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Original research article

Study of immunohistochemical markers HBME-1, CD56 and CK19 aiding in the differentiation of thyroid nodules in tertiary care hospital

[1]Dr. R.P. Sushma Kumari, [2]Dr. Zaheda Kauser, [3]Dr. Vandhana, [4]Dr. Mohmed Chand Moula, [5]Dr. N Srivani

[1]Post-Graduate, Department of Pathology, Osmania Medical College Hyderabad, Telangana, India
[2,4]Associate Professor, Department of Pathology, Osmania Medical College Hyderabad, Telangana, India
[3]Assistant Professor, Department of Pathology, Osmania Medical College Hyderabad, Telangana, India
[5]Professor & HOD, Department of Pathology, Osmania Medical College, Hyderabad, Telangana, India

Corresponding Author:
Dr. Mohmed Chand Moula

Abstract

Background and Objectives: The frequency of thyroid nodules is high and rises significantly with age. The purpose of this study is to examine the utility of the immunohistochemical markers HBME-1, CD56, and CK19 in distinguishing hyperplastic, benign, and malignant thyroid lesions.

Material and Methods: Research was conducted both proactively and retrospectively. From October 2020-September 2022, a total of two years' worth of cases were accumulated. Location: Afzalgunj, Hyderabad; Osmania General Hospital. Fifty patients who presented with thyroid nodular swellings were surgically removed and referred to the histopathology section for analysis. Age, sex, and clinical differential diagnosis were all considered as well as other clinical information.

Results: The present study is a cross sectional study carried over a period of 24 months (October 2020 to September 2022) in the upgraded department of pathology, Osmania General Hospital, Afzalgunj, Hyderabad. Age range was 20-60 years with mean age being 36.44 years. Female preponderance was noted with a male to female ratio of 1:11.5. Majority of cases were seen in 3rd and 4th decades. Routine H&E along with immunostaining with HBME-1, CK 19 and CD 56 was performed. Out of 50 cases, 38 were benign lesions 12 were malignant lesions. HBME-1 and CK 19 expression was decreased in benign lesions and showed high expression in malignant lesions. Whereas CD56 expression was high in benign lesions and decreased in malignant lesions.

Positive staining with HBME-1 was noted in 2.63% of benign lesions which (focal and weak) and 100 % of malignant lesions, with 100% sensitivity and 97.4% specificity in differentiating malignant from benign lesions. Positive staining with CK 19 was noted in 10.52% of benign lesions and 91.6% of malignant lesions, with 91.7% sensitivity and 89.5% specificity in differentiating malignant from benign lesions. Positive staining with CD56 was in 100% of benign lesions and 25% of malignant lesions, with 75% sensitivity and 100% specificity in differentiating malignant from benign lesions. Expression of HBME-1, CK 19 and CD56 showed a statistically significant correlation with many studies.

Conclusion: Therefore, IHC markers that can aid in better assessment of morphologic features should be incorporated into the diagnostic strategy for these cancers. HBME1 AND CK 19 are helpful antibodies for the differential diagnostic markers to identify malignant lesion and also increase the diagnostic accuracy when used with CD56.

Keywords: HBME-1, CD56, CK19, thyroid nodules, immunohistochemical markers

Introduction

Thyroid nodules are a very common finding, and their prevalence steadily increases with age. Nodular thyroid disease refers to the presence of a solid nodule, multi- nodular gland or one or more cystic lesions [1]. During a radiologic procedure such as Ultrasonography (US) Imaging, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the neck, thyroid nodules are being diagnosed incidentally with increasing frequency in the recent years. Their clinical significance is mainly related to excluding malignancy [2, 3]. In the diagnosis of thyroid nodules and tumours, the gold standard is the histological evaluation using routine Haematoxylin and Eosin-stained tissue sections. Papillary thyroid Carcinoma is the most common form of malignant thyroid neoplasm. Its diagnosis is based on the presence of papillary processes and nuclear features such as nuclear clearing, overlapping, grooves and pseudo-inclusions [4, 5]. Diagnostic dilemma may arise especially in, Lesions having a follicular growth pattern. e.g., Distinguishing follicular adenoma from encapsulated follicular variant of papillary carcinoma becomes difficult when an encapsulated nodule with a follicular pattern exhibits only few of the typical nuclear

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features of papillary thyroid carcinoma. Benign papillary hyperplasia and hyperplastic nodules in nodular goitre may show nuclear clearing and may be confused with papillary thyroid carcinoma. Severe chronic lymphocytic thyroiditis, Hashimoto thyroiditis and reactive atypia attributed to inflammation result in nuclear morphology similar to that of papillary carcinoma, with nuclear enlargement, chromatin clearing and even grooves [6, 7].

All of these diagnostic dilemmas have important consequences for the management and prognosis of these patients. In such cases, which have morphological overlap, Immunohistochemistry (IHC) is needed for differential diagnosis [8-10].

Aim of the study was, to test the applicability of IHC markers HBME-1, CD56 and CK19 in differentiating the thyroid nodules. Objectives of the study was, to identify cases with nodular thyroid pathologies. To predict and confirm the diagnosis of thyroid hyperplasia, benign thyroid neoplasm and thyroid carcinoma. To study the expression of HBME-1, CD56 & CK19 in paraffin embedded blocks obtained from thyroidectomy specimens. To evaluate the pattern of expression of these IHC markers in different thyroid pathologies.

Material and Methods

Both prospective and retrospective study was done. Total cases were amassed over a period of two years, from October 2020 to September 2022. Osmania General Hospital, Afzalgunj, Hyderabad. A total of 50 thyroidectomy tissue specimens sent to histopathology section which were surgically excised from patients presented with thyroid nodular swellings were studied. Clinical details like age, gender and clinical differential diagnosis were taken into consideration.

Inclusion criteria

- All cases presented with solitary thyroid nodule and multinodular goitre were included.
- Adequate tumor tissue.

Exclusion criteria

- Cases presented with diffuse thyroid swelling.

Method

The specimens were fixed in 10% neutral buffered formalin. They were examined grossly and sections were taken from representative sites. These sections were then processed in automated tissue processor and embedded in paraffin wax. 4-5-micron thickness sections were prepared from the corresponding paraffin blocks, one on albumin coated slide for Haematoxylin and Eosin (H&E) staining and the others on Poly-L-lysine coated slide for immune-histochemical staining (HBME-1, CD56, CK19).

Results

The immune-stained slides are examined for, membranous staining with or without cytoplasmic staining in case of HBME-1 and CD56, cytoplasmic and /or membranous staining in case of CK 19. Scoring method used was Immunoreactive score (IRS), a semiquantitative method. Immunoreactive score gives a range of 0-12 as a product of multiplication between positive cells proportion score and staining intensity score.

Table 1: IRS positive cell proportion score

Sr. No.	Percentage of cells stained	Score
1.	0	0
2.	1-10%	1+
3.	10-50%	2+
4.	50-80%	3+
5.	>80%	4+

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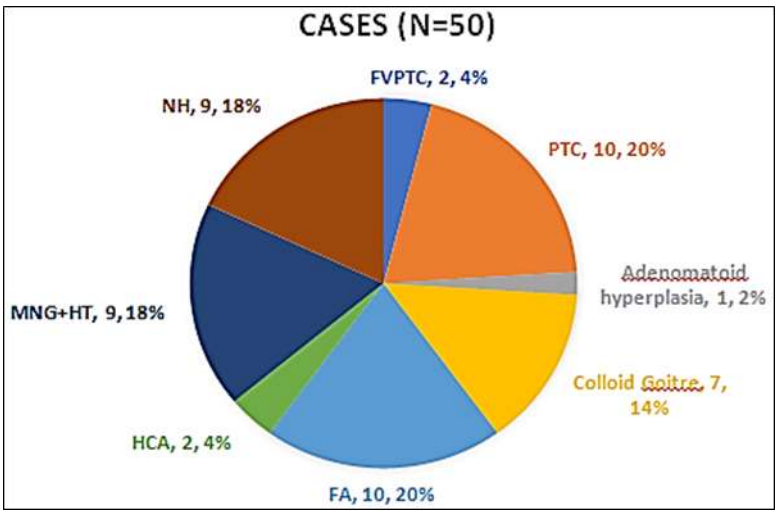

Fig 1: Number of various thyroid lesions in the present study

Table 2: Age distribution in benign and malignant lesions

Age Category	PTC	FVPTC	FA	NH	MNG+HT	Colloid Goitre	HCA	AH	Total
<=20 y			1						1
21 to 30 y	4	1	5	5	2	2			19
31 to 40 y	5	1	1	4	2	1	1		15
41 to 50 y	1		2		3	1	1	1	9
51 to 60 y			1		2	3			6
Total	10		10	9	9	7	2	1	50

In the present study, the youngest patient was 20 years old (female) and the oldest patient was 60 years old (female). The highest incidence of thyroid lesions was observed in the 3rd and 4th decades of life. The age distribution ranged from 20-60 years.

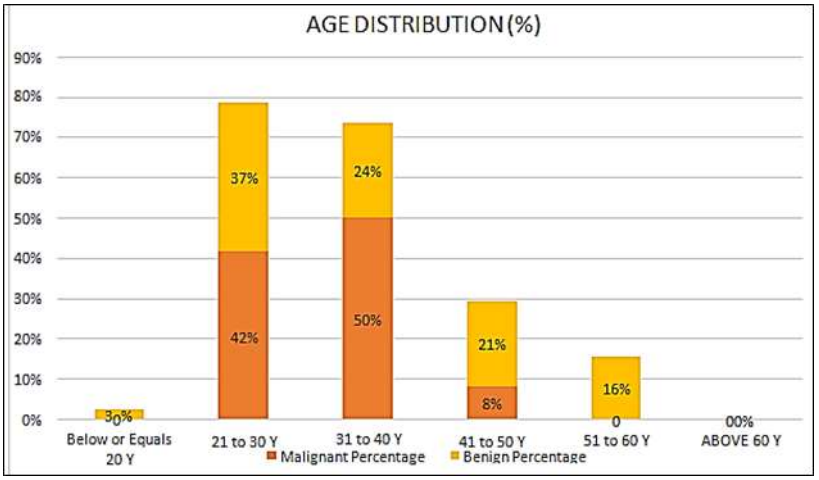

Fig 2: Age Distribution

Table 3: Sex distribution

Thyroid Category	Female (46) 92%		Male (4) 8%	
Follicular variant of PTC	1	2%	1	2%
Conventional PTC	9	18%	1	2%
Adenomatoid hyperplasia	1	2%	0	0%
Colloid Goitre	7	14%	0	0%
Follicular adenoma	8	16%	2	4%
Hurthle cell adenoma	2	4%	0	0%
MNG+ Hashimoto thyroiditis	9	18%	0	0%
Nodular hyperplasia	9	18%	0	0%

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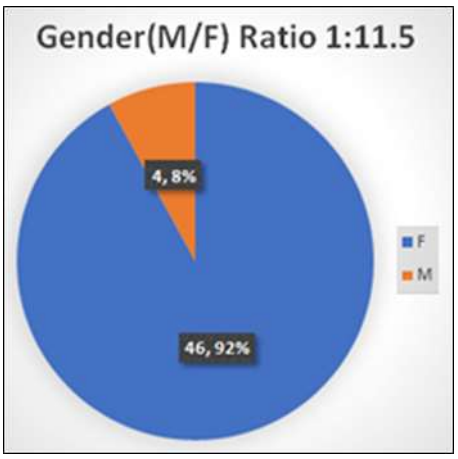

Fig 3: Showing male to female ratio in the present study

Out of total 50 cases, 4 (8%) were males and 46 (92%) were females. The male to female sex ratio (M: F) was 1:11.5. The incidence of thyroid lesions was higher in females.

Table 4: CK19 expression in PTC (Conventional) and FVPTC

	Total (n)	Positive	Weak	Moderate	Strong	Negative
cPTC	10	9 (90%)	-	3	6	1 (10%)
FVPTC	2	2 100%)	-	-	2	-

In the present study, cPTC cases showed 90% positivity for CK 19 and FVPTC cases showed 100% positivity, with an overall 91.6% positivity.

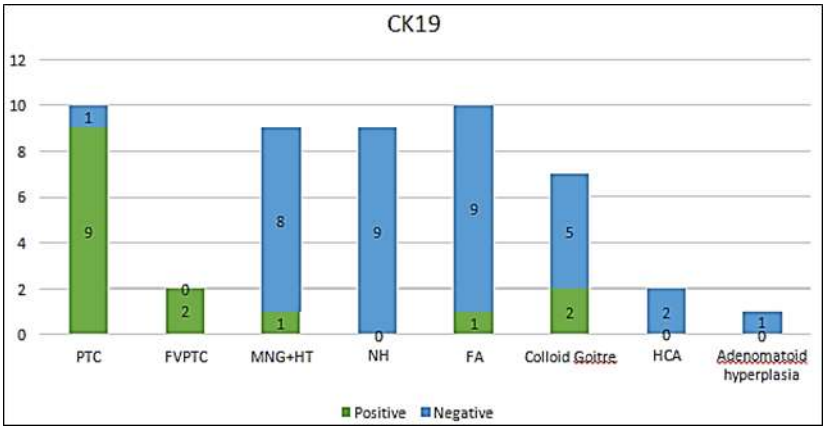

Fig 4: Showing CK 19 expression

CK 19 expression is high in malignant lesions (PTC, FVPTC) and decreased or absent in benign thyroid lesions.

Table 5: Diagnostic value of cd 56 in differentiating malignant from benign lesions

Sr. No.	Parameter	Value
1.	Sensitivity	75%
2.	Specificity	100%
3.	Positive Predictive Value	100%
4.	Negative Predictive Value	92.7%
5.	P value	0.0001 (Significant association)

In the present study, HBME-1 is found to be most sensitive and specific marker in differentiating benign from malignant thyroid lesions (PTC & FVPTC). Next is CK 19 with 91.7% sensitivity and 89.5% specificity. Sensitivity of CD56 found to be low and specificity of 100%.

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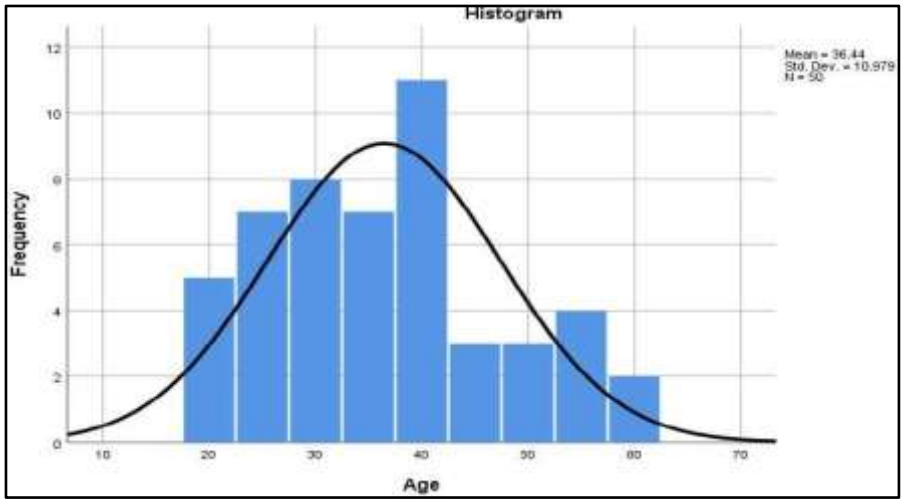

Fig 5: Histogram showing age distribution

The incidence of thyroid lesions in this study is highest in the age range of 31-40 years, with Mean age of 36.44 years.

Microscopy evaluation by histopathological study

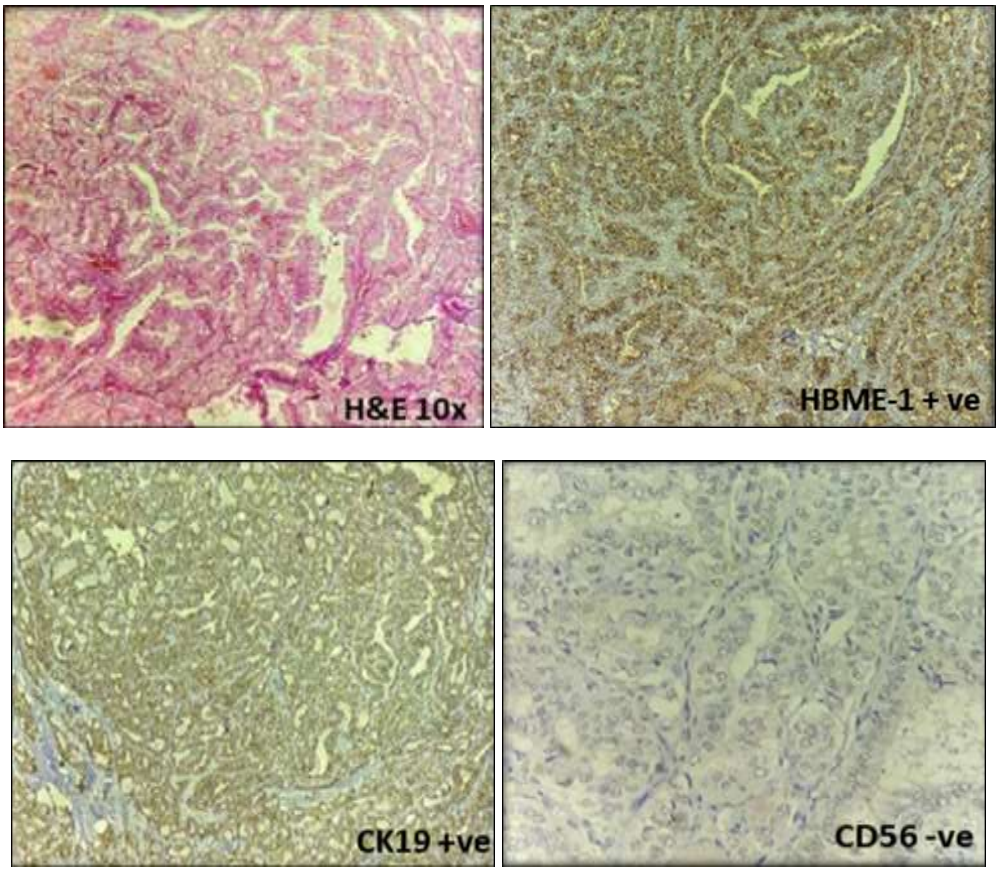

Fig 6: (A-D)

A) Upper Left (10x): A case of Conventional Papillary thyroid carcinoma on H&E.
B) Upper Right (10x): Strong and diffuse membranous expression of HBME-1.
C) Lower Left (10x): Strong and diffuse membranous expression of CK 19.
D) Lower Right (40x): Absent CD56 expression.

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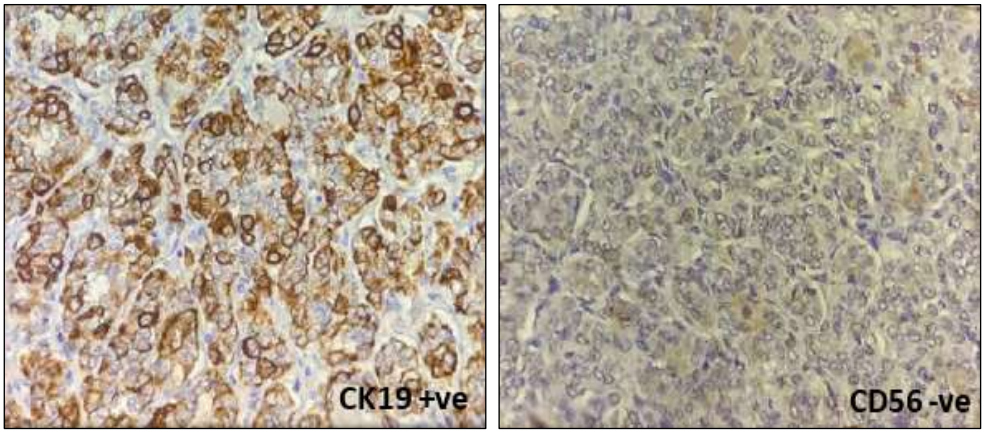

Fig 7: (A-D)

A) Upper Right (40x): A case of Follicular variant of papillary thyroid carcinoma on H&E.
B) Upper Left (40x): Strong membranous expression of HBME-1.
C) Lower Right (40x): Diffuse and strong expression of CK 19.
D) Lower Left (40x): Absent CD56 expression.

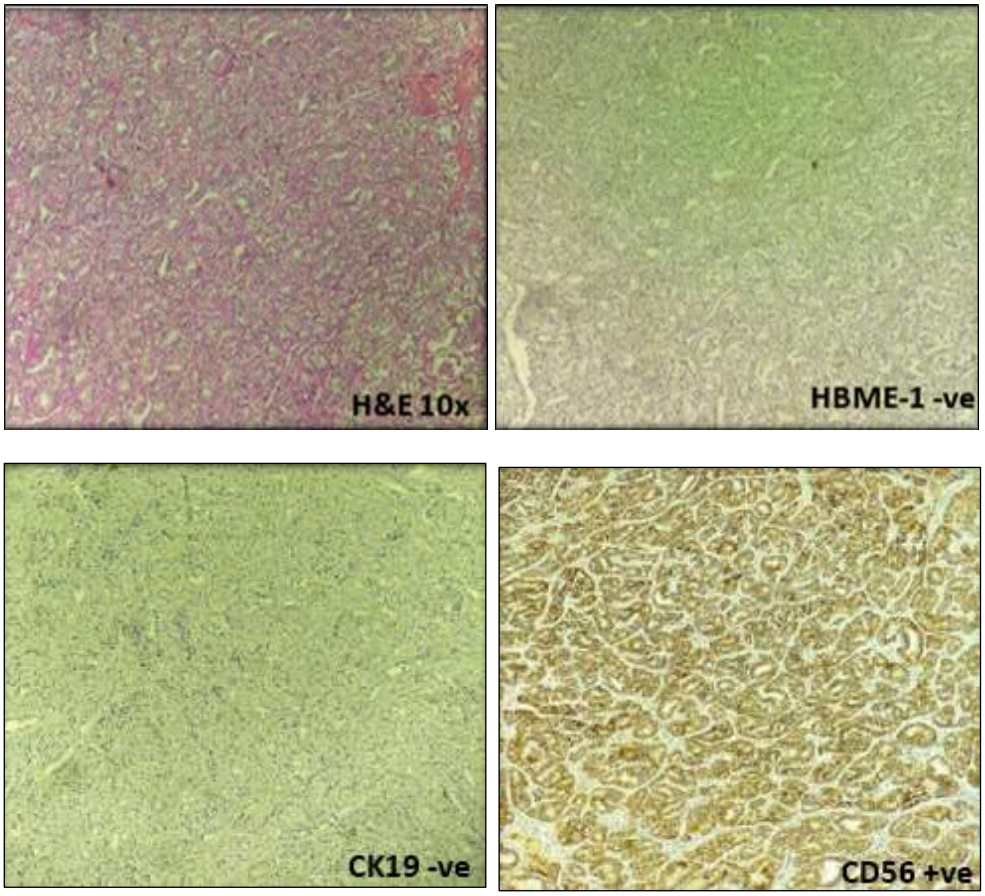

Fig 8: (A-D)

A) Upper Right (10x): A case of Follicular adenoma on H & E.
B) Upper Left (10x): Absent HBME-1 expressions.
C) Lower Right (10x): Absent CK 19 expressions.
D) Lower Left (10x): Diffuse and strong membranous expression of CD56.

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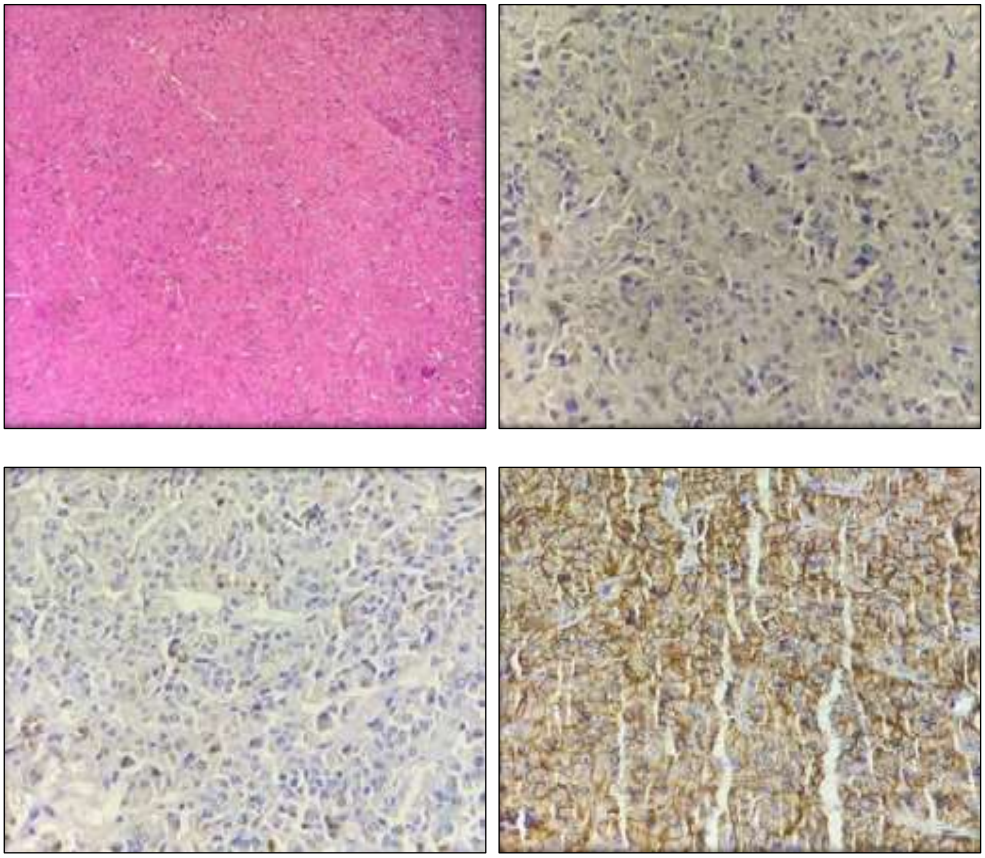

Fig 9: (A-D)

A) Upper Left (10x): A case of Hurthle cell adenoma on H&E.
B) Upper Right (40x): Absent HBME-1 expression.
C) Lower left (40x): Absent CK 19 expressions.
D) Lower Right (40x): Diffuse and strong membranous CD56 expression.

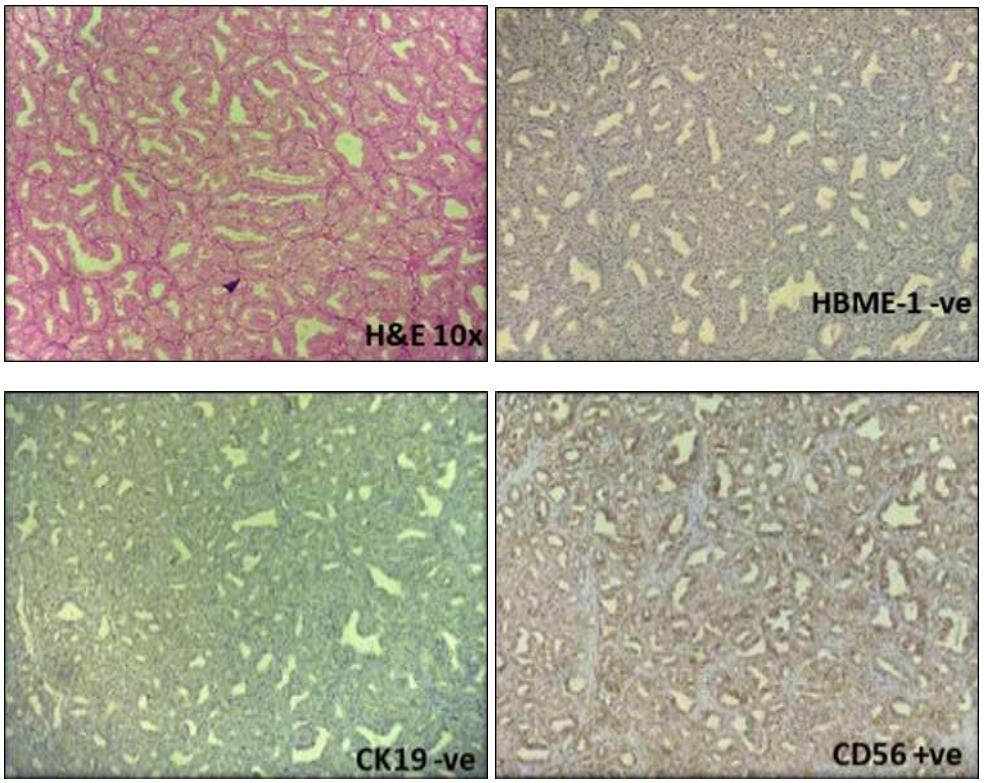

Fig 10: (A-D)

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A) Upper Left (10x): A case of Nodular hyperplasia on H&E.
B) Upper Right (10x): Absent HBME-1 expression.
C) Lower Left (10x): Absent CK 19 expressions.
D) Lower Right (10x): Diffuse and strong membranous CD56 expression.

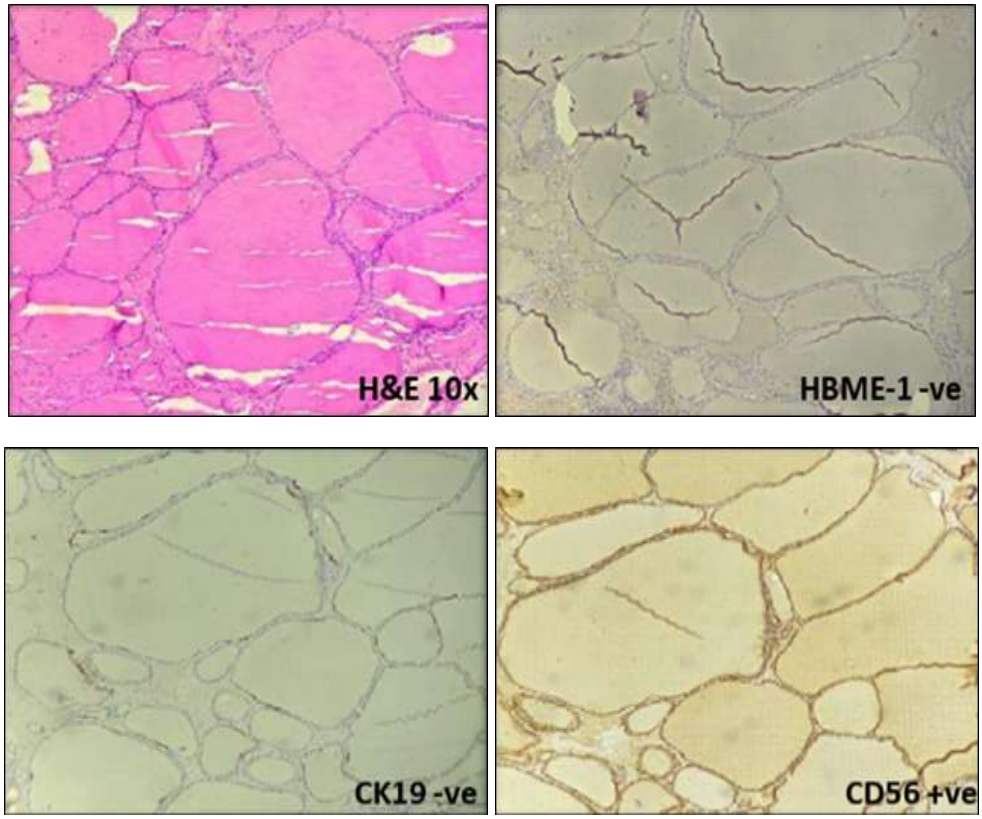
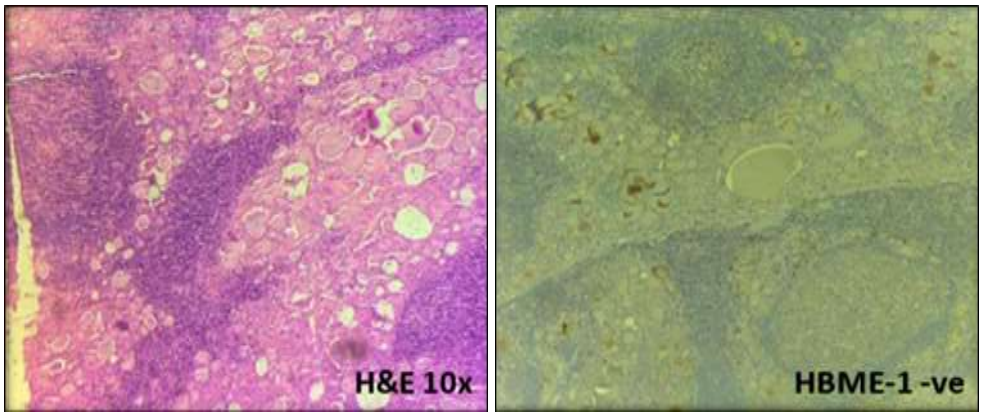


Fig 11: (A-D)

A) Upper Left (10x): A case of Colloid goitre on H&E.
B) Upper Right (10x): Absent HBME-1 expression.
C) Lower Left (10x): Absent CK 19 expressions.
D) Lower Right (10x): Diffuse and strong membranous CD56 expression.



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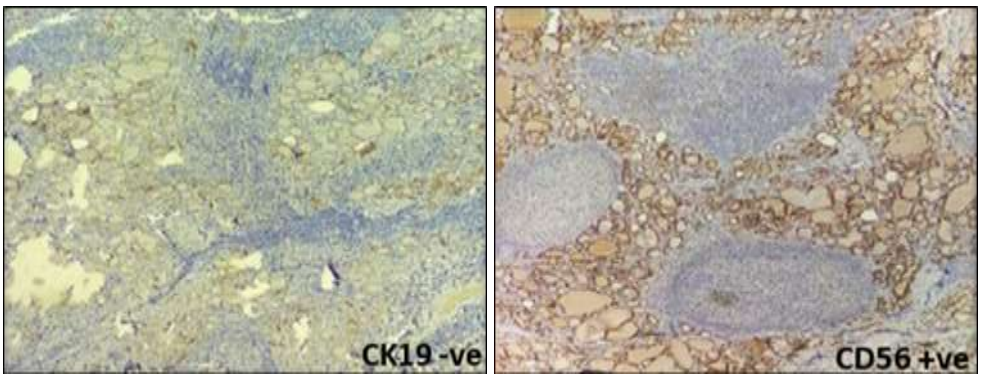

Fig 12: (A-D)

a) **Upper Left (10x):** A case of Hashimoto thyroiditis on H&E.
b) **Upper Right (10x):** Absent HBME-1 expression.
c) **Lower Left (10x):** Absent CK 19 expressions.
d) **Lower Right (10x):** Diffuse and strong membranous CD56 expression.

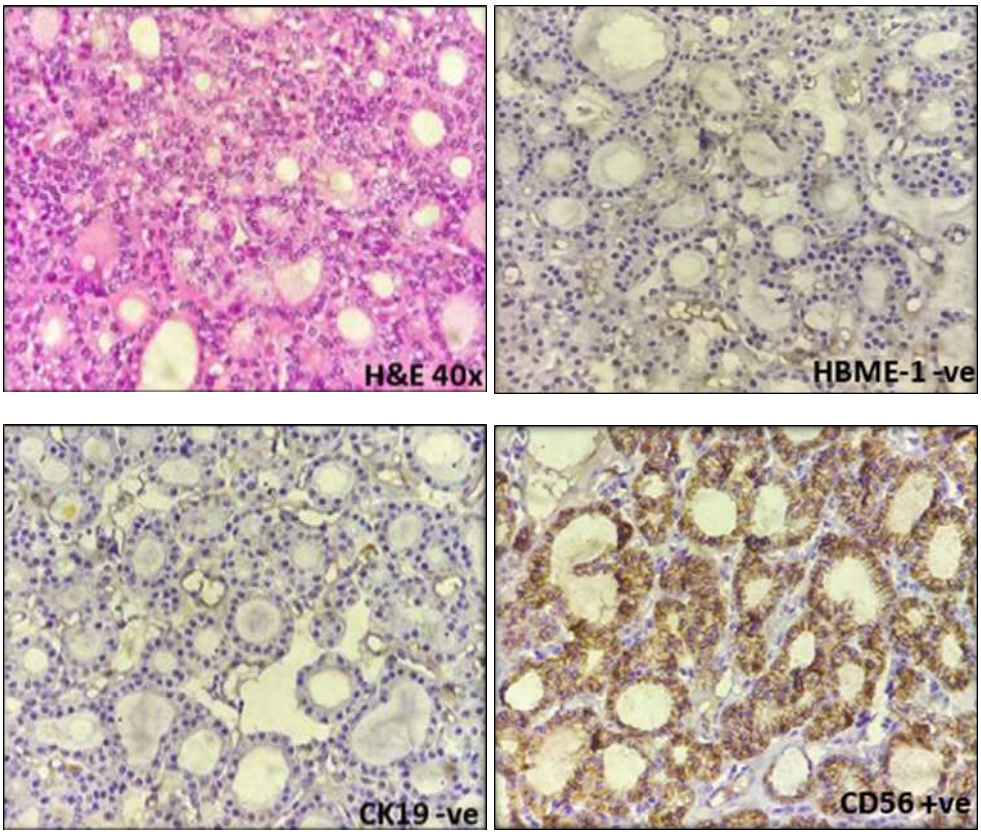

Fig 13: A-D

a) **Upper left (40x):** A case of Adenomatoid hyperplasia with nuclear clearing H&E.
b) **Lower right (40x):** Absent HBME-1 expression.
c) **Lower left (40x):** Absent CK 19 expression.
d) **Upper Right (40x):** CD56 showing strong & diffuse positivity.

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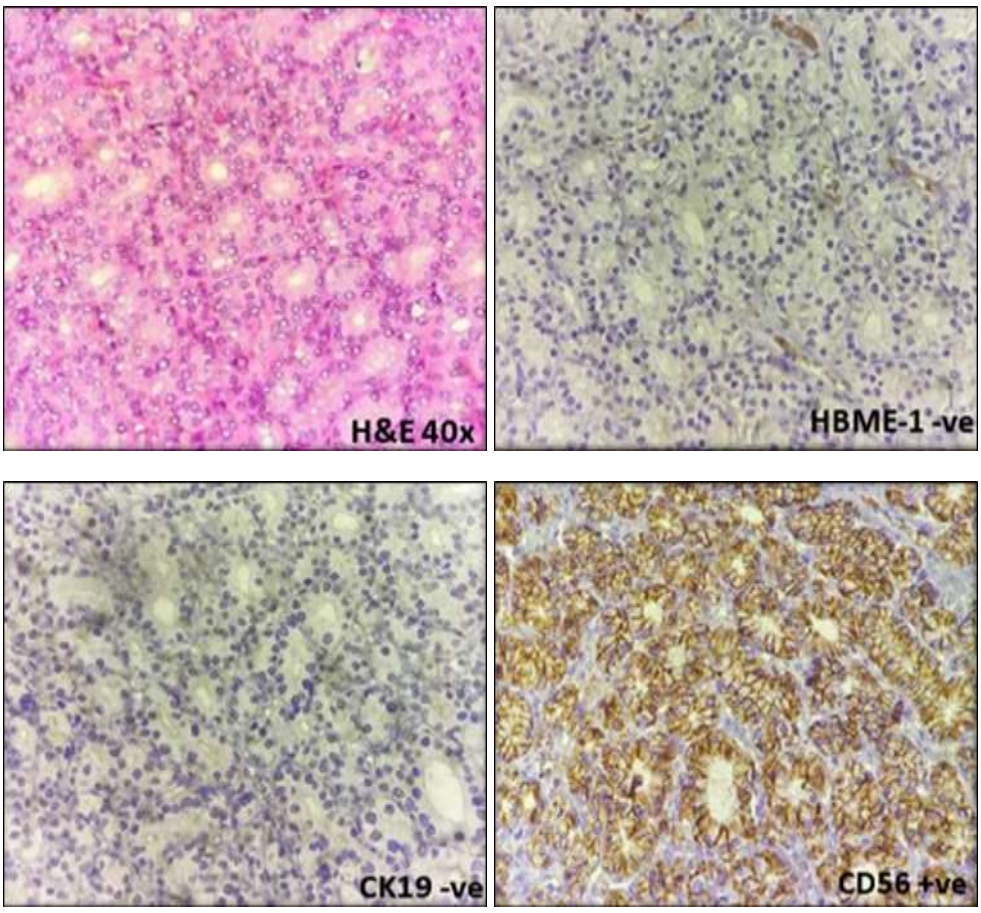

Fig 14: (A-D)

a) **Upper left (40x):** A case of encapsulated follicular neoplasm with PTC like nuclear features on H&E.
b) **Upper right (40x):** Loss of HBME-1 staining.
c) **Lower left (40x):** Loss of CK 19 staining.
d) **Lower right (40x):** CD 56 showing diffuse strong positivity.

Table 6: Diagnostic Value of each marker HBME-1, CK 19 and CD 56 in differentiating malignant from Benign Lesions

IHC Markers	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	P Value
HBME-1	100%	97.4%	92.3%	100%	0.0001 (Significant association)
CK19	91.7%	89.5%	73.3%	97.1%	0.0001 (Significant association)
CD 56	75%	100%	100%	92.7%	0.0001 (Significant association)

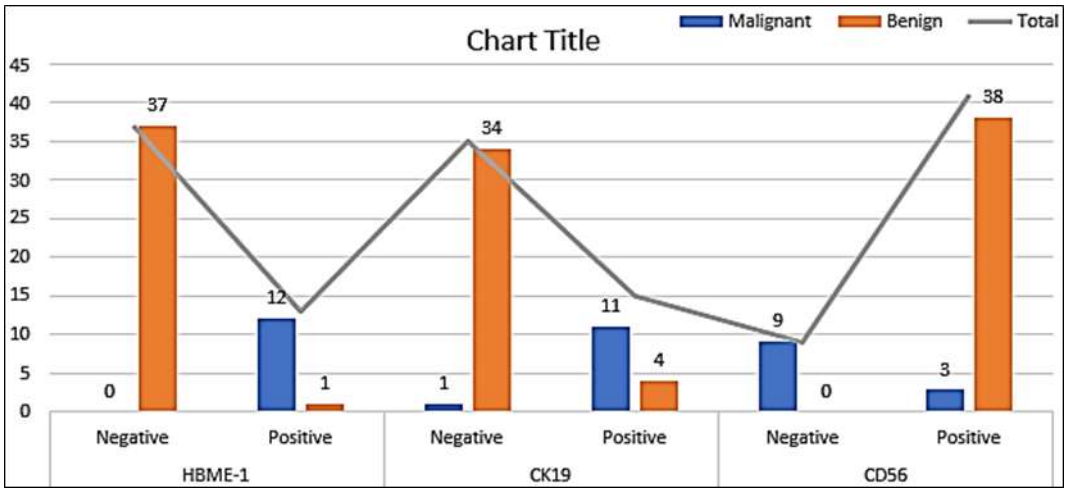

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Fig 15: Showing immunoexpression of hbme-1, ck 19 and cd56 in benign and malignant thyroid lesions

Discussion

Thyroid nodules are quite prevalent, and are often discovered as incidental findings on a physical examination, or through radiographic studies. The prevalence of thyroid nodules increases with age, and population surveys suggest nearly 5%-15% of the adult population may harbour a clinically significant nodule requiring evaluation. Palpable thyroid nodules are found in approximately 5% of women and 1% of men living in iodine-sufficient parts of the world. High-resolution ultrasound can detect thyroid nodules in 19%-67% of randomly selected individuals, with higher frequencies in women and the elderly [34]. In contrast, the prevalence of thyroid nodular lesions from autopsy studies in clinically normal thyroid glands is approximately 50%-60% [11-13].

The clinical importance of thyroid nodules rests with the need to exclude ones that may harbour malignancy. Numerous studies have documented that the risk of malignancy in patients with thyroid nodules is 5%-17%, whether detected by palpation or ultrasonography. Usually, the size of the thyroid nodule does not predict the likelihood of thyroid cancer. The cancer rates for patients with solitary nodules versus those with multiple nodules are virtually identical [14-16].

The majority of thyroid nodules are benign and represent hyperplastic multinodular goitre, colloid nodules, Hashimoto's thyroiditis, simple or haemorrhagic cysts, or follicular adenomas, all of which need to be differentiated from thyroid cancer. Malignancies of the thyroid gland include papillary, follicular, Hurthle cell, medullary, and anaplastic carcinomas, as well as primary thyroid lymphomas and extra-thyroid metastases to the thyroid gland. Several clinical features must be considered during thyroid nodule evaluation, including age, sex, status of thyroid function, family history, history of radiation exposure and pre-existing thyroid disorders [17-19].

Patients under the age of 20 or over 70 years with thyroid nodules have an increased risk of malignancy, as do men. A history of persistent hoarseness, dysphagia, or dyspnoea also increases the risk, although these symptoms may also occur with benign nodules. A rapid painless growth of a solid nodule is concerning. On physical examination, thyroid nodules may be smooth or nodular, diffuse or localized, soft or hard, mobile or fixed, and painful or nontender. While palpation is the clinically relevant method of examining the thyroid gland, it can be insensitive and inaccurate, depending on the skill of the examiner. Nonetheless, a nodule that is firm, fixed to the adjacent structures in the neck, and associated with cervical lymphadenopathy or paralysis of the vocal folds should be considered highly suspicious for thyroid cancer [20-22].

Ultrasound is often the first imaging modality employed to evaluate a patient with a thyroid nodule since it is readily accessible, inexpensive and non-invasive. Ultrasound is effective at delineating intrathyroidal architecture, distinguishing cystic from solid lesions, determining if a nodule is solitary or part of a multinodular gland, and accurately locating and measuring a nodule. In addition, ultrasound is extremely useful in patients who are managed conservatively for follow-up of possible increased volume of a suspicious lesion [23-26].

FNA biopsy of thyroid nodules can be used to categorize tissue into the following diagnostic categories: Nondiagnostic, Benign, Follicular lesion of undetermined significance (atypia of undetermined significance), Follicular or Hurthle cell neoplasm (or suspicious for follicular or Hurthle cell neoplasm), Suspicious for malignancy and Malignant [28-31].

In the diagnosis of thyroid nodules and tumours, the gold standard is the histological evaluation using routine Haematoxylin and Eosin-stained tissue sections. Papillary thyroid Carcinoma is the most common form of malignant thyroid neoplasm. Its diagnosis is based on the presence of papillary processes and nuclear features such as nuclear clearing, overlapping, grooves and pseudo-inclusions [32-33].

All of these diagnostic dilemmas have important consequences for the management and prognosis of these patients. In such cases, which have morphological overlap, Immunohistochemistry (IHC) is needed for differential diagnosis. Many immunohistochemical markers have been studied with respect to their expression in thyroid lesions. Some markers are promising like CD56, Hector Battifora Mesothelial cell-1 (HBME-1), Galectin 3 and Cytokeratin 19 (CK 19) considering differential diagnosis, nevertheless, none of them is individually conclusive. The present study is based on application of panel of immunohistochemistry markers HBME-1, CD 56 and CK19 in differentiating benign and malignant thyroid nodules especially papillary thyroid carcinoma [34, 35].

In the present study, in case of benign lesions CK 19 immunostaining is mild positive with IRS of 2 and 3 in 4 out of 38 cases (10.52%) i.e., in 1/9 Hashimoto thyroiditis, 1/10 follicular adenoma, 2/7 colloid goitre. In other similar studies done by Singh V. *et al*., Seetu PALO *et al*., & Siderova *et al*., CK 19 immunostaining benign lesions was positive in 16.6% cases, 25% cases & 10% cases respectively. Therefore CK 19 expression is low or decreased in benign thyroid lesions which is correlating well with other similar studies [34-36].

Conclusion

Present study focuses mainly on utility of HBME-1, CK 19 and CD56 expression in differentiating

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malignant thyroid lesions from benign lesions. Many cases especially benign lesions like benign papillary hyperplasia and hyperplastic nodules showing nuclear clearing and also reactive atypia resulting in nuclear morphology similar to that of Papillary thyroid carcinoma (PTC) create difficulties in diagnosis by histopathology. The decision favouring benign or malignant lesion has clinical consequence and implies different modalities of further treatment and management. In this regard the diagnostic approach to these tumors should include IHC markers that can aid in better assessment of morphologic details. HBME1 AND CK 19are helpful antibodies for the differential diagnostic markers to identify malignant lesion and also increase the diagnostic accuracy when used with CD56.

Funding: None.

Conflict of Interest: None.

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