

A Study of BRAF V600E Gene Mutation Among Patients With Follicular Cell-Derived Thyroid Malignant Neoplasms

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Abstract

Background: Thyroid carcinoma is the most common endocrine malignancy, with most cases arising from follicular epithelial cells. BRAF V600E mutation has important diagnostic, prognostic and therapeutic relevance, particularly in papillary thyroid carcinoma.

Aim: To evaluate BRAF V600E expression in follicular cell-derived thyroid malignant neoplasms using immunohistochemistry and correlate it with clinicopathological parameters.

Materials and Methods: This hospital-based cross-sectional observational study included 40 patients with follicular cell-derived thyroid malignant neoplasms. Thyroidectomy specimens were evaluated histopathologically and BRAF V600E immunohistochemistry was performed. BRAF expression was assessed using the H-score method, with a score of ≥ 100 considered positive.

Results: Most patients belonged to the 31–50 years age group, with a mean age of 42.98 ± 12.81 years. Female predominance was noted. Papillary thyroid carcinoma was the most common tumor type. BRAF positivity was observed in 14 cases (35.0%), while 26 cases (65.0%) were negative. BRAF positivity was significantly associated with tumor type ($p < 0.001$) and background lymphocytic thyroiditis ($p = 0.014$). Higher BRAF expression was also significantly associated with lymphocytic thyroiditis ($p = 0.049$).

Conclusion: BRAF V600E expression was observed in 35.0% of cases and was predominantly associated with papillary thyroid carcinoma. Its absence in NIFTP supports its diagnostic utility in differentiating papillary thyroid carcinoma from low-risk follicular-patterned lesions.

Keywords: BRAF V600E, thyroid carcinoma, papillary thyroid carcinoma, immunohistochemistry, NIFTP, lymphocytic thyroiditis.

INTRODUCTION

Thyroid carcinoma is the most common malignancy of the endocrine system and accounts for the majority of endocrine-related cancers. Its incidence has increased steadily worldwide over the past few decades. Although improved imaging techniques and increased screening have contributed to the detection of small and clinically silent thyroid nodules, these factors do not completely explain the rising burden of disease.^[1,2] Epidemiological trends suggest that a true increase in the occurrence of thyroid carcinoma may also be contributing to this rise.^[3]

Thyroid nodules are frequently encountered in routine clinical practice; however, most are benign, and only a small proportion are malignant. Accurate distinction between benign and malignant thyroid lesions is essential, as it directly influences treatment planning and helps avoid unnecessary surgical intervention. The diagnostic evaluation of thyroid nodules includes clinical examination, radiological assessment, cytology, histopathological examination, and, increasingly, molecular testing.^[4,5]

Most thyroid malignancies arise from follicular epithelial cells. Follicular cell-derived thyroid neoplasms include papillary thyroid carcinoma, follicular thyroid carcinoma, poorly differentiated thyroid carcinoma, and anaplastic thyroid carcinoma. Among these, papillary thyroid carcinoma is the most common subtype and is generally associated with a favorable prognosis. However, its biological behavior may vary considerably depending on histological subtype, extent of disease, and underlying molecular alterations.^[6,7] The molecular pathogenesis of thyroid carcinoma involves genetic alterations that regulate cellular proliferation, differentiation, survival, and apoptosis. Several molecular abnormalities have been implicated in thyroid tumorigenesis, including BRAF mutations, RAS mutations, RET/PTC rearrangements, and other pathway-related alterations. Among these, the BRAF V600E mutation has gained particular importance

because of its strong association with papillary thyroid carcinoma and its possible role in tumor aggressiveness.^[8]

The BRAF gene encodes a serine/threonine kinase that functions as an important component of the mitogen-activated protein kinase signaling pathway. This pathway plays a central role in regulating cell growth, differentiation, and survival. The BRAF V600E mutation occurs due to substitution of valine by glutamic acid at codon 600, resulting in constitutive activation of the BRAF kinase. This persistent activation leads to continuous downstream signaling and promotes uncontrolled cellular proliferation and tumor progression.^[9]

BRAF V600E mutation has been associated with several adverse clinicopathological features, including extrathyroidal extension, lymph node metastasis, tumor recurrence, advanced disease stage, and reduced response to radioactive iodine therapy. However, its prognostic significance remains a subject of debate, as some studies have reported a strong association with aggressive tumor behavior, whereas others have shown variable results. Therefore, evaluation of BRAF mutation status in different populations and tumor subtypes remains clinically relevant.^[10,11]

Immunohistochemistry is a practical and widely available method for detecting BRAF V600E mutant protein expression in formalin-fixed paraffin-embedded tissue sections. It is cost-effective, reproducible, and can be incorporated into routine histopathological practice. BRAF immunohistochemistry may serve as a useful diagnostic adjunct, particularly in cases with overlapping histomorphological features between papillary thyroid carcinoma, follicular-patterned lesions, and low-risk neoplasms such as non-invasive follicular thyroid neoplasm with papillary-like nuclear features.^[12]

In the era of precision medicine, molecular profiling has become increasingly important in the management of thyroid carcinoma. Identification of BRAF mutation may assist in diagnosis, risk stratification, prognostic assessment, therapeutic decision-making and selection of patients who may benefit from targeted therapy. Therefore, the present study was conducted to evaluate BRAF V600E expression by immunohistochemistry in follicular cell-derived thyroid malignant neoplasms and to correlate BRAF mutation status with various clinicopathological parameters.

MATERIALS AND METHODS

Study Design

This was a hospital-based cross-sectional observational study conducted to assess the prevalence and clinicopathological relevance of BRAF V600E mutation in patients diagnosed with follicular cell-derived thyroid malignant neoplasms.

Study Setting

The study was carried out in the Department of Pathology in coordination with the Department of Surgery/Oncology at a tertiary care teaching institution. Histopathological evaluation and immunohistochemical analysis were performed in the institutional laboratory.

Study Duration

The study was conducted over a period of 18 months.

Study Population

The study included patients diagnosed with follicular cell-derived thyroid malignant neoplasms who underwent surgical excision and had adequate tissue available for histopathological and immunohistochemical evaluation.

Inclusion Criteria

Patients with histologically confirmed follicular cell-derived thyroid malignancies, including papillary thyroid carcinoma, follicular thyroid carcinoma, and their variants, were included. Patients who underwent partial or total thyroidectomy and provided informed consent were considered eligible.

Exclusion Criteria

Patients with non-follicular epithelial thyroid malignancies such as medullary carcinoma, lymphoma, and metastatic tumors were excluded. Inadequate or poorly preserved specimens, patients who had received prior treatment for thyroid malignancy before tissue collection, and patients who declined consent were

also excluded.

Sample Size

A total of 40 cases were included in the study.

Sampling Technique

All eligible patients presenting during the study period were included using consecutive sampling until the required sample size was achieved.

Study Variables

The variables evaluated in the study included age, sex, type of surgical specimen, tumor type, histological variant, extrathyroidal extension, capsular invasion, vascular invasion, lymphovascular invasion, background lymphocytic thyroiditis, and BRAF V600E expression.

Histopathological Evaluation

Thyroidectomy specimens were fixed in 10% neutral buffered formalin, routinely processed, and embedded in paraffin. Sections of 3–5 µm thickness were prepared and stained with hematoxylin and eosin. Histopathological diagnosis was made according to standard diagnostic criteria.

Immunohistochemistry

Immunohistochemistry was performed for the detection of BRAF V600E mutation using a BRAF V600E-specific monoclonal antibody/VE1 antibody. Appropriate positive and negative controls were included with each staining run. Staining results were independently evaluated by pathologists using the H-score method. H-score = 1 × percentage of weak staining + 2 × percentage of moderate staining + 3 × percentage of strong staining

The total H-score ranged from 0 to 300. An H-score of ≥100 was considered positive for BRAF expression, whereas an H-score of <100 was considered negative.

Statistical Analysis

Data were analyzed using statistical software. Descriptive statistics were expressed as frequency, percentage, mean and standard deviation. Associations between categorical variables were evaluated using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

Ethical approval was obtained from the Institutional Ethics Committee before commencement of the study. Written informed consent was obtained from all participants. Patient confidentiality was maintained throughout the study.

RESULTS

Demographic Characteristics

A total of 40 patients diagnosed with follicular cell-derived thyroid malignant neoplasms were included in the study. The majority of patients belonged to the 31–50 years age group, comprising 22 cases (55.0%). Seven patients (17.5%) were below 30 years of age, while 11 patients (27.5%) were above 50 years. The mean age of the study population was 42.98 ± 12.81 years (Table 1).

A marked female predominance was observed in the present study. Females constituted 35 cases (87.5%), while males constituted 5 cases (12.5%) (Table 2).

Distribution of Surgical Specimens

Total thyroidectomy was the most commonly performed surgical procedure. Out of 40 cases, 34 specimens (85.0%) were total thyroidectomy specimens, 4 cases (10.0%) were right hemithyroidectomy specimens, 1 case (2.5%) was completion thyroidectomy, and 1 case (2.5%) was total thyroidectomy with left modified radical neck dissection (Table 3).

BRAF Mutation Status

BRAF positivity was observed in 14 cases, accounting for 35.0% of the study population. Twenty-six cases were BRAF-negative, accounting for 65.0% (Table 4).

Distribution of Tumor Types

Papillary thyroid carcinoma was the most common tumor type, accounting for 26 cases (65.0%), followed by non-invasive follicular thyroid neoplasm with papillary-like nuclear features in 9 cases (22.5%). Thyroid

tumor of uncertain malignant potential was seen in 2 cases (5.0%). Follicular thyroid carcinoma, invasive encapsulated follicular variant of papillary thyroid carcinoma, and poorly differentiated thyroid carcinoma were observed in 1 case each (2.5% each) (Table 5).

Representative histopathological sections showed classic papillary thyroid carcinoma architecture and nuclear features on hematoxylin and eosin staining, including classic subtype morphology and oncocytic variant morphology (Figures 1–4).

Histopathological Parameters

Extrathyroidal extension was absent in most cases. It was absent in 32 cases (80.0%) and present in 8 cases (20.0%) (Table 6).

Capsular invasion was absent in 38 cases (95.0%) and present in 2 cases (5.0%) (Table 7).

Vascular invasion was absent in 39 cases (97.5%) and present in only 1 case (2.5%) (Table 8).

Lymphovascular invasion was absent in 38 cases (95.0%) and present in 2 cases (5.0%) (Table 9).

Background Lymphocytic Thyroiditis

Background lymphocytic thyroiditis was absent in 32 cases (80.0%) and present in 8 cases (20.0%) (Table 10).

Immunohistochemical H-score and Staining Intensity

The mean immunohistochemical H-score was 91.00 ± 105.67 , indicating marked variability in BRAF immunoexpression among the cases. The mean value for no staining was 30.78 ± 36.11 , while the mean values for 1+, 2+, and 3+ staining were 6.00 ± 6.12 , 5.30 ± 5.73 , and 24.80 ± 32.58 , respectively (Table 11).

Representative immunohistochemistry showed negative BRAF staining in NIFTP (Figure 5). BRAF immunohistochemistry in papillary thyroid carcinoma showed variable staining intensity, ranging from moderate positivity to strong positivity, including strong positivity in the background of lymphocytic thyroiditis (Figures 6–8).

Association of Sex and Age with Clinicopathological Variables

Female patients constituted the majority of cases across almost all tumor categories. Papillary thyroid carcinoma was the most common tumor among both female and male patients. However, no statistically significant association was observed between sex and tumor type, capsular invasion, vascular invasion, lymphovascular invasion, or lymphocytic thyroiditis.

Patients aged 31–50 years formed the largest age group in the study, and papillary thyroid carcinoma was most frequently observed in this age group. No statistically significant association was observed between age category and tumor type, capsular invasion, vascular invasion, lymphovascular invasion, or background lymphocytic thyroiditis.

Association of BRAF Mutation Status with Tumor Type

BRAF mutation status showed a statistically significant association with tumor type ($\chi^2 = 20.081$, $p < 0.001$). BRAF positivity was mainly associated with papillary thyroid carcinoma, while all NIFTP cases were BRAF-negative. BRAF positivity was also observed in the case of poorly differentiated thyroid carcinoma with papillary thyroid carcinoma areas.

Association of BRAF Mutation Status with Clinicopathological Variables

On correlation with clinicopathological variables, BRAF mutation status showed a statistically significant association with background lymphocytic thyroiditis ($\chi^2 = 6.000$, $p = 0.014$). Lymphocytic thyroiditis was more frequently observed among BRAF-positive cases. Capsular invasion was observed only in BRAF-positive cases and showed borderline significance ($\chi^2 = 3.509$, $p = 0.061$). Vascular invasion was also seen only in a BRAF-positive case, but the association was not statistically significant ($\chi^2 = 1.709$, $p = 0.191$). Lymphovascular invasion did not show a significant association with BRAF status ($\chi^2 = 0.140$, $p = 0.708$) (Table 12).

BRAF Expression and Lymphocytic Thyroiditis

Patients with background lymphocytic thyroiditis showed a higher proportion of moderate-to-strong BRAF expression compared with patients without lymphocytic thyroiditis. This association was statistically significant ($\chi^2 = 4.821$, $p = 0.049$), suggesting that the inflammatory thyroid background may be associated with increased BRAF expression intensity.

DISCUSSION

Thyroid carcinoma is the most common endocrine malignancy, with most cases arising from follicular epithelial cells. Although histopathological examination remains the diagnostic gold standard, molecular markers have become increasingly important in the evaluation of thyroid neoplasms, particularly in lesions with overlapping morphology. Among these markers, BRAF V600E mutation has gained considerable importance because of its close association with papillary thyroid carcinoma and its diagnostic, prognostic, and therapeutic relevance.^[1,13]

In the present study, most patients belonged to the 31–50 years age group, with a mean age of 42.98 ± 12.81 years, indicating that follicular cell-derived thyroid malignant neoplasms were more frequently encountered in middle-aged individuals. A marked female predominance was observed, with females comprising 87.5% of cases. However, neither age nor sex showed a significant association with the evaluated clinicopathological parameters, suggesting that tumor behavior was more closely related to histological and molecular features than to demographic factors alone.

Papillary thyroid carcinoma was the most common tumor type, accounting for 26 cases (65.0%), followed by non-invasive follicular thyroid neoplasm with papillary-like nuclear features in 9 cases (22.5%). This was consistent with the known predominance of papillary thyroid carcinoma among follicular cell-derived thyroid malignancies. The identification of NIFTP as a separate low-risk entity was important, as it helped differentiate indolent follicular-patterned lesions from invasive papillary thyroid carcinoma and may prevent overtreatment.

BRAF positivity was observed in 14 cases (35.0%). This prevalence fell within the lower-to-intermediate range reported in previous studies and may have varied because of differences in sample size, population characteristics, tumor subtype distribution, immunohistochemical protocols, scoring criteria and inclusion of low-risk lesions such as NIFTP. BRAF mutation status showed a statistically significant association with tumor type ($\chi^2 = 20.081$, $p < 0.001$). BRAF positivity was predominantly associated with papillary thyroid carcinoma, while all NIFTP cases were BRAF-negative. This supported the role of BRAF V600E mutation in papillary thyroid carcinoma pathogenesis. Xu et al. (2003) reported BRAF mutations in a significant proportion of papillary thyroid carcinoma cases and observed their absence in benign thyroid lesions.^[14] Santarpia et al. (2010) also emphasized the role of MAPK pathway activation in follicular variant papillary thyroid carcinoma.^[15]

The absence of BRAF positivity in all NIFTP cases supported the concept that NIFTP was biologically distinct from invasive papillary thyroid carcinoma and had a low-risk molecular profile. This finding also supported the utility of BRAF V600E immunohistochemistry as an adjunctive tool in differentiating papillary thyroid carcinoma from selected follicular-patterned thyroid neoplasms. Nikiforov et al. (2014) highlighted the value of molecular profiling in improving diagnostic accuracy, especially in thyroid nodules with indeterminate or overlapping morphology.^[16]

Capsular invasion and vascular invasion were observed only among BRAF-positive tumors; however, capsular invasion showed only borderline significance ($\chi^2 = 3.509$, $p = 0.061$), and vascular invasion was not statistically significant ($\chi^2 = 1.709$, $p = 0.191$). Lymphovascular invasion also did not show a significant association with BRAF mutation status ($\chi^2 = 0.140$, $p = 0.708$). These findings may have suggested a possible trend toward invasive behavior in BRAF-positive tumors, but the small number of cases with invasive features limited definitive interpretation.

Background lymphocytic thyroiditis was identified in 8 cases (20.0%) and showed a statistically significant association with BRAF mutation status ($\chi^2 = 6.000$, $p = 0.014$). Higher BRAF expression was also significantly associated with lymphocytic thyroiditis ($\chi^2 = 4.821$, $p = 0.049$). This suggested a possible interaction between tumor-related molecular alterations and the inflammatory thyroid microenvironment. The relationship between lymphocytic thyroiditis and papillary thyroid carcinoma remained complex, as it may represent either an immune response against tumor antigens or a chronic inflammatory background contributing to tumor development.

The mean H-score was 91.00 ± 105.67 , indicating marked variability in BRAF immunoexpression. This heterogeneity emphasized the need for careful interpretation and standardized scoring of BRAF immunohistochemistry. Rossi et al. (2014) reported that VE1 immunostaining could be useful as a screening

method for BRAF V600E mutation, although molecular testing remained more reliable in equivocal cases.^[17] Rossi et al. (2015) further observed that strong VE1 expression correlated with BRAF V600E mutation in papillary thyroid carcinoma.^[18]

The biological and therapeutic relevance of BRAF mutation has also been supported by experimental and clinical studies. Chakravarty et al. (2011) showed that BRAFV600E expression in thyroid follicular cells resulted in aggressive thyroid tumors, while inhibition of the MAPK pathway reduced tumor growth and partially restored thyroid function.^[19] Kim et al. (2016) reported that TERT promoter mutations were associated with aggressive tumor behavior, particularly when coexisting with BRAF mutations.^[20] Stenman et al. (2021) also described thyroid carcinoma progression with acquisition of additional alterations, including coexisting BRAF and TERT mutations.^[21]

The strength of the present study was that it evaluated BRAF V600E expression in a defined cohort of follicular cell-derived thyroid malignant neoplasms using immunohistochemistry, a practical method applicable in routine diagnostic pathology. It also correlated BRAF expression with multiple clinicopathological parameters and included NIFTP as a separate category. However, the study was limited by its small sample size, lack of uniform molecular confirmation, and absence of long-term follow-up data regarding recurrence, survival, lymph node metastasis, and treatment response. Other molecular markers such as TERT, RAS, RET/PTC, and PAX8/PPAR γ were also not evaluated.

Future studies should include larger multicentric cohorts with molecular validation and long-term follow-up. Additional molecular markers should be assessed to better understand tumor behavior and prognostic risk. Further research is also required to clarify the relationship between BRAF expression and lymphocytic thyroiditis.

Overall, the present study supported the role of BRAF V600E immunohistochemistry as a useful adjunct in the evaluation of follicular cell-derived thyroid neoplasms. Its significant association with papillary thyroid carcinoma and absence in NIFTP suggested diagnostic utility, while its association with lymphocytic thyroiditis warranted further investigation.

CONCLUSION

The present study concluded that BRAF V600E mutation was detected in 14 out of 40 cases, accounting for 35.0% of follicular cell-derived thyroid malignant neoplasms. BRAF positivity was predominantly associated with papillary thyroid carcinoma, while all NIFTP cases were negative, supporting the low-risk biological behavior of NIFTP and highlighting the diagnostic utility of BRAF immunohistochemistry in differentiating papillary thyroid carcinoma from selected follicular-patterned lesions. The observed association of BRAF positivity with background lymphocytic thyroiditis suggested a possible interaction between the inflammatory thyroid microenvironment and tumor molecular behavior. Thus, BRAF V600E immunohistochemistry may serve as a useful adjunct in the diagnostic evaluation, risk stratification, and potential therapeutic planning of thyroid malignancies. However, larger studies with molecular confirmation and long-term follow-up are required to further clarify its prognostic significance in follicular cell-derived thyroid neoplasms.

DECLARATIONS

Ethical Approval

Ethical approval was obtained from the Institutional Ethics Committee before commencement of the study.

Informed Consent

Written informed consent was obtained from all participants included in the study.

Conflict of Interest

The authors declare no conflict of interest.

Funding

No external funding was received for this study.

TABLES

Table 1. Age distribution of patients

Age category	Frequency	Percentage
Below 30 years	7	17.5%
31–50 years	22	55%
More than 50 years	11	27.5%
Total	40	100%

Table 2. Sex distribution of patients

Sex	Frequency	Percentage
Female	35	87.5%
Male	5	12.5%
Total	40	100%

Table 3. Distribution of surgical specimens

Type of specimen	Frequency	Percentage
Completion thyroidectomy	1	2.5%
Right hemithyroidectomy	4	10%
Total thyroidectomy	34	85%
Total thyroidectomy with left MRND	1	2.5%
Total	40	100%

Table 4. Distribution of BRAF mutation status

BRAF status	Frequency	Percentage
Negative	26	65%
Positive	14	35%
Total	40	100%

Table 5. Distribution of tumor types

Tumor type	Frequency	Percentage
NIFTP	9	22.5%
Thyroid tumor of uncertain malignant potential	2	5%
Follicular thyroid carcinoma	1	2.5%
Invasive encapsulated follicular variant PTC	1	2.5%
Papillary thyroid carcinoma	26	65%
Poorly differentiated thyroid carcinoma	1	2.5%
Total	40	100%

Table 6. Distribution of extrathyroidal extension

Status	Frequency	Percentage
Absent	32	80%
Present	8	20%
Total	40	100%

Table 7. Distribution of capsular invasion

Status	Frequency	Percentage
Absent	38	95%
Present	2	5%
Total	40	100%

Table 8. Distribution of vascular invasion

Status	Frequency	Percentage
Absent	39	97.5%
Present	1	2.5%
Total	40	100%

Table 9. Distribution of lymphovascular invasion

Status	Frequency	Percentage
Absent	38	95%
Present	2	5%
Total	40	100%

Table 10. Distribution of lymphocytic thyroiditis

Status	Frequency	Percentage
Absent	32	80.0%
Present	8	20.0%
Total	40	100.0%

Table 11. Descriptive statistics of immunohistochemical parameters

Variable	Mean	Standard deviation
H-score	91.00	105.67
0 staining	30.78	36.11
1+ staining	6.00	6.12
2+ staining	5.30	5.73
3+ staining	24.80	32.58

Table 12. Association of BRAF mutation status with clinicopathological variables

Variable	Finding	χ^2 value	p-value	Interpretation
Tumor type	BRAF positivity was mainly associated with PTC; NIFTP was BRAF-negative	20.081	<0.001	Significant
Capsular invasion	Seen only in BRAF-positive cases	3.509	0.061	Borderline
Vascular invasion	Seen only in one BRAF-positive case	1.709	0.191	Not significant
Lymphovascular invasion	Seen in both BRAF-positive and BRAF-negative groups	0.140	0.708	Not significant
Lymphocytic thyroiditis	More common in BRAF-positive cases	6.000	0.014	Significant
BRAF expression with/without lymphocytic thyroiditis	Higher expression with lymphocytic thyroiditis	4.821	0.049	Significant

FIGURES

Figure 1: Papillary thyroid carcinoma – classic subtype (H&E 40X)

Figure 2: Papillary thyroid carcinoma – classic subtype (H&E 100X)

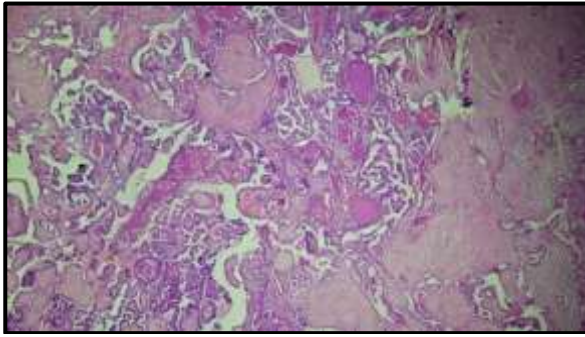


Figure 3: Papillary thyroid carcinoma – Nuclear features (H&E 400X)

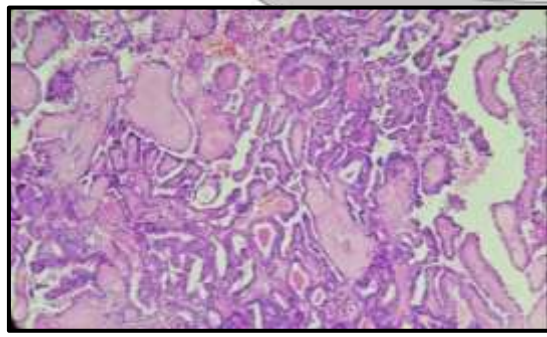


Figure 4: Papillary thyroid carcinoma – Oncocytic Variant (H&E 100X)

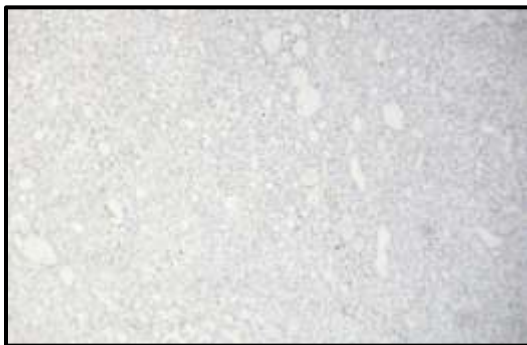
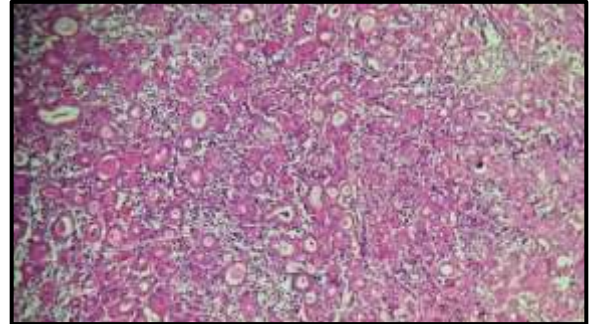
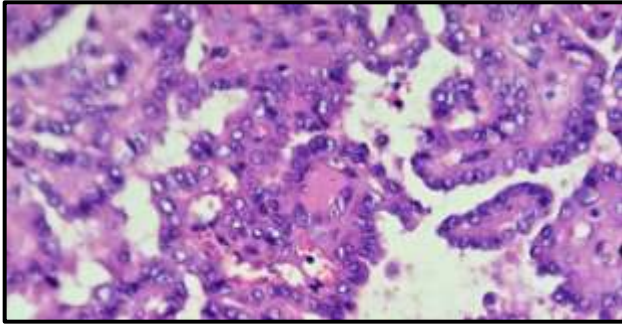


Figure 5: IHC For BRAF mutation (40X)- NIFTP - Negative for BRAF mutation

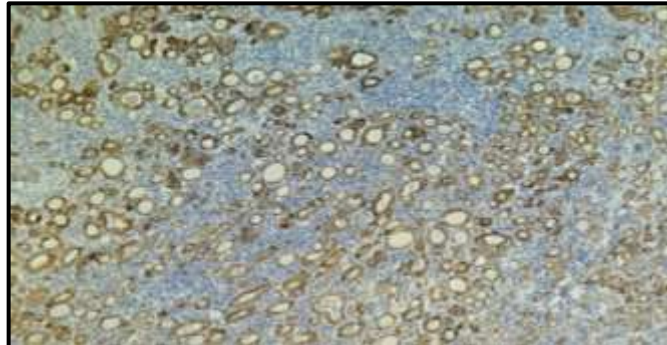


Figure 6: IHC For BRAF mutation in Oncocytic variant of Papillary thyroid carcinoma-Strongly positive in the background of lymphocytic thyroiditis (100X)

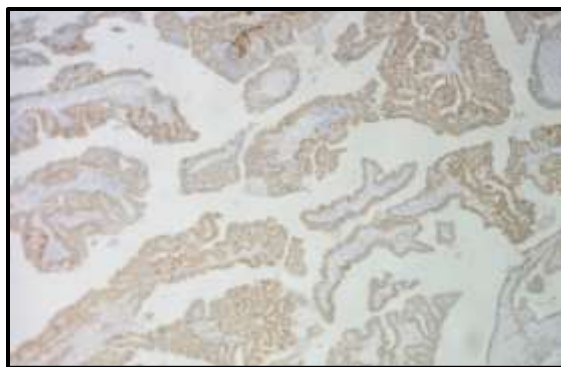


Figure 7: IHC For BRAF mutation (100X)- PTC - Moderately positive for BRAF mutation

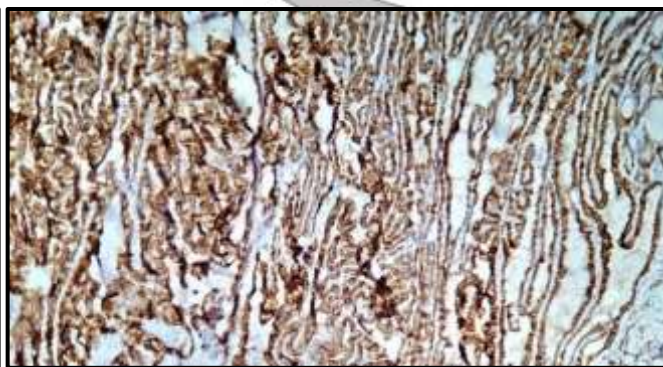


Figure 8: IHC For BRAF mutation (100X)- PTC – Strongly positive for BRAF mutation

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