary carcinoma (24.2%) and papillary microcarcinoma (21.2%). Optical nuclear clearing was present in all cases, while nuclear grooving, psammoma bodies, intranuclear inclusions, and papillary configuration were observed in 84.8%, 51.5%, 42.4%, and 30.3% of cases, respectively. CK19 expression was positive in all 33 cases, with predominantly 3+ and 4+ staining. HBME-1 positivity was observed in only 7 cases (21.2%). ***Conclusion:*** Characteristic nuclear morphology remained central to the diagnosis of PTC. CK19 showed consistent expression and appeared to be a useful adjunctive marker, whereas HBME-1 expression was variable and substantially lower.

Keywords: Papillary thyroid carcinoma; CK19; HBME-1; Immunohistochemistry; Nuclear features.

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INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the thyroid gland and represents the predominant subtype of differentiated thyroid carcinoma.[1] It generally follows an indolent clinical course and is associated with favorable long-term survival when diagnosed and treated appropriately. [2] Despite its overall good prognosis, PTC exhibits considerable heterogeneity in its clinical presentation, histopathological appearance, and biological behavior. Accurate recognition of its morphological spectrum is therefore essential for diagnosis, classification, and appropriate patient management. [3]

The diagnosis of PTC is primarily based on characteristic histopathological features, particularly its distinctive nuclear morphology. [4] Typical nuclear findings include optical clearing, nuclear enlargement and overlapping, nuclear grooves, and intranuclear cytoplasmic inclusions. [5] Papillary architecture and psammoma bodies may provide additional diagnostic support; however, papillary structures are not invariably present in all cases. This is particularly relevant in follicular-patterned lesions, where recognition of the characteristic nuclear features assumes greater diagnostic importance. [6]

PTC encompasses several histopathological variants with differences in architectural pattern and, in some instances, clinical behavior. [7] Classical papillary carcinoma and the follicular variant constitute important morphological forms, while papillary microcarcinoma, oncocytic, sclerosing, and other less common variants contribute to the broader spectrum of the disease. Identification of these variants is important because some may pose diagnostic challenges or demonstrate biological characteristics different from conventional PTC. [8]

Although routine hematoxylin and eosin examination remains the cornerstone of diagnosis, immunohistochemistry may serve as a useful adjunct in morphologically difficult cases. Several immunohistochemical markers have been investigated in thyroid pathology to assist in distinguishing PTC from benign follicular lesions and other thyroid neoplasms. [9] Among these, cytokeratin 19 (CK19) and Hector Battifora mesothelial-1 (HBME-1) have been widely evaluated because of their reported expression in papillary thyroid carcinoma. [10]

CK19 is a low-molecular-weight cytokeratin that is frequently expressed in PTC, often showing strong and diffuse staining. HBME-1 is a monoclonal antibody initially developed as a mesothelial marker but subsequently found to have diagnostic utility in thyroid neoplasms. [11] However, the expression of these markers is variable, and neither marker should be interpreted independently of morphological findings. Their diagnostic value is therefore best considered in conjunction with histological architecture and nuclear characteristics rather than as stand-alone determinants of malignancy. [12]

Given the morphological diversity of PTC and the potential diagnostic utility of ancillary immunohistochemical markers, evaluation of clinicopathological features together with CK19 and HBME-1 expression may provide a more comprehensive understanding of the disease. The present study was undertaken to characterize the demographic, clinical, histopathological, and nuclear features of PTC and to assess the expression patterns of CK19 and HBME-1 across different histopathological variants, with particular emphasis on their role as adjunctive diagnostic markers.

Aims and Objectives

Aim

To evaluate the clinicopathological characteristics of papillary thyroid carcinoma and to assess the immunohistochemical expression of CK19 and HBME-1 in relation to its histopathological variants and characteristic nuclear features.

Objectives

1. To describe the demographic, clinical, histopathological, and nuclear features of papillary thyroid carcinoma and determine the distribution of its various histopathological variants.
2. To assess the expression patterns of CK19 and HBME-1 in papillary thyroid carcinoma and examine their distribution across different histopathological variants.

MATERIALS AND METHODS

Study Design and Setting

A descriptive study was conducted in the Department of Pathology in a tertiary care hospital in Tamil Nadu. The study evaluated the clinicopathological characteristics of papillary thyroid carcinoma (PTC), with particular emphasis on histological and nuclear features and the immunohistochemical expression of CK19 and HBME-1.

Study Population

The study population consisted of patients who presented with thyroid swelling and were subsequently diagnosed histopathologically as having papillary thyroid carcinoma. Resected thyroid specimens received in the Department of Pathology during the study period constituted the study material. A total of 33 histologically confirmed cases of PTC were included in the final analysis.

Study Duration

The study was conducted over a period of 2 years

Inclusion and Exclusion Criteria

Resected thyroid specimens with solitary thyroid nodules that were subsequently diagnosed histopathologically as papillary thyroid carcinoma were included in the study. Specimens with incomplete records and thyroid malignancies other than papillary thyroid carcinoma were excluded.

Sample Size and Sampling Technique

A total of 33 cases of papillary thyroid carcinoma were included. No separate formal sample-size calculation was reported in the thesis. Consecutive sampling was employed, and all eligible cases of papillary thyroid carcinoma received during the study period that fulfilled the inclusion criteria were included in the analysis.

Study Procedure

Clinical information was obtained from the pathology laboratory records and requisition forms. The received thyroidectomy specimens were fixed in 10% neutral buffered formalin and subjected to routine tissue processing and paraffin embedding. Sections approximately 4–5 µm thick were prepared and stained with hematoxylin and eosin. The stained sections were examined under light microscopy, and cases were classified according to their histopathological

variant. Characteristic histological and nuclear features, including optical nuclear clearing, nuclear grooves, intranuclear inclusions, papillary configuration, and psammoma bodies, were recorded.

Representative paraffin-embedded tissue sections were subsequently subjected to immunohistochemistry for CK19 and HBME-1. Sections were mounted on positively charged or poly-L-lysine-coated slides, deparaffinized, rehydrated, and subjected to antigen retrieval. Endogenous peroxidase activity was blocked, after which the sections were incubated with the respective mouse monoclonal primary antibodies. The antigen–antibody reaction was visualized using a horseradish peroxidase-polymer detection system with diaminobenzidine as the chromogen, followed by hematoxylin counterstaining. The stained slides were then examined microscopically and graded according to the immunohistochemical staining score.

Operational Definitions

Papillary thyroid carcinoma was defined histopathologically by the presence of characteristic morphological and nuclear features on hematoxylin and eosin-stained sections. The nuclear and histological features evaluated included optical nuclear clearing, nuclear grooves, intranuclear cytoplasmic inclusions, papillary configuration, and psammoma bodies. Histopathological variants were categorized as follicular variant, classical papillary carcinoma, papillary microcarcinoma, invasive, oncocytic, sclerosing, and Warthin type according to the morphology documented in the thesis.

Immunohistochemical expression of CK19 and HBME-1 was graded on an ordinal scale from 0 to 4+. For the manuscript analysis, a staining score of 0 was considered negative, while scores from 1+ to 4+ were considered positive. The thesis reported CK19 and HBME-1 expression using these five staining categories.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics version 26. Descriptive statistics were expressed as frequencies, percentages, means, medians, and standard deviations, as applicable. Categorical variables were summarized using frequency and percentage distributions. The thesis specified the chi-square test for assessment of associations between categorical variables, with statistical significance set at a 5% level ($p < .05$).

Ethical Consideration

The study was undertaken after obtaining approval from the Institutional Ethics Committee. Only specimens submitted to the pathology laboratory as part of routine clinical care were considered for inclusion, and patient-related information was obtained from available laboratory records.

RESULTS

Table 1. Demographic and Clinical Characteristics of Patients with Papillary Thyroid Carcinoma (N = 33)

Characteristic	Category	n	%
Sex	Male	1	3.0
	Female	32	97.0
Age group (years)	≤20	1	3.0
	21–30	10	30.3
	31–40	10	30.3
	41–50	10	30.3
	51–60	2	6.1
Presenting symptom	Swelling	13	39.4
	Weight loss	9	27.3
	Dysphagia	7	21.2
	Pain	4	12.1
Specimen/procedure	Total thyroidectomy	17	51.5
	Right hemithyroidectomy	9	27.3
	Left hemithyroidectomy	5	15.2
	Pretracheal lymph node	1	3.0
	Subtotal thyroidectomy	1	3.0

Among the 33 patients with papillary thyroid carcinoma, the majority were female (97.0%), with only one male patient (3.0%). Most patients were distributed between 21 and 50 years of age, with 30.3% each in the 21–30, 31–40, and 41–50 year age groups. Swelling was the most common presenting symptom, observed in 39.4% of cases, followed by weight loss (27.3%), dysphagia (21.2%), and pain (12.1%). Total thyroidectomy was the most commonly performed procedure (51.5%), followed by right hemithyroidectomy (27.3%) and left hemithyroidectomy (15.2%) (Table 1).

Table 2. Distribution of Histopathological Variants of Papillary Thyroid Carcinoma (N = 33)

Histopathological variant	n	%
Follicular variant	14	42.4
Classical papillary carcinoma	8	24.2
Papillary microcarcinoma	7	21.2
Invasive variant	1	3.0
Oncocytic variant	1	3.0
Sclerosing type	1	3.0
Warthin type	1	3.0
Total	**33**	**100.0**

With regard to histopathological variants, the follicular variant was the most frequent, accounting for 42.4% of cases. Classical papillary carcinoma constituted 24.2% of cases, while papillary microcarcinoma accounted for 21.2%. Invasive, oncocytic, sclerosing, and Warthin variants were uncommon, each contributing 3.0% of the study population (Table 2).

Table 3. Distribution of Histological and Nuclear Features Among Papillary Thyroid Carcinoma Cases (N = 33)

Histological/nuclear feature	Present, n (%)	Absent, n (%)
Optical nuclear clearing	33 (100.0)	0 (0.0)
Nuclear grooving	28 (84.8)	5 (15.2)
Psammoma bodies	17 (51.5)	16 (48.5)
Intranuclear inclusions	14 (42.4)	19 (57.6)
Papillary configuration	10 (30.3)	23 (69.7)

Assessment of histological and nuclear features showed that optical nuclear clearing was present in all cases (100.0%). Nuclear grooving was identified in 84.8% of cases, while psammoma bodies were observed in 51.5%. Intranuclear inclusions were present in 42.4% of cases, and papillary configuration was seen in 30.3% of cases (Table 3).

Table 4. Immunohistochemical Expression of CK19 and HBME-1 According to Histopathological Variants of Papillary Thyroid Carcinoma (N = 33)

Histopathological variant	**n**	**CK19 positive, n (%)**	**CK19 negative, n (%)**	**HBME-1 positive, n (%)**	**HBME-1 negative, n (%)**
Follicular variant	14	14 (100.0)	0 (0.0)	1 (7.1)	13 (92.9)
Classical papillary carcinoma	8	8 (100.0)	0 (0.0)	2 (25.0)	6 (75.0)
Papillary microcarcinoma	7	7 (100.0)	0 (0.0)	2 (28.6)	5 (71.4)
Invasive variant	1	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Oncocytic variant	1	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Sclerosing type	1	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Warthin type	1	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Total	**33**	**33 (100.0)**	**0 (0.0)**	**7 (21.2)**	**26 (78.8)**

CK19 expression was positive in all 33 cases across all histopathological variants. In contrast, HBME-1 positivity was observed in only 7 cases (21.2%), while 26 cases (78.8%) were negative. Among the major variants, HBME-1 positivity was seen in 25.0% of classical papillary carcinoma cases, 28.6% of papillary microcarcinomas, and 7.1% of follicular variant cases. The oncocytic and Warthin variants each showed HBME-1 positivity in their single respective cases, whereas the invasive and sclerosing variants were negative (Table 4).

Table 5. Overall Immunohistochemical Expression Pattern of CK19 and HBME-1 in Papillary Thyroid Carcinoma (N = 33)

IHC staining score	**CK19, n (%)**	**HBME-1, n (%)**
0	0 (0.0)	26 (78.8)
1+	0 (0.0)	1 (3.0)
2+	4 (12.1)	2 (6.1)
3+	20 (60.6)	2 (6.1)
4+	9 (27.3)	2 (6.1)
Total	**33 (100.0)**	**33 (100.0)**

The overall immunohistochemical staining pattern demonstrated predominantly strong CK19 expression. A 3+ staining score was observed in 60.6% of cases and a 4+ score in 27.3%, while 12.1% showed 2+ staining. No case was negative or showed only 1+ staining for CK19. In contrast, HBME-1 was negative in 78.8% of cases, with 3.0% showing 1+ staining and 6.1% each showing 2+, 3+, and 4+ staining (Table 5).

DISCUSSION

In the present study, PTC showed a striking female predominance, with 32 of 33 patients (97.0%) being women, and most cases occurring between 21 and 50 years of age. This pattern is broadly consistent with the established demographic profile of PTC, although the female predominance in the present series was more pronounced than that reported in larger cohorts. Rao et al. observed a male-to-female ratio of approximately 1:5.4, with nearly three-fourths of patients presenting between the second and fifth decades of life [13]. Karkuzhali et al., in a large tertiary-care series from Chennai, similarly demonstrated a clear female predominance and substantial representation of patients in the middle adult age groups [14]. Liu et al., in a series of 257 patients with PTC, reported 201 women and 56 men, further supporting the female preponderance of the disease [15]. Girardi et al. also observed that 81.9% of 517 patients with PTC were women, with a mean age of 47.2 years [16]. The higher proportion of women in the present study may partly reflect the relatively small sample size and local referral patterns.

The follicular variant was the most common histopathological subtype in the present study, accounting for 42.4% of cases, followed by classical papillary carcinoma (24.2%) and papillary microcarcinoma (21.2%). This distribution differs somewhat from several larger series in which the classical variant predominated. Rao et al. reported the classical and follicular variants as the major subtypes and also documented uncommon variants such as oncocytic, clear-cell, tall-cell, and macrofollicular forms [13]. Karkuzhali et al. found conventional PTC to be the most frequent subtype, comprising 68.7% of cases, followed by follicular variant at 17.8%, while oncocytic, diffuse sclerosing, and other uncommon variants were infrequent [14]. Girardi et al. reported microcarcinoma as the most prevalent subtype in their cohort, followed by classical and follicular variants, illustrating that subtype distribution may vary considerably across study populations [16]. A population-based analysis of more than 32,000 surgically treated PTC cases reported classical PTC in approximately two-thirds and follicular variant in approximately one-third of cases, confirming the substantial contribution of follicular-patterned tumors to the spectrum of PTC [17]. These differences may be influenced by sample size, diagnostic criteria, case selection, and evolving classification of follicular-patterned thyroid tumors.

Characteristic nuclear morphology was prominent in the present series. Optical nuclear clearing was identified in all cases, nuclear grooves in 84.8%, intranuclear cytoplasmic inclusions in 42.4%, psammoma bodies in 51.5%, and papillary configuration in 30.3%. These findings reinforce the importance of nuclear rather than purely architectural features in the diagnosis of PTC. Kunjumon and Upadhyaya emphasized the diagnostic importance of nuclear clearing, grooving, overlapping, and intranuclear inclusions across different PTC variants [18]. Rao et al. similarly reported nuclear overcrowding and ground-glass nuclei in more than 90% of their cases [13]. Shurbaji et al. found nuclear grooves in all PTC cases studied cytologically, while intranuclear inclusions and papillary fragments were less consistently present, supporting nuclear grooves as a particularly sensitive morphological feature [19]. More recently, Kumari et al. demonstrated that nuclear grooves, intranuclear inclusions, papillary structures, cellular swirls, and psammoma bodies collectively improved the diagnostic performance for PTC, with papillae and nuclear grooves among the most sensitive findings [20]. Thus, the present results are consistent with the concept that diagnosis is strengthened by recognition of a constellation of characteristic nuclear changes rather than dependence on papillary architecture alone.

CK19 demonstrated positive immunoreactivity in all 33 cases in the present study, with most tumors showing strong staining; 60.6% demonstrated 3+ expression and 27.3% showed 4+ expression. This high expression is comparable with several published studies supporting CK19 as a highly sensitive marker for PTC. Nasr et al. found CK19 positivity in all 51 PTC cases examined, with predominantly strong and diffuse cytoplasmic staining [10]. Liu et al. reported CK19 expression in 96.3% of 257 PTC cases and identified it as the most sensitive individual marker among CK19, HBME-1, and thyroid peroxidase [15]. Palo and Biligi documented diffuse strong CK19 expression in 27 of 31 PTC cases, while most benign follicular lesions were negative or showed only focal weak staining [21]. Erdogan-Durmus et al. reported 3+ CK19 staining in 83% of PTC cases, again demonstrating frequent strong expression in malignant papillary lesions [22]. The complete positivity observed in the current series therefore lies at the upper end of previously reported values and supports CK19 as a useful adjunctive marker, particularly when interpreted as strong and diffuse staining in the appropriate morphological setting.

In contrast to CK19, HBME-1 positivity was identified in only 7 of 33 cases (21.2%) in the present study, with 78.8% showing no staining. This rate is considerably lower than that reported in most published series. Nasr et al. observed HBME-1 positivity in 49 of 51 PTC cases and reported high sensitivity and specificity for distinguishing PTC from benign mimics [10]. Liu et al. found HBME-1 expression in 85.3% of PTC specimens, substantially higher than that observed in the present study [15]. Palo and Biligi reported HBME-1 positivity in 86.1% of malignant thyroid lesions and identified HBME-1 as a highly useful marker in differentiating benign from malignant lesions [21]. Erdogan-Durmus et al. also demonstrated strong 3+ HBME-1 staining in 72.3% of PTC cases [22]. The markedly lower HBME-1 expression in the present series therefore represents an important divergence from the literature and may reflect differences in antibody clone, dilution, antigen retrieval, staining threshold, fixation, tissue preservation, or interpretation of membrane versus

cytoplasmic staining. It also underscores the need to interpret negative HBME-1 staining cautiously rather than use it to exclude PTC.

Taken together, the present findings indicate that conventional morphology remained central to the diagnosis of PTC, while CK19 provided consistent supportive immunohistochemical evidence and HBME-1 showed substantially more variable expression. This interpretation agrees with studies emphasizing that no single immunohistochemical marker should replace careful histopathological assessment. Sanuvada et al. demonstrated the usefulness of CK19, HBME-1, and galectin-3 in the evaluation of thyroid neoplasms but emphasized their role as ancillary rather than independent diagnostic tools [11]. De Matos et al. similarly showed that HBME-1, CK19, and galectin-3 could aid in identifying thyroid malignancy, particularly when used as a panel [12]. Saleh et al. found that malignant follicular-derived lesions expressed CK19, HBME-1, galectin-3, and RET more frequently and more diffusely than benign nodules, but the sensitivity of individual or combined markers remained imperfect [23]. Nasr et al. likewise concluded that combining HBME-1 and CK19 improved diagnostic utility because the two markers possess complementary characteristics [10]. The present study therefore supports the use of CK19 and HBME-1 as adjuncts to morphology, while the discordantly low HBME-1 positivity highlights the importance of laboratory-specific validation and cautious interpretation of immunohistochemical findings.

Limitations

The study was limited by its small sample size and single-center design, which may restrict the generalizability of the findings. In addition, the absence of a benign or non-PTC comparison group limited the assessment of the true diagnostic specificity and predictive performance of CK19 and HBME-1.

CONCLUSION

Papillary thyroid carcinoma demonstrated a marked female predominance and most commonly occurred between 21 and 50 years of age. The follicular variant was the most frequent histopathological subtype, followed by classical papillary carcinoma and papillary microcarcinoma. Characteristic nuclear features, particularly optical nuclear clearing and nuclear grooving, were commonly observed and remained important for histopathological diagnosis. CK19 showed consistent expression across all PTC cases, whereas HBME-1 expression was considerably lower and more variable.

Histomorphological assessment should remain the primary basis for the diagnosis of papillary thyroid carcinoma, with careful evaluation of characteristic nuclear features. CK19 may be used as a useful adjunctive immunohistochemical marker in diagnostically challenging cases, while HBME-1 should be interpreted cautiously and in conjunction with morphology. Larger multicenter studies including benign and other malignant thyroid lesions are recommended to further evaluate the diagnostic performance of CK19 and HBME-1 and to determine their optimal role in immunohistochemical panels.

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