Section: Pathology

Original Research Article

"ONCE IN A BLUE MOON"– A STUDY ON UNCOMMON THYROID NEOPLASMS – EXPERIENCE FROM A TERTIARY CARE CENTRE IN SOUTH INDIA

Priavadhana Rajan Prasaad[1], Usha Rani T.H[2], K. Meenakshisundaram[3]

[1]Associate Professor, Department of Pathology, ESIC Medical College and Hospital, KK Nagar, Chennai, India.
[2]Senior Resident, Department of Pathology, ESIC Medical College and Hospital, KK Nagar, Chennai, India.
[3]Professor and HOD, Department of Pathology, ESIC Medical College and Hospital, KK Nagar, Chennai, India.

Received : 15/05/2026
Received in revised form : 04/07/2026
Accepted : 20/07/2026

Keywords:
Papillary Thyroid Carcinoma, Hurthle cell adenoma, NIFTP.

Corresponding Author:
Dr. Priavadhana Rajan Prasaad,
Email: drpriarajan@gmail.com

DOI: 10.47009/jamp.2026.8.4.166

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2026; 8 (4); 993-1000

ABSTRACT

Background: The rising incidence of thyroid neoplasms is largely attributed to increased detection of thyroid swellings on clinical examination and widespread use of diagnostic investigations such as fine-needle aspiration cytology (FNAC). This has led to a significant increase in thyroid surgeries in recent years, driven by cosmetic concerns, symptomatic nodules, and fear of malignancy. Various epidemiological and environmental risk factors further contribute to the growing spectrum of thyroid malignancies and lesions. Objectives/Aims: 1.To study the uncommon tumors described in WHO classification of thyroid neoplasms in a tertiary care centre. 2. To analyse clinico-radiological-pathological findings in the uncommon tumors experienced in the centre. 3. To employ risk categorisation of these uncommon tumors **Materials and Methods:** The study was a retrospective observational study, which was conducted in the Department of Pathology for the period of January 2025 – December 2025. All the cases of thyroid surgeries, which were reported in histopathology during the above-mentioned period, were included in the study. The radiological findings and cytological diagnoses of these cases were collected retrospectively and the results compared with the histopathological diagnoses. The concordance and discordance rates were observed and statistical analysis done for the same. **Results:** There were 75 cases of thyroid Fine needle aspiration cytologies, which were reported according to the Bethesda system for reporting thyroid cytopathology. In the same year, we had 112 cases of thyroid specimens in the form of lobectomies, subtotal thyroidectomies and total thyroidectomies. Here we emphasize seven cases of thyroidectomies, which was either reported as variant of papillary thyroid carcinoma or unique lesions. Rest of the cases among the 112, were reported as Nodular hyperplasia or adenomatoid hyperplasia. Among the seven cases included, there was a female predominance (female:male = 4:3) and it includes cases with ages ranging from 25 to 71 years. The variants presented here include, Tall cell variant, Hobnail variant, Warthin-like variant, Oncocytic variants of PTC along with benign neoplasms like Hurthle adenoma, Clear cell adenoma and the borderline category of NIFTP. **Conclusion:** This study emphasizes the increasing incidence of malignancy in FNAC-proven benign thyroid nodules and the growing recognition of rare thyroid neoplasms. Detailed understanding of their characteristic histopathological features is essential for accurate diagnosis. Awareness of these uncommon entities and their characteristic morphological features is vital for accurate diagnosis, appropriate risk stratification, and optimal clinical management.

INTRODUCTION

The thyroid gland demonstrates a wide spectrum of pathological entities, ranging from immune-mediated and functional disorders to benign and malignant neoplasms. According to the WHO Classification of Tumours of Endocrine Organs (5th edition, 2022), thyroid neoplasms encompass a heterogeneous group

ISSN (O): 2687-5365; ISSN (P): 2753-6556

of lesions with distinct histomorphological, molecular, and clinical characteristics. Papillary thyroid carcinoma (PTC) remains the most common malignant tumor of the thyroid and is typically associated with an indolent clinical course. However, a subset of thyroid carcinomas, including specific histological subtypes of PTC, exhibits aggressive behaviour and poorer prognosis compared to conventional PTC.

Epidemiological data from India indicate a prevalence of 12.2% for thyroid nodules and 8.7% for thyroid cancers.[1,2] Among established risk factors, ionizing radiation and genetic alterations play a pivotal role in thyroid tumorigenesis. Due to its superficial anatomical location and ability to concentrate iodine, the thyroid gland is particularly vulnerable to radiation exposure. The increased use of diagnostic medical and dental imaging has significantly augmented thyroid radiation burden, with computed tomography contributing to more than half of cumulative patient radiation exposure.[2,3]

At the molecular level, BRAF (V600E) mutation represents a hallmark genetic alteration in a significant proportion of PTCs and is more frequently identified in aggressive histological subtypes.[6,7] A global increase in iodine intake has been paralleled by a rising prevalence of BRAF-mutated PTCs, suggesting a potential association, although a definitive causal relationship remains unclear.[4,5]

While the majority of PTCs are well-differentiated tumors with low rates of recurrence and metastasis, the WHO 2022 classification recognizes several distinct histological subtypes associated with increased risk of recurrence, metastasis, and radioiodine refractoriness. For a diagnosis of a specific subtype, at least 30% of the tumor must demonstrate characteristic morphological features.[8] Accurate recognition of these aggressive variants is critical, as they have important implications for prognosis, risk stratification, and therapeutic decision-making.

MATERIALS AND METHODS

The study was a retrospective observational study, which was conducted in the Department of Pathology for the period of January 2025 – December 2025. There were 75 cases of thyroid Fine needle aspiration cytologies, which were reported according to the Bethesda system for reporting thyroid cytopathology. In the same year, we had 112 cases of thyroid specimens in the form of lobectomies, subtotal thyroidectomies and total thyroidectomies.

This study highlights the clinical radiological and histopathological correlation of all the variants of Papillary thyroid carcinoma with few cases describing the rarer entities as well as the grey zone categories in thyroid lesions namely, the NIFTP (Non-invasive follicular thyroid lesion with papillary like nuclear features).

Here we emphasize the seven cases of thyroidectomies, which was either reported as variant of papillary thyroid carcinoma or unique lesions. Rest of the cases among the 112, were reported as Nodular hyperplasia or adenomatoid hyperplasia. Among the seven cases included, there was a female predominance (female:male = 4:3) and it includes cases with ages ranging from 25 to 71 years.

RESULTS

In this study, we describe seven cases of midline neck swellings with emphasis on the different variants of PTC reported on histopathology in a single tertiary care institute.

The clinical and radiological findings of the cases are summarized in [Table 1] as below

All cases underwent fine needle aspiration cytology followed by surgical resections, and specimens were sent for histopathological examination.

The details of the cytomorphological diagnosis and the gross morphological and microscopy findings of the cases reported here are summarized in [Table 2] as below. This also describes the risk stratification of the reported variants.

The histomorphological findings and the radiological findings were correlated and concordance and discordance rates are as shown below in [Table 3].

Following the histo-radiological findings concordance analysis, the cytomorphological findings and Bethesda categories were correlated with the histopathological diagnosis and the concordance was recorded as below in [Table 4].

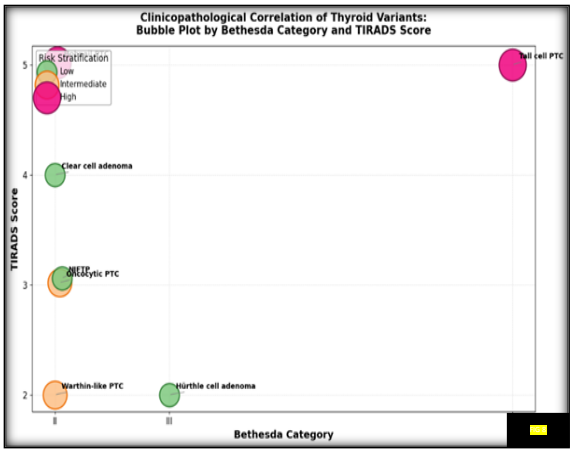
It was observed that, among the seven cases reported here, radiological findings and histopathological diagnosis had a concordance rate of 43%. The discordant cases included the aggressive forms of PTC namely the Warthin-like and Oncocytic PTC. In addition, the indeterminate category (NIFTP) with intermediate risk was also given a Category III by radiology.

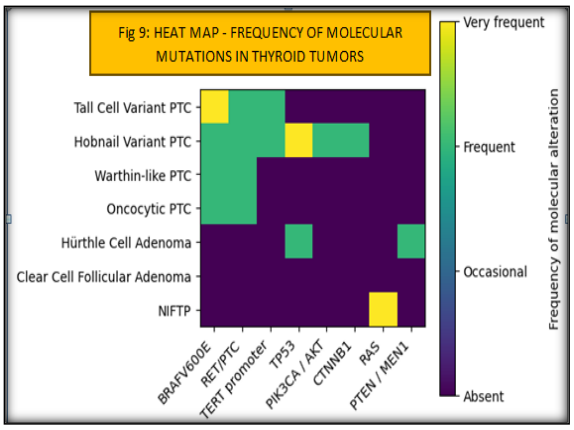
On further observations, it was found that the Bethesda categories of thyroid cytopathology correlated with the classical PTC and few of the variants like Tall cell variant. Rest of the histopathological variants like Hobnail, Warthin-Like and Oncocytic PTC were reported as Benign Category II lesions in cytopathology.

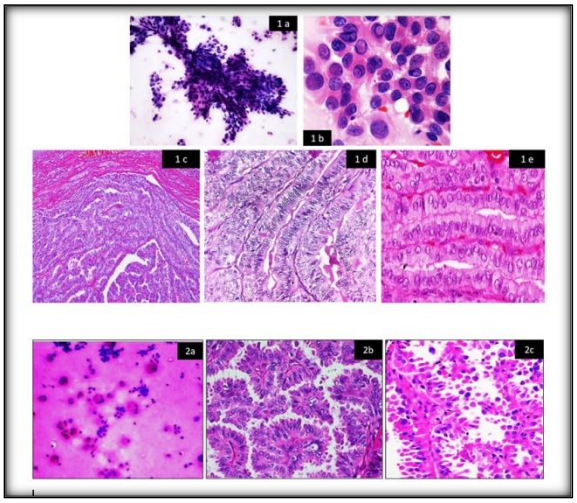
NIFTP lesions are frequently reported as benign as was in our case.

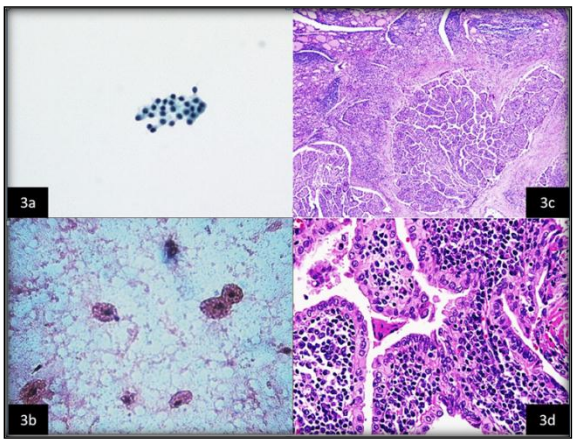
[Figure 8] Bubble plot showing the relationship between Bethesda category, TIRADS score, and final histopathological risk stratification among thyroid variants.

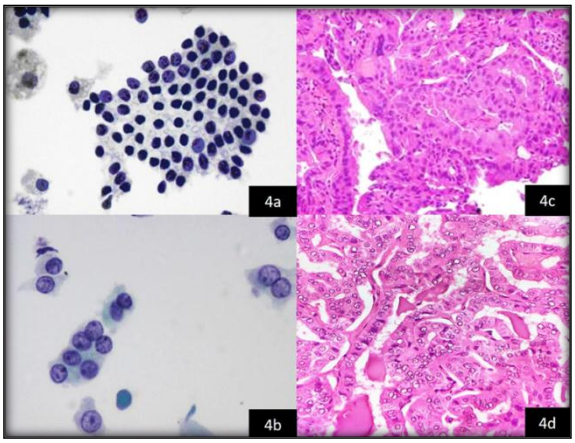
ISSN (O): 2687-5365; ISSN (P): 2753-6556

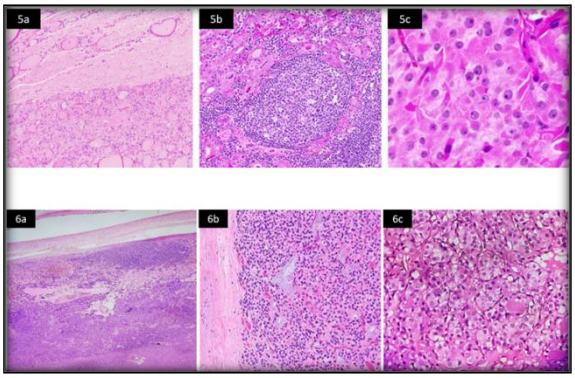












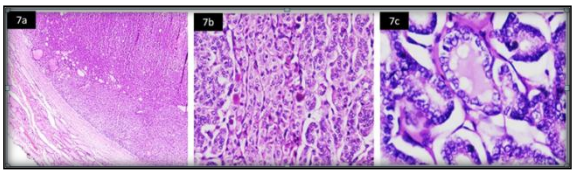


Figure 1a, 1b: Cytological features of tall cell variant of papillary carcinoma; displays monolayer sheets of cells arranged in papillary architecture having enlarged overlapping nuclei with intra-nuclear inclusions, irregular contours, pale fine chromatin and nuclear grooves H & E stain 40x.

Figure 1c-1e : Histopathology of tall cell variant of papillary carcinoma; 1c-shows an encapsulated tumor arranged in papillary pattern 1d, 1e : Papillae are lined by tall columnar cells (the breadth of a cell is three times its height) which showed nuclear features of PTC H & E stain 40x.

Figure 2a: Cytology of Hobnail variant of Papillary thyroid carcinoma; 2a -shows few clusters of thyroid follicular epithelial cells and cyst macrophages in a colloid background 2b, 2c: Histopathology of Hobnail variant of PTC- tumor with micropapillae lined by cells with apically placed nuclei and a hobnail appearance with PTC nuclear features H & E stain 40x.

Figure 3a, 3b: shows clusters of thyroid follicular epithelial cells and numerous cyst macrophages in a colloid mixed haemorrhagic background Pap stain 40x

Figure 3c, 3d: Histopathological features of Warthin-Like variant of PTC; shows thyroid follicular epithelial cells lining the papillae with nuclear

ISSN (O): 2687-5365; ISSN (P): 2753-6556

clearing, grooving, overlapping and stratification along with oncocytic changes in tumor cells. Papillary stalks were seen infiltrated by lymphocytes. H & E stain 40x.

Figure 4a, 4b: Aspirate smears from a case of Oncocytic variant of PTC; shows follicular epithelial clusters showing oncocytic change and scattered hemosiderin laden macrophages H & E stain 40x.

Figure 4c, 4d: Histopathology of Oncocytic variant of PTC; 4c-demonstrates a tumor with a fibrovascular core made of cells organized in a papillary pattern; these cells have moderate amount of granular eosinophilic cytoplasm and PTC nuclear features. H & E stain 40x.

Figure 5a: Histopathological features of Hurthle cell adenoma; shows a well circumscribed neoplasm with no vascular or capsular invasion seen. 5b, 5c: Hurthle cell adenoma with atrophic follicles, lymphoid aggregates and germinal centre along with Hurthle cell changes H & E stain 40x.

Figure 6a, 6b: Histopathological features of Clear Cell Adenoma of Thyroid; shows an encapsulated neoplasm composed of cells arranged as closely packed follicles, few filled with colloid. No capsular or vascular invasion seen. 6c: Individual cells have round nuclei, fine chromatin and moderate amount of clear and eosinophilic cytoplasm. H & E stain 40x.

Figure 7a: Histopathological features of NIFTP; show a well circumscribed encapsulated neoplasm. No vascular or capsular invasion seen.

Figure 7b: The follicular epithelial cells are arranged in microfollicular, trabecular pattern and small nests with intervening areas of edema and hyalinisation

Figure 7c: These cells had nuclear features of PTC like nucleomegaly, overlapping, overcrowding, chromatin with Orphan Annie eye like appearance, nuclear grooving and pseudo inclusion. No papillae seen. H & E stain 40x.

Figure 8. Bubble plot showing the relationship between Bethesda category, TIRADS score, and final histopathological risk stratification among thyroid variants.

Figure 9 Heat map showing the frequency of molecular mutations in thyroid tumors observed in this study.

Table 1: Clinical and Radiological Findings

Case	Age / Sex	Clinical History	Clinical Examination	Thyroid Function	Radiological Findings
1	60 / F	Thyroid swelling with sudden increase over 3 months; history of irregular treatment for thyrotoxicosis (5 years)	Firm 5 × 4 cm swelling in right lobe	Not available	USG: Hyperechoic nodule with calcifications and retrosternal extension-suggestive of malignancy TIRADS - 5
2	71 / M	Thyroid swelling for 6 years with rapid increase over 8 months; pain, dyspnoea, stridor, dysphagia	Firm 6 × 4 cm swelling in right lobe	Within Normal Limits	USG: Hypoechoic lesion with cystic degeneration (right lobe), calcifications (left lobe) TIRADS - 5 CECT: Lobulated hypo dense nodule with peripheral calcifications along with cervical lymphadenopathy
3	50 / F	Midline neck swelling for 6 months; no significant past or present history of thyroid lesions or medications	Firm 5 × 4 cm swelling in right lobe	Not available	USG: Multiple nodules, largest 28 × 20 mm, suggestive of benign lesion TIRADS -2
4	32 / M	Anterior neck swelling for 6 months with pain for 1 month	Firm 4 × 4 cm swelling in Left lobe	Within Normal Limits	USG & CECT: Well-defined hypoechoic nodule with cystic degeneration (4 × 3 × 3 cm), no calcification TIRADS -3
5	30 / F	Anterior neck swelling for 5 months with pain; known hypothyroidism for 9 years, on treatment	Firm 5 × 4 cm swelling, in Right lobe	Hypothyroid	USG: Multiple nodules in both lobes and isthmus; largest 21 × 11 mm (right lobe) with increased vascularity – multinodular goitre TIRADS - 2
6	25 / M	Neck swelling for 2 years, gradually increasing in size; no significant pain or altered voice	Firm 5 × 5 cm swelling in Right lobe	Within Normal Limits	USG: Hypoechoic nodule 2.3 × 2.1 cm with increased vascularity, no calcification – TIRADS 4
7	48 / F	Neck swelling for 7 years with sudden increase over 3 months and pain	Firm 7.5 × 6 × 4 cm swelling in midline	Within Normal Limits	USG: Well-defined hypoechoic lesion with cystic areas 6.5 × 5.1 × 3.4 cm – TIRADS 3

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 2: Cytomorphological diagnosis, gross morphological and microscopy findings of the cases

Case	FNAC / TBSRTC Category	Gross Findings	Microscopy of the lesion	Final Histopathological Diagnosis	Risk Stratification
1	Cat VI – Papillary thyroid carcinoma	Grey-white lesion 4 × 3.5 cm in right lobe, granular cut surface	Papillary architecture lined by tall columnar cells (height ≥3× width) with nuclear grooves and pseudoinclusions	Tall cell variant of papillary thyroid carcinoma	High – aggressive variant, higher risk of recurrence/metastasis
2	Cat II – Benign follicular nodule	Solid–cystic lesion; grey-white solid area 3 × 2.5 cm with calcifications	Micropapillae with hobnail cells; background shows features of Hashimoto thyroiditis	Hobnail variant of papillary thyroid carcinoma	High – aggressive variant, poor prognosis, higher metastatic potential
3	Cat II – Benign follicular nodule with cystic degeneration	Grey-white solid lesion 1 × 0.6 cm	Papillae lined by oncocytic cells with classical PTC nuclear features and stalk infiltrated with dense lymphoplasmacytic infiltrate (Warthin's like)	Warthin-like variant of papillary thyroid carcinoma	Intermediate – generally indolent, low recurrence, favourable prognosis
4	Cat II – Benign follicular nodule	Encapsulated grey-brown nodule 3.9 × 3.4 × 3.4 cm with cystic areas	Papillary architecture with oncocytic cells showing optically clear nuclei and prominent nucleoli	Oncocytic variant of papillary thyroid carcinoma	Intermediate–High – more aggressive than conventional PTC, moderate recurrence/metastasis risk
5	Cat III – AUS/FLUS	Well-circumscribed grey-white nodule 1.9 × 1.9 × 1.3 cm in isthmus	Follicular neoplasm of oncocytic cells without capsular or vascular invasion; background shows features of Hashimoto thyroiditis	Hürthle cell adenoma	Low – benign lesion, excellent prognosis
6	Cat II – Benign (Colloid goitre)	Encapsulated grey-white nodule 3.2 × 2.8 × 2 cm	Follicular adenoma with clear and eosinophilic cytoplasm; no invasion	Clear cell follicular adenoma	Low – benign lesion, excellent prognosis
7	Cat II – Benign follicular nodule	Well-circumscribed grey-tan lesion 6 × 4 × 3 cm	Encapsulated follicular-patterned neoplasm with PTC nuclear features; no invasion	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)	Low – non-invasive, excellent prognosis

Table 3: Histopathological and Radiological Correlation

Case	TIRADS	Final Histology	Status
1	5	Tall cell PTC	Concordant (Malignant)
2	5	Hobnail PTC	Concordant (Malignant)
3	2	Warthin-like PTC	Discordant
4	3	Oncocytic PTC	Discordant
5	2	Hürthle cell adenoma	Concordant (Benign)
6	4	Clear cell follicular adenoma	Discordant
7	3	NIFTP	Discordant (Indeterminate)

Table 4: Cyto-Histopathological Correlation

Case	FNAC Category	Final Histology	Status
1	Cat VI (Malignant)	PTC – Tall cell	Concordant
2	Cat II (Benign)	Hobnail PTC	Discordant
3	Cat II (Benign)	Warthin-like PTC	Discordant
4	Cat II (Benign)	Oncocytic PTC	Discordant
5	Cat III (AUS/FLUS)	Hürthle cell adenoma	Concordant
6	Cat II (Benign)	Clear cell follicular adenoma	Concordant
7	Cat II (Benign)	NIFTP	Discordant

DISCUSSION

Case 1: Tall Cell Variant of Papillary Thyroid Carcinoma

The tall cell variant (TCV) of papillary thyroid carcinoma (PTC) was first described by Hazard and Hawk in 1976.[11] Morphologically, tall cells resemble those of conventional PTC with eosinophilic cytoplasm and classical nuclear features; however, they are distinguished by a height at least three times their width.[28] TCV is clinically significant due to its association with aggressive behavior, relative resistance to radioactive iodine therapy, increased extrathyroidal extension, and higher rates of recurrence and metastasis compared to conventional PTC.

Earlier studies suggested that a minimum of 30% tall cells was required for diagnosis; however, Beninato et al,[14] Oh et al,[15] and Ganly et al,[13] reported aggressive behavior even in tumors with >10% tall cells. The 2022 WHO classification currently mandates ≥30% tall cells for definitive diagnosis.[28]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Nevertheless, adverse outcomes have been documented even when the tall cell component is <30%,[12] prompting experts such as LiVolsi,[16] to recommend reporting the presence of tall cell foci regardless of proportion. TCV shows a female predominance, with a reported female-to-male ratio of approximately 2.9:1, and typically, affects older patients (41–66 years) compared with conventional PTC.[17–19] Histologically, elongated follicles producing a distinctive "tram-track" appearance at low magnification characterize TCV. The tumor cells exhibit oncocytic cytoplasm, indistinct cell borders, numerous intranuclear pseudoinclusions, prominent central nucleoli, and a characteristic "soap-bubble" nuclear appearance.[20,21]

Molecularly, BRAFV600E mutations are present in 80–100% of cases. Wong et al,[22] reported a higher prevalence of BRAF mutations in tumors with >50% tall cells, frequently accompanied by secondary mutations such as TERT promoter alterations. RET/PTC3 rearrangements are also more common in TCV than in conventional PTC.[15,23,24]

Case 2: Hobnail Variant of Papillary Thyroid Carcinoma

The hobnail variant (HV) of PTC is a rare and aggressive subtype first clearly defined by Asioli et al. in 2010.[25] Earlier Japanese studies had already associated this morphology with increased recurrence and poor outcomes.[26,27] According to the 2022 WHO classification, a diagnosis of HV requires ≥30% of tumor cells to exhibit hobnail morphology.[28] Clinically, patients often present with a rapidly enlarging neck mass and cervical lymphadenopathy.[25]

The hobnail morphology—characterized by apically placed nuclei creating surface protrusions—is thought to reflect loss of cellular polarity and cohesion, suggestive of epithelial-mesenchymal transition and higher-grade transformation.[25,30] Compared with conventional PTC, HV demonstrates increased radioiodine refractoriness, disease progression, and mortality.[29]

Immunohistochemically, HV expresses TTF-1, thyroglobulin, EMA, CK7, CK19, and HBME-1, with a mean Ki-67 index of approximately 10%, correlating with its high mitotic activity.[29,30] Aberrant p53 overexpression is seen in approximately 77% of cases, and altered β-catenin and E-cadherin expression reflects impaired cell adhesion.

Molecular studies reveal frequent BRAFV600E mutations (57–80%), RET/PTC1 rearrangements, and high rates of TP53 mutations.[25,31] Morandi et al,[32] demonstrated additional alterations involving PIK3CA, TERT, EGFR, CTNNB1, NOTCH1, and AKT1, underscoring the molecular complexity and aggressive nature of this variant.

Case 3: Warthin-Like Variant of Papillary Thyroid Carcinoma

The Warthin-like variant of PTC (WL-PTC) was first described by Apel et al. in 1995.[33] This tumor closely resembles papillary cystadenoma lymphomatosum (Warthin tumor) of the salivary gland and predominantly affects middle-aged women.[37] It is frequently associated with Hashimoto thyroiditis and dense lymphocytic infiltration. Histologically, WL-PTC displays classical papillary architecture lined by oncocytic cells with characteristic nuclear grooves and optical clearing. The defining feature is dense lymphoplasmacytic infiltration of the papillary stalks and tumor stroma.[33–35] This prominent immune response, composed of both B and T lymphocytes, has been proposed to confer a protective effect, contributing to the generally favorable prognosis of this variant.[33,36]

Most WL-PTCs demonstrate RET/PTC rearrangements and BRAFV600E mutations, supporting their classification as a well-differentiated subtype of PTC [36]. Clinically, this variant behaves more indolently than other aggressive PTC subtypes.

Case 4: Oncocytic Variant of Papillary Thyroid Carcinoma

The oncocytic variant of PTC is an uncommon subtype, accounting for approximately 1–11% of PTCs.[38,39] It is defined by >75% oncocytic transformation of follicular cells exhibiting classical PTC nuclear features, in the absence of tumor necrosis or increased mitotic activity.[40]

Oncocytic PTCs may display either papillary or follicular architecture, with complex branching papillae lined by large polygonal or columnar oncocytic cells possessing abundant granular eosinophilic cytoplasm.[41] The biological behavior of oncocytic PTC remains controversial, partly due to heterogeneity within oncocytic thyroid neoplasms and variable radioactive iodine uptake.[42–44]

Molecular alterations frequently include BRAFV600E mutations and RET/PTC rearrangements, aligning oncocytic PTCs more closely with classical PTC rather than Hürthle cell carcinoma.[41]

Case 5: Hürthle Cell Adenoma

Hürthle cell adenoma (HCA) is a rare thyroid neoplasm, constituting less than 5% of all thyroid tumors.[45] Preoperative differentiation between benign and malignant Hürthle cell neoplasms remains challenging, as clinical, cytological, and molecular findings often overlap.[46] Consequently, histopathological evaluation remains the gold standard for diagnosis.

Diagnostic criteria include an intact capsule, absence of capsular and vascular invasion, and predominance (>75%) of oncocytic follicular cells.[47,48] Although most studies indicate a benign course in approximately 80% of cases, earlier reports suggested malignant potential even in lesions initially classified as adenomas.[49,50] This uncertainty supports surgical excision as the preferred management.

Molecular alterations in HCA may include aneuploidy and mutations involving PTEN, TP53, and occasional MEN1 loss of function.

Case 6: Clear Cell Follicular Adenoma

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Clear cell follicular adenoma is an exceptionally rare thyroid lesion, accounting for 0.14–3.0% of thyroid neoplasms. These tumors are composed predominantly (75–100%) of clear cells, which may exhibit signet-ring or balloon-cell morphology due to cytoplasmic accumulation of thyroglobulin, mucopolysaccharides, or lipid.[51–55]

Diagnostic criteria include encapsulation, follicular differentiation, predominance of clear cells, and absence of capsular or vascular invasion. Immunohistochemically, these tumors express pan-cytokeratin (AE1/AE3), PAX8, thyroglobulin, and TTF-1, confirming thyroid follicular origin.

Case 7: Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)

NIFTP, first introduced in 2016, represents a paradigm shift in thyroid tumor classification and is recognized in the WHO classification of endocrine tumors.[56,57] It denotes an indolent neoplasm with extremely low malignant potential, accounting for 9–22% of tumors previously classified as follicular variant PTC.[61] Diagnosis is established exclusively on surgical specimens and requires strict histopathological criteria, including encapsulation, follicular growth pattern, papillary-like nuclear features, and complete absence of invasion, papillae, psammoma bodies, tumor necrosis, high mitotic activity, and aggressive PTC variants.[60] Molecularly, NIFTP typically lacks BRAFV600E mutations and may harbor RAS mutations, supporting its indolent behavior.

The following is a heat map [Figure 9]showing the occurrence of molecular genetic mutations in the various variants of Papillary carcinoma of thyroid and other tumors seen in our cases.

CONCLUSION

In the majority of instances, Thyroid carcinoma is a curable disease with a favorable prognosis over the long term when several conventional surgical and adjuvant therapies are used strategically and appropriately. However, doctors must be aware of the famous idiom ‘Wolf in sheep clothing’ that refers to every patient with suspected thyroid carcinoma; what may first seem straightforward and manageable may ultimately turn out to be quite complex and unsolvable.

Even for experienced histopathologists, correctly diagnosing the most aggressive PTC types can be difficult. Every aggressive variant produces a worse result than traditional PTC. The prognostic significance of the aggressive PTC variants morphology alone is unknown at this time. Because of this ambiguity, skilled doctors will decide on an individual basis how much surgical intervention and adjuvant therapy is needed based on the size of the tumor at the time of initial presentation. New molecular discoveries may pave the path for future targeted therapies that could increase these patient’s chances of survival.

REFERENCES

1. Unnikrishnan AG, Kalra S, Baruah M. Endocrine society of India management guidelines for patients with thyroid nodules- A position statement. Indian J Endocrinol Metab. 2011;15(1)2-8. doi: 10.4103/2230-8210.77566.
2. Mettler FAJR, Wiest PW, Locken JA. CT scanning patterns of use and dose. J Radiol Prot. 2000;20(4)353-359. doi: 10.1088/0952-4746/20/4/301
3. Linton OW, Mettler FA, Locken JA. National conference on dose reduction in CT, with an emphasis on pediatric patients. Am J Roentgenol. 2003;181(2)321-329. doi: 10.2214/ajr.181.2.1810321
4. Mathur A, Moses W, Rahbari, R, Khanafshar E, Duh QY, Clark O, et al. Higher rate of BRAF mutation in papillary thyroid cancer over time- a single-institution study. Cancer. 2011;117(19)4390-4395. doi:10.1002/cncr.26072
5. Feildt-rasmussem U. Iodine and cancer. Thyroid. 2001;11(5)483-486. doi:10.1089/105072501300176435
6. Harach, HR, Escalante DA, Onativia, A, Lederer Outes J, Saravia Day E, Williams ED. Thyroid carcinoma and thyroiditis in an endemic goitre region before and after iodine prophylaxis. Acta Endocrinologica. 1985;108(1)55-60. doi: 10.1530/acta.0.1080055
7. Peterson E, De P, Nuttall R. BMI, diet and female reproductive factors as risks for thyroid cancer a systematic review. PLoS One. 2012;7(1)54- 76.
8. Pravanya PK, Anila KR, Thomas S, Sreekumar A, Jayasree K. Aggressive histopathological variants of papillary thyroid carcinoma, diagnostic challenge, and clinical significance—A case series. Med J DY Patil Vidyapeeth 2022;15:922-5.
9. M Gauthamraj., et al. “A Rare Case of Nodular Goiter Presenting as Follicular Variant of Papillary Thyroid Carcinoma”. Medicon Medical Sciences 4.2 (2023): 36-38.
10. Coca-Pelaz, Andrés; Shah, Jatin P.; Hernandez-Prera, Juan C.; Ghossein, Ronald A.; Rodrigo, Juan P.; Hartl, Dana M.; et al. (2020). Papillary Thyroid Cancer—Aggressive Variants and Impact on Management: A Narrative Review. Adis Journals.https://doi.org/10.6084/m9.figshare.12302081.v1
11. Hawk WA, Hazard JB. The many appearances of papillary carcinoma of the thyroid. Cleve Clin Q. 1976;43:207–15.
12. Wang X, Cheng W, Liu C, Li J. Tall cell variant of papillary thyroid carcinoma: Current evidence on clinicopathologic features and molecular biology. Oncotarget 2016;7:4079299.
13. Ganly I, Ibrahimpasic T, Rivera M, et al. Prognostic implications of papillary thyroid carcinoma with tall-cell features. Thyroid. 2014;24:662–70
14. Beninato T, Scognamiglio T, Kleiman DA, et al. Ten percent tall cells confer the aggressive features of the tall cell variant of papillary thyroid carcinoma. Surgery. 2013;154:1331–6.
15. Oh WJ, Lee YS, Cho U, et al. Classic papillary thyroid carcinoma with tall cell features and tall cell variant have similar clinicopathologic features. Korean J Pathol. 2014;48:201–8.
16. LiVolsi VA. Papillary carcinoma tall cell variant (TCV): a review. Endocr Pathol. 2010;21:12–5.
17. Wang X, Cheng W, Liu C, Li J. Tall cell variant of papillary thyroid carcinoma: current evidence on clinicopathologic features and molecular biology. Oncotarget. 2016;7:40792–9.
18. Kazaure HS, Roman SA, Sosa JA. Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. Ann Surg Oncol. 2012;19:1874–80.
19. Morris LGT, Shaha AR, Tuttle RM, Sikora AG, Ganly I. Tall-cell variant of papillary thyroid carcinoma: a matched-pair analysis of survival. Thyroid. 2010;20: 153–8.
20. Solomon A, Gupta PK, LiVolsi VA, Baloch ZW. Distinguishing tall cell variant of papillary thyroid carcinoma from usual variant of papillary thyroid carcinoma in cytologic specimens. Diagn Cytopathol. 2002;27:143–8
21. Das DK, Mallik MK, Sharma P, et al. Papillary thyroid carcinoma and its variants in fine needle aspiration smears. A cytomorphologic study with special reference to tall cell variant. Acta Cytol. 2004;48:325–36
22. Wong KS, Higgins SE, Marqusee E, Nehs MA, Angell T, Barletta JA. Tall cell variant of papillary thyroid carcinoma:

ISSN (O): 2687-5365; ISSN (P): 2753-6556

impact of change in WHO definition and molecular analysis. Endocr Pathol. 2019;30: 43–8.
23. Erler P, Keutgen XM, Crowley MJ, et al. Dicer expression and microRNA dysregulation associate with aggressive features in thyroid cancer. Surgery. 2014;156:1342–50.
24. Basolo F, Giannini R, Monaco C, et al. Potent mitogenicity of the RET/PTC3 oncogene correlates with its prevalence in tall-cell variant of papillary thyroid carcinoma. Am J Pathol. 2002;160:247–54.
25. Asioli S, Erickson LA, Sebo TJ, et al. Papillary thyroid carcinoma with prominent hobnail features: a new aggressive variant of moderately differentiated papillary carcinoma. A clinicopathologic, immunohistochemical, and molecular study of eight cases. Am J Surg Pathol. 2010;34:44–52.
26. Kakudo K, Tang W, Ito Y, Mori I, Nakamura Y, Miyauchi A. Papillary carcinoma of the thyroid in Japan: subclassification of common type and identification of low risk group. J Clin Pathol. 2004;57: 1041–6.
27. Motosugi U, Murata S-I, Nagata K, Yasuda M, Shimizu M. Thyroid papillary carcinoma with micropapillary and hobnail growth pattern: a histological variant with intermediate malignancy? Thyroid. 2009;19:535–7
28. Jung, C. K., Bychkov, A., & Kakudo, K. (2022). Update from the 2022 World Health Organization Classification of Thyroid Tumors: A Standardized Diagnostic Approach. Endocrinology and Metabolism, 37(5), 703-718. https://doi.org/10.3803/EnM.2022.1553
29. Asioli S, Maletta F, Pagni F, et al. Cytomorphologic and molecular features of hobnail variant of papillary thyroid carcinoma: case series and literature review. Diagn Cytopathol. 2014;42:78–84
30. Ambrosi F, Righi A, Ricci C, Erickson LA, Lloyd RV, Asioli S. Hobnail variant of papillary thyroid carcinoma: a literature review. Endocr Pathol. 2017;28: 293–301
31. Lubitz CC, Economopoulos KP, Pawlak AC, et al. Hobnail variant of papillary thyroid carcinoma: an institutional case series and molecular profile. Thyroid. 2014;24:958–65.
32. Morandi L, Righi A, Maletta F, et al. Somatic mutation profiling of hobnail variant of papillary thyroid carcinoma. Endocr Relat Cancer. 2017;24: 107–17.
33. Apel RL, Asa SL, LiVolsi VA. Papillary Hurthle cell carcinoma with lymphocytic stroma.Warthin-like tumor of the thyroid. Am J Surg PathoI 1995;19:810- 14.
34. LiVolsi VA.Surgical Pathology of the Thyroid. Philadelphia: W.B. Saunders, 1990.
35. Rosai J. Carcangiu ML, DeLe llis R. Tumors of the thyroid gland. In: Atlas of Tumor Pathology. 3rd series, fascicle 5. Washington , D.C.: Armed Forces Institute of Pathology, 1992
36. Antonio A, De Chiara A, Santoro M, et al. Warthin-like tumour of the thyroid gland: RET/PTC expressionindicates it is a variant of papillary carcinoma. Histopathology 2000;36:493-8.
37. Paliogiannis P, Attene F, Trogu F, Trignano M. Warthin-like papillary carcinoma of the thyroid gland: case report and review of the literature. Case Rep Oncol Med. 2012;2012:689291. doi: 10.1155/2012/689291. Epub 2012 Dec 2. PMID: 23243533; PMCID: PMC3518096.
38. Berho M, Suster S. The oncocytic variant of papillary carcinoma of the thyroid: A clinicopathologic study of 15 cases. Hum Pathol 1997;28:47-53.
39. Mishra A, Jayalakshmi V, Chaturvedi UP, Chikhale NP, Patel RD, Cherian S. Oncocytic variant of papillary thyroid carcinoma and associated lymphocytic thyroiditis: A case report with review of literature. Int J Head Neck Surg 2013;4:89-91.
40. Lukovic J, Petrovic I, Liu Z, Armstrong SM, Brierley JD, Tsang R, Pasternak JD, Gomez-Hernandez K, Liu A,Asa SL and Mete O (2021) Oncocytic Papillary Thyroid Carcinoma and Oncocytic Poorly Differentiated Thyroid Carcinoma: Clinical Features, Uptake, and Response to Radioactive Iodine Therapy, and Outcome. Front. Endocrinol. 12:795184. doi: 10.3389/fendo.2021.795184
41. Mishra A, Jayalakshmi V, Chaturvedi UP, Chikhale NP, Patel RD, Cherian S. Oncocytic Variant of Papillary Thyroid Carcinoma and Associated Lymphocytic Thyroiditis: A Case Report with Review of Literature. Int J Head Neck Surg 2013;4(2):89-91.
42. Yang Q, Zhao Z, Zhong G, Jin A, Yu K. Effect of Adjuvant Radioactive Iodine Therapy on Survival in Rare Oxyphilic Subtype of Thyroid Cancer (Hurthle Cell Carcinoma). PeerJ (2019) 7:e7458. doi: 10.7717/peerj.7458
43. Goffredo P, Roman SA, Sosa JA. Hurthle Cell Carcinoma: A Population-Level Analysis of 3311 Patients. Cancer (2013) 119(3):504–11. doi: 10.1002/ cncr.27770
44. Zhou X, Zheng Z, Chen C, Zhao B, Cao H, Li T, et al. Clinical Characteristics and Prognostic Factors of Hurthle Cell Carcinoma: A Population Based Study. BMC Cancer (2020) 20(1):407. doi: 10.1186/s12885-020-06915-0
45. Stojadinovic A, Hoos A, Ghossein RA, et al. Hurthle cell carcinoma: a 60-year experience. Ann Surg Oncol 2002;9:197–203
46. Bremer AA, Feldman BJ, Iezza G, et al. Report of a hurthle cell neoplasm in a peripubertal girl. Thyroid 2007;17:175–8.
47. Kochummen E, Tong S, Umpaichitra V, et al. A unique case of bilateral Hurthle cell adenoma in an adolescent. Horm Res Paediatr 2017; 87:136–42.
48. Baloch ZW, LiVolsi VA, Asa SL, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008;36:425–37.
49. Montone KT, Baloch ZW, LiVolsi VA. The thyroid Hurthle (oncocytic) cell and its associated pathologic conditions: a surgical pathology and cytopathology review. Arch Pathol Lab Med 2008;132:1241–50.
50. Grant CS, Barr D, Goellner JR, et al. Benign Hurthle cell tumors of the thyroid: a diagnosis to be trusted? World J Surg 1988;12:488–95.
51. Farhat NA, Onenerk AM, Krane JF, Dias-Santagata D, Sadow PM, Faquin WC. Primary benign and malignant thyroid neoplasms with signet ring cells: cytologic, histologic, and molecular features. Am J Clin Pathol, 2017, 148(3):251–258. https://doi.org/10.1093/ajcp/aqx074 PMID: 28821194
52. Yalta T, Elagoz S, Uyar M, Topuz O, Ozer H, Tuncer E. Signet ring cell adenoma of the thyroid: a very rare entity. Med Princ Pract, 2010, 19(1):76–78. https://doi.org/10.1159/000252840 PMID: 19996625
53. Rigaud C, Peltier F, Bogomoletz WV. Mucin producing microfollicular adenoma of the thyroid. J Clin Pathol, 1985, 38(3): 277–280. https://doi.org/10.1136/jcp.38.3.277 PMID: 3973051 PMCID: PMC499124
54. Ranaldi R, Goteri G, Bearzi I. Lipid-rich adenoma of the thyroid. Pathol Res Pract, 1993, 189(9):1101–1106; discussion 1106– 1107. https://doi.org/10.1016/S0344-0338(11)80693-X PMID: 8302729
55. Chetty R. Thyroid follicular adenoma composed of lipid-rich cells. Endocr Pathol, 2011, 22(1):31–34. https://doi.org/10.1007/s12022-010-9143-6 PMID: 21165779
56. E. Nikiforov, R.R. Seethala, G. Tallini, et al., Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors, JAMA Oncol. 2 (2016) 1023–1029.
57. O.R. Lloyd, G. Kloppel, J. Rosai, WHO Classification of Tumours of Endocrine Organs 4, International Agencyfor Research on Cancer, Lyon, France, 2017.
58. Z. Baloch, V.A. LiVolsi, W.H. Henricks, B.A. Sebak, Encapsulated follicular variant of papillary thyroid carcinoma, Am. J. Clin. Pathol. 118 (2002) 603–605.
59. M. Vivero, S. Kraft, J.A. Barletta, Risk stratification of follicular variant of papillary thyroid carcinoma, Thyroid 23 (2013) 273–279.
60. Y.E. Nikiforov, Z.W. Baloch, S.P. Hodak, et al., Change in diagnostic criteria for noninvasive follicular thyroid neoplasm with papillary like nuclear features, JAMA Oncol. 4 (2018) 1125–1126.
61. Chanchal Rana, Huy Gia Vuong, Thu Quynh Nguyen, Hoang Cong Nguyen, Chan Kwon Jung, Kennichi Kakudo, and Andrey Bychkov.The Incidence of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: A Meta-Analysis Assessing Worldwide Impact of the Reclassification.Thyroid®.Oct 2021.1502-1513.

ISSN (O): 2687-5365; ISSN (P): 2753-6556