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ORIGINAL RESEARCH

Clinicopathological Profile and Immunohistochemical Expression of CK19 and HBME-1 in Papillary Thyroid Carcinoma: A Descriptive Study from a Tertiary Care Centre in South India

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is diagnosed mainly on its nuclear morphology, but follicular-patterned and less common variants can be difficult to recognise on routine histology. Cytokeratin 19 (CK19) and Hector Battifora mesothelial-1 (HBME-1) are widely used as adjunctive immunohistochemical markers. This study describes the clinicopathological profile of PTC and the expression of CK19 and HBME-1 across its histological variants. **Methods:** This retrospective descriptive study was carried out in the Department of Pathology, Karpaga Vinayaga Institute of Medical Sciences, Maduranthagam, Tamil Nadu, India, from July 2019 to June 2021. Thirty-three consecutive, histologically confirmed cases of PTC were included. Demographic and clinical details, histological variant, nuclear features, and immunohistochemical expression of CK19 and HBME-1 (scored 0 to 4+) were recorded and analysed descriptively. **Results:** Thirty-two patients (97.0%) were women, and 30 (90.9%) were aged 21–50 years. The follicular variant was the most common subtype (42.4%), followed by classical PTC (24.2%) and papillary microcarcinoma (21.2%). Optical nuclear clearing was present in all cases; nuclear grooves, psammoma bodies, intranuclear inclusions, and papillary architecture were seen in 84.8%, 51.5%, 42.4%, and 30.3% of cases, respectively. CK19 was expressed in all 33 cases (100%; 95% CI 89.6–100), with 3+ or 4+ staining in 29 (87.9%). HBME-1 was expressed in only 7 cases (21.2%; 95% CI 10.7–37.8). **Conclusion:** Nuclear morphology remains the mainstay of PTC diagnosis. CK19 was consistently and strongly expressed and is a useful adjunct in difficult cases, whereas HBME-1 positivity was low in this series; a negative HBME-1 stain should therefore not be used to exclude PTC.

Keywords: Biomarkers, tumor; Hector Battifora mesothelial-1; Immunohistochemistry; Keratin-19; Thyroid cancer, papillary

Introduction

Papillary thyroid carcinoma (PTC) is the most common malignant tumour of the thyroid gland and the predominant form of differentiated thyroid carcinoma [1]. It usually follows an indolent course, and long-term survival is excellent when the disease is diagnosed and treated appropriately [2]. Nevertheless, PTC is heterogeneous in its clinical presentation, histological appearance, and biological behaviour, so accurate recognition of its morphological spectrum is essential for diagnosis, classification, and management [3].

The diagnosis of PTC rests primarily on its characteristic nuclear features [4]: optical clearing, nuclear enlargement and overlapping, nuclear grooves, and intranuclear cytoplasmic pseudoinclusions [5]. Papillary architecture and psammoma bodies offer additional support, but papillae are not present in every case. In follicular-patterned lesions, the diagnosis therefore depends largely on recognising these nuclear changes [6].

PTC comprises several histological variants that differ in architecture and, in some instances, in clinical behaviour [7]. The classical and follicular variants are the principal forms, while papillary microcarcinoma and the oncocytic, sclerosing, and

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other less common variants complete the spectrum. Recognising these variants matters because some are diagnostically challenging or behave differently from conventional PTC [8].

Although haematoxylin and eosin (H&E) examination remains the cornerstone of diagnosis, immunohistochemistry is a useful adjunct in morphologically difficult cases, particularly in distinguishing PTC from benign follicular lesions and other thyroid neoplasms [9]. Among the markers studied, cytokeratin 19 (CK19) and Hector Battifora mesothelial-1 (HBME-1) have been evaluated most widely [10]. CK19 is a low-molecular-weight cytokeratin that frequently shows strong, diffuse staining in PTC, while HBME-1, a monoclonal antibody first developed as a mesothelial marker, has also proved useful in thyroid neoplasms [11]. The expression of both markers is variable, however, and neither should be interpreted independently of morphology [12].

The present study was undertaken to describe the demographic, clinical, histological, and nuclear features of PTC and to assess the expression of CK19 and HBME-1 across its histological variants, with emphasis on their role as adjunctive diagnostic markers.

Materials and Methods

Study design and setting

This retrospective descriptive study was conducted in the Department of Pathology, Karpaga Vinayaga Institute of Medical Sciences, Maduranthagam, a tertiary care teaching hospital in Tamil Nadu, India, from July 2019 to June 2021. Archived H&E-stained slides, paraffin blocks, and the corresponding laboratory records of all cases of PTC reported during this period were retrieved and reviewed.

Study population and sampling

All cases diagnosed histologically as PTC in the department during the study period were eligible, irrespective of the type of surgical specimen (hemithyroidectomy, subtotal thyroidectomy, or total thyroidectomy). Cases with incomplete records and thyroid malignancies other than PTC were excluded. All eligible cases were included consecutively, giving a final sample of 33 cases. No formal sample size calculation was performed. In one patient, the only specimen received was a pretracheal lymph node. This case was included because the diagnosis of PTC was established on the metastatic tumour, and its histological variant and nuclear features were assessed on the nodal deposit.

Histopathological examination

Clinical information was obtained from pathology requisition forms and laboratory records. Specimens were fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin. Sections 4–5 µm thick were stained with H&E and examined by light microscopy. Each case was assigned to a histological variant (follicular, classical, papillary microcarcinoma, infiltrative follicular, oncocytic, diffuse sclerosing, or Warthin-like), named according to current World Health Organization terminology, and the following features were recorded: optical nuclear clearing, nuclear grooves, intranuclear cytoplasmic inclusions, papillary configuration, and psammoma bodies.

Immunohistochemistry

Representative paraffin sections were mounted on positively charged or poly-L-lysine-coated slides, deparaffinised, rehydrated, and subjected to heat-induced antigen retrieval. After endogenous peroxidase was blocked, sections were incubated with mouse monoclonal primary antibodies against CK19 and HBME-1. Reactions were visualised with a horseradish peroxidase–polymer detection system (EnVision FLEX, Dako/Agilent, Glostrup, Denmark) using diaminobenzidine as the chromogen and counterstained with haematoxylin. Positive controls (tonsil for CK19 and a previously confirmed HBME-1-positive PTC for HBME-1) and negative controls (primary antibody omitted) were run with each batch. The primary antibodies were CK19 (clone RCK108, Dako/Agilent, ready-to-use) and HBME-1 (clone HBME-1, Dako/Agilent, 1:50); antigen retrieval was performed in Tris-EDTA buffer, pH 9.0, at 97 °C for 20 minutes.

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Staining was graded on an ordinal scale of 0, 1+, 2+, 3+, and 4+ according to the percentage of tumour cells stained: 0, no staining; 1+, <25%; 2+, 25–50%; 3+, 51–75%; and 4+, >75%. Cytoplasmic staining was accepted as positive for CK19, and membranous/luminal staining, with or without cytoplasmic staining, for HBME-1. For analysis, a score of 0 was considered negative and scores of 1+ to 4+ were considered positive.

Statistical analysis

Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as frequencies and percentages, and 95% confidence intervals (CIs) for the main proportions were calculated using the Wilson score method. Because several variants were represented by only one or a few cases, the analysis was descriptive and no tests of association were applied.

Ethical considerations

The study was approved by the Institutional Ethics Committee, Karpaga Vinayaga Institute of Medical Sciences and Research Centre (Ref. No. KIMS/PG/2019/60; dated 25.03.2019). Only specimens submitted for routine diagnostic care were studied, and patient information was obtained from existing laboratory records. The committee waived the requirement for informed consent because the study used only archived specimens and existing records, and patient identifiers were removed before analysis.

Results

Of the 33 patients, 32 (97.0%) were women and one (3.0%) was a man. The mean age was 36.4 ± 9.8 years (range 19–58 years). Thirty patients (90.9%) were aged 21–50 years, distributed equally across the 21–30, 31–40, and 41–50-year groups. Swelling was the most common chief presenting complaint (39.4%), followed by weight loss (27.3%), dysphagia (21.2%), and pain (12.1%). Each patient was counted once, under the chief complaint. Total thyroidectomy was the most frequent procedure (51.5%) [Table 1]. In one patient, only a pretracheal lymph node was received.

Table 1. Demographic and clinical characteristics of patients with papillary thyroid carcinoma (n=33)

Characteristic	Category	n (%)
Sex	Female	32 (97.0)
	Male	1 (3.0)
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 complaint*	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)
	Subtotal thyroidectomy	1 (3.0)
	Pretracheal lymph node†	1 (3.0)

*Chief presenting complaint as recorded on the pathology requisition form; each patient is counted once. †Only a pretracheal lymph node containing metastatic PTC was received for this patient; the histological variant and nuclear features were assessed on the nodal tumour.

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The follicular variant was the most common subtype (42.4%), followed by classical PTC (24.2%) and papillary microcarcinoma (21.2%). The infiltrative follicular, oncocytic, diffuse sclerosing, and Warthin-like variants were each represented by a single case (3.0%) [Table 2].

Table 2. Distribution of histological variants of papillary thyroid carcinoma (n=33)

Histological variant	n (%)
Follicular variant	14 (42.4)
Classical PTC	8 (24.2)
Papillary microcarcinoma	7 (21.2)
Infiltrative follicular variant	1 (3.0)
Oncocytic variant	1 (3.0)
Diffuse sclerosing variant	1 (3.0)
Warthin-like variant	1 (3.0)
Total	33 (100.0)

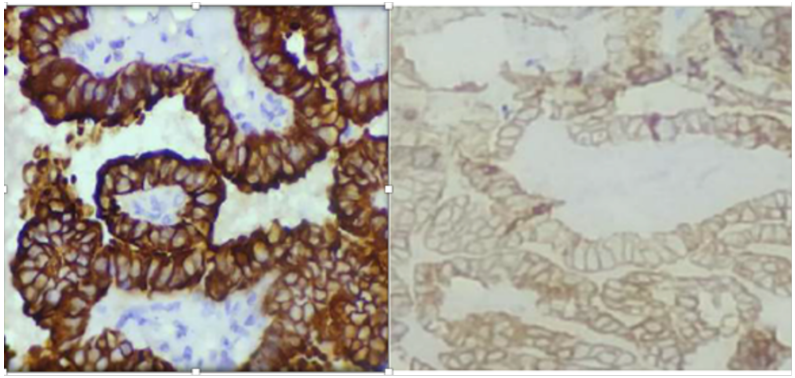


Figure 1. *Figure 1. Immunohistochemistry by CK 19 images*

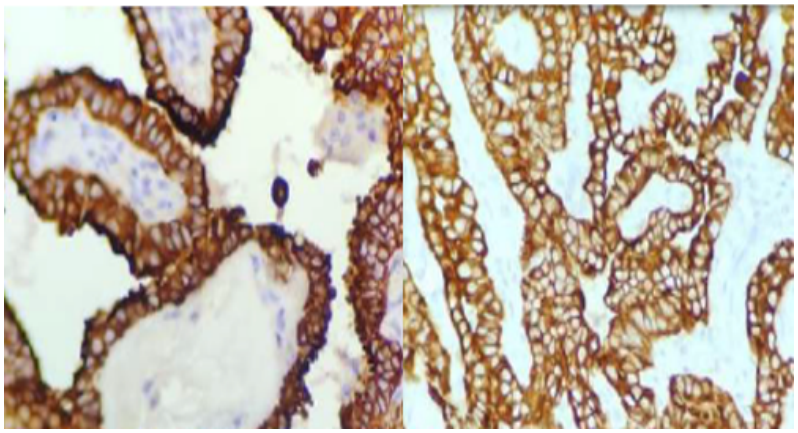


Figure 2. *Figure 2. Immunohistochemistry by HBME11 images*

PTC: Papillary thyroid carcinoma

Optical nuclear clearing was present in every case. Nuclear grooves were seen in 84.8%, psammoma bodies in 51.5%, intranuclear inclusions in 42.4%, and papillary configuration in 30.3% of cases [Table 3].

Table 3. Histological and nuclear features in papillary thyroid carcinoma (n=33)

Feature	Present, n (%)	Absent, n (%)
Optical nuclear clearing	33 (100.0)	0
Nuclear grooves	28 (84.8)	5 (15.2)

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Feature	Present, n (%)	Absent, n (%)
Psammoma bodies	17 (51.5)	16 (48.5)
Intranuclear inclusions	14 (42.4)	19 (57.6)
Papillary configuration	10 (30.3)	23 (69.7)

CK19 was positive in all 33 cases (100%; 95% CI 89.6–100), irrespective of variant. HBME-1 was positive in only 7 cases (21.2%; 95% CI 10.7–37.8): 2 of 8 classical PTCs (25.0%), 2 of 7 papillary microcarcinomas (28.6%), 1 of 14 follicular variant tumours (7.1%), and the single oncocytic and Warthin-like cases. The infiltrative follicular and diffuse sclerosing variants were negative [Table 4].

Table 4. Expression of CK19 and HBME-1 by histological variant of papillary thyroid carcinoma (n=33)

Histological variant	n	CK19 positive, n (%)	CK19 negative, n (%)	HBME-1 positive, n (%)	HBME-1 negative, n (%)
Follicular variant	14	14 (100.0)	0	1 (7.1)	13 (92.9)
Classical PTC	8	8 (100.0)	0	2 (25.0)	6 (75.0)
Papillary microcarcinoma	7	7 (100.0)	0	2 (28.6)	5 (71.4)
Infiltrative follicular variant	1	1 (100.0)	0	0	1 (100.0)
Oncocytic variant	1	1 (100.0)	0	1 (100.0)	0
Diffuse sclerosing variant	1	1 (100.0)	0	0	1 (100.0)
Warthin-like variant	1	1 (100.0)	0	1 (100.0)	0
Total	33	33 (100.0)	0	7 (21.2)	26 (78.8)

PTC: Papillary thyroid carcinoma; CK19: Cytokeratin 19; HBME-1: Hector Battifora mesothelial-1

CK19 staining was predominantly strong: 3+ in 60.6% and 4+ in 27.3% of cases, with the remaining 12.1% showing 2+ staining. No case was negative or 1+ for CK19. HBME-1 was negative in 78.8% of cases; among the positive cases, staining was 1+ in one case and 2+, 3+, and 4+ in two cases each [Table 5].

Table 5. Immunohistochemical staining scores for CK19 and HBME-1 in papillary thyroid carcinoma (n=33)

Staining score	CK19, n (%)	HBME-1, n (%)
0	0	26 (78.8)
1+	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)

CK19: Cytokeratin 19; HBME-1: Hector Battifora mesothelial-1

Discussion

In the present study, PTC showed a striking female predominance (97.0%), and most patients were aged 21–50 years. This pattern agrees broadly with the known demographic profile of PTC, although the female predominance here was more pronounced than in larger series. Rao *et al.* reported a male-to-female ratio of about 1:5.4, with nearly three-quarters of patients presenting between the second and fifth decades [13]. Karkuzhali *et al.*, in a large tertiary care series from Chennai, likewise found a clear female predominance concentrated in the middle adult years [14]. Liu *et al.* reported 201 women among 257 patients [15], and Girardi *et al.* found that 81.9% of 517 patients were women, with a mean age of 47.2 years [16]. The higher proportion of women in our series may partly reflect the small sample and local referral patterns.

The follicular variant was the most common subtype in our series (42.4%), followed by classical PTC (24.2%) and papillary microcarcinoma (21.2%). This differs from several larger series in which the classical variant predominated. Rao

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et al. identified the classical and follicular variants as the main subtypes, along with uncommon oncocytic, clear-cell, tall-cell, and macrofollicular forms [13]. Karkuzhali *et al.* found conventional PTC in 68.7% and the follicular variant in 17.8% of cases [14], whereas Girardi *et al.* reported microcarcinoma as the most frequent subtype [16]. A population-based analysis of more than 32,000 surgically treated cases found classical PTC in about two-thirds and the follicular variant in about one-third, confirming the substantial contribution of follicular-patterned tumours [17]. These differences may reflect sample size, case selection, and diagnostic criteria.

Classification changes are also relevant when interpreting the high proportion of follicular variant tumours. Since 2016, non-invasive encapsulated follicular variant tumours with papillary-like nuclear features have been reclassified as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [18], and the 2022 World Health Organization classification no longer recognises papillary microcarcinoma as a separate subtype [19]. Some cases in this series may therefore be categorised differently under current criteria, and future studies should apply these definitions.

Characteristic nuclear morphology was prominent in the present series: optical clearing was seen in all cases, nuclear grooves in 84.8%, psammoma bodies in 51.5%, intranuclear inclusions in 42.4%, and papillary configuration in only 30.3%. These findings reinforce the primacy of nuclear rather than architectural features in diagnosing PTC. Kunjumon and Upadhyaya emphasised the diagnostic importance of nuclear clearing, grooving, overlapping, and inclusions across PTC variants [5], and Rao *et al.* reported nuclear overcrowding and ground-glass nuclei in more than 90% of cases [13]. Shurbaji *et al.* found nuclear grooves in all cytological PTC samples, whereas inclusions and papillary fragments were less consistent [20]. More recently, Kumari *et al.* showed that a combination of nuclear grooves, intranuclear inclusions, papillae, cellular swirls, and psammoma bodies improved diagnostic accuracy on cytology [21]. Our results support the view that the diagnosis is best made on a constellation of nuclear changes rather than on papillary architecture alone.

CK19 was positive in all 33 cases, with 3+ staining in 60.6% and 4+ staining in 27.3%. This is consistent with published evidence that CK19 is a highly sensitive marker of PTC. Nasr *et al.* found CK19 positivity in all 51 PTCs examined, mostly strong and diffuse [10], and Liu *et al.* reported CK19 expression in 96.3% of 257 cases, making it the most sensitive single marker in their panel [15]. Palo and Biligi observed diffuse, strong CK19 staining in 27 of 31 PTCs, whereas most benign follicular lesions were negative or only focally and weakly positive [22]. Erdogan-Durmus *et al.* reported 3+ CK19 staining in 83% of PTCs [23]. The complete positivity in our series lies at the upper end of reported values and supports CK19 as a useful adjunct, particularly when strong, diffuse staining is seen in the appropriate morphological context.

In contrast, HBME-1 was positive in only 21.2% of our cases, considerably lower than in most published series. Nasr *et al.* found HBME-1 positivity in 49 of 51 PTCs [10], Liu *et al.* in 85.3% [15], Palo and Biligi in 86.1% of malignant thyroid lesions [22], and Erdogan-Durmus *et al.* reported strong 3+ staining in 72.3% [23]. This marked discrepancy may reflect differences in antibody clone, dilution, antigen retrieval, fixation and tissue preservation, positivity threshold, or interpretation of membranous versus cytoplasmic staining. It also indicates that a negative HBME-1 result should be interpreted with caution and should not be used to exclude PTC.

Taken together, our findings indicate that morphology remains central to the diagnosis of PTC, with CK19 providing consistent supportive evidence and HBME-1 showing much more variable expression. This agrees with studies emphasising that no single immunohistochemical marker can replace careful histological assessment. Sanuvada *et al.* demonstrated the value of CK19, HBME-1, and galectin-3 in thyroid neoplasms but stressed their ancillary role [11]. De Matos *et al.* found these markers most helpful when used as a panel [12], and Saleh *et al.* showed that, although malignant follicular-derived lesions expressed CK19, HBME-1, galectin-3, and RET more often and more diffusely than benign nodules, the sensitivity of individual and combined markers remained imperfect [24]. Nasr *et al.* likewise concluded that HBME-1 and CK19 are complementary and more useful in combination [10]. The unexpectedly low HBME-1 positivity in our series underlines the need for laboratory-specific validation of immunohistochemical markers.

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Limitations

This study has several limitations. The sample was small and drawn from a single centre, which limits generalisability, and several variants were represented by a single case. Because no benign or non-PTC comparison group was included, the specificity and predictive values of CK19 and HBME-1 could not be assessed. The study was retrospective and relied on existing laboratory records, interobserver agreement in morphological and immunohistochemical scoring was not evaluated, and cases were not reclassified according to current World Health Organization criteria. Tumour size, focality, and lymph node status were not consistently available in the records and could not be analysed.

Conclusion

In this series, PTC showed a marked female predominance and occurred mostly between 21 and 50 years of age, with the follicular variant being the most frequent subtype. Characteristic nuclear features, particularly optical clearing and nuclear grooves, were consistently present and remain the basis of diagnosis. CK19 was expressed in all cases and is a useful adjunct in diagnostically challenging cases, whereas HBME-1 expression was low and variable and should be interpreted cautiously alongside morphology. Larger multicentre studies that include benign and other malignant thyroid lesions are needed to define the diagnostic performance of CK19 and HBME-1 and their optimal place in immunohistochemical panels.

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Data availability: The data supporting the findings of this study are available from the corresponding author on reasonable request.

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