Med & Health Jun 2020; 15(1): 187-197 https://doi.org/10.17576/MH.2020.1501.17

ORIGINAL ARTICLE

HBME-1 Expression in Differentiating Benign and Malignant Thyroid Lesions

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ABSTRAK

Karsinoma tiroid biasanya didiagnoskan berdasarkan kriteria morfologi tertentu. Dalam sesetengah kes, diagnosis yang tepat mungkin sukar apabila ciri-ciri morfologi adalah tidak ketara. Kajian ini menilai kegunaan Hector Battifora Mesothelial-1 (HBME-1) sebagai penanda immunohistokimia untuk membezakan tisu tiroid barah dengan bukan barah dan untuk membandingkan ekspresi HBME-1 dalam pelbagai jenis tisu tiroid. Sensitiviti dan spesifisiti HBME-1 sebagai penanda khusus untuk karsinoma tiroid juga dikaji. Sejumlah 54 kes barah dan 54 kes bukan barah tiroid yang didiagnos di Pusat Perubatan Universiti Kebangsaan Malaysia untuk tempoh tujuh tahun telah dikumpul. Semua kes diwarnai dengan HBME-1 dan dinilai oleh tiga pemerhati bebas. Kes-kes tersebut diberi skor berdasarkan nisbah pewarnaan dan dinilai sebagai skor 0 (kurang daripada 10%), 1+ (10-25%), 2+ (26-50%) atau 3+ (lebih daripada 50%). Di samping itu, perkaitan antara skor bagi kes barah dengan peringkat patologi tumor juga dikaji. HBME-1 menunjukkan ungkapan pewarnaan yang lebih signifikan dalam kes barah berbanding bukan barah (P<0.001) dengan karsinoma tiroid papilari menunjukkan ungkapan tertinggi di kalangan kes karsinoma (87.1%). Kes bukan barah kebanyakannya adalah negatif (96%), kecuali dua kes adenoma folikular yang menunjukkan skor 1+. HBME-1 mempunyai sensitiviti sebanyak 57% dan spesifisiti setinggi 96% bagi karsinoma tiroid. Tiada perkaitan antara ekspresi HBME-1 dengan peringkat patologi tumor berdasarkan klasifikasi TNM (pT). Kesimpulannya, HBME-1 berkemungkinan boleh menjadi penanda yang berguna dalam membezakan kes tiroid barah daripada bukan barah, terutamanya dalam kes-kes karsinoma tiroid papilari.

Kata kunci: adenoma folikular, antigen HBME-1, karsinoma tiroid papilari, tiroid

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ABSTRACT

Thyroid carcinomas are classically diagnosed based on specific morphological criteria. In some cases, a definitive diagnosis may be difficult when morphological features are equivocal. This study evaluated the utility of Hector Battifora Mesothelial-1 (HBME-1) as an immunohistochemical marker to differentiate malignant from benign thyroid lesions and to compare its expression in different types of thyroid lesions. The sensitivity and specificity of HBME-1 as a specific marker for thyroid carcinoma were also studied. A total of 54 malignant and 54 benign thyroid cases diagnosed were collected in Universiti Kebangsaan Malaysia Medical Centre for a period of seven years. All cases were stained with HBME-1 and evaluated by three independent observers. The cases were scored based on the proportion of staining and graded as 0 (less than 10%), 1+ (10-25%), 2+ (26-50%) or 3+ (more than 50%). In addition, the score of malignant cases was correlated with their pathological tumour stage. HBME-1 showed significantly higher expression in malignant compared to benign lesions (P<0.001) with papillary thyroid carcinoma (PTC) showed the highest expression among the carcinoma cases (87.1%). Benign lesions were mostly negative (96%), except for two follicular adenoma cases having focal positivity. HBME-1 had a sensitivity of 57% and specificity of 96% in thyroid carcinoma. There was no correlation between HBME-1 expression and TNM primary tumour stage (pT). HBME-1 might be a useful marker in distinguishing malignant from benign thyroid lesions, especially in PTC cases.

Keywords: follicular adenoma, HBME-1 antigen, papillary thyroid carcinoma, thyroid

INTRODUCTION

Thyroid follicular lesions denote the presence of either benign or malignant solid nodules, multinodular goitre, Graves' disease or thyroiditis (Alshenawy 2014). Most of the thyroid lesions are benign. Nonetheless, cancer of the thyroid is the commonest malignancy of the endocrine system. There is a drastic increase in the worldwide incidence of thyroid cancer from 298,000 new reported cases in 2012 to 567,233 cases in 2018 (Bray et al. 2018; Ferlay et al. 2015). Globally, it was ranked ninth place for incidence, and the incidence rate among females is three times higher than males (Bray et al. 2018). In Malaysia, thyroid cancer was ranked seventeenth among males and ninth among females (Azizah et al. 2016). Solitary thyroid nodule was the chief mode of presentation of thyroid cancer followed by a generalised thyroid enlargement, either multinodular or diffused (Abdullah 2002; Sherma 2003).

Thyroid cancers constitute a few different histologic subgroups based on specific morphological features. The commonest subgroups are follicular carcinoma (FC), papillary

thyroid carcinoma (PTC), medullary carcinoma (MC), poorly-differentiated carcinoma and anaplastic carcinoma. A recent study from USA Surveillance, Epidemiology and End Results database carried out on 59,892 thyroid cancer patients showed that PTC was the commonest type of thyroid carcinoma (92.2%). The next commonest is FC (5.8%), followed by MC (1.9%) and anaplastic carcinoma (0.7%) (Shi et al. 2018). PTC is further divided into variants, which include classic, follicular, tall cell, clear cell and other variants. The classic variant of PTC is the most common, followed by follicular variant (Nosé 2018). Follicular variant PTC can be difficult to distinguish with other thyroid lesions with a follicular pattern, such as follicular adenoma and FC due to overlapping histomorphology (Erdogan-Durmus et al. 2016; Zargari & Mokhtari 2019).

Thyroid nodules are generally diagnosed by histopathology evaluation using haematoxylin and eosin (H&E) stained sections. In most cases, the diagnoses are quite straightforward. Sometimes, the pathologists may encounter lesions that exhibit equivocal features, making it difficult to distinguish between benign and malignant lesions (Haiyan & Fan 2015). For instance, even though the diagnostic criteria for PTC and FC are clearly outlined in the World Health Organisation (WHO) Classifications and other textbooks, the discrepancies in the diagnosis of thyroid follicular lesions are very well documented, even among experienced pathologists (Franc et al. 2003; Lloyd et al. 2004). The diagnostic dilemma in distinguishing follicular variant PTC with FC or follicular adenoma may arise due to the presence of focal nuclear features of PTC, or interpretation of capsular or vascular invasion (Zargari & Mokhtari 2019).

Thus, the efforts to identify biomarkers in differentiating thyroid lesions are of great importance. Recently, many studies were conducted not only to look for useful immunohistochemical markers that are able to differentiate benign from malignant thyroid lesions but also differentiating variants in thyroid carcinomas (Alshenawy 2014; Cheung et al. 2001; Haiyan & Fan 2015). The panel of markers has been proposed; however, to date, no single marker has been established as a sensitive and specific marker in differentiating the thyroid lesions. Among the previously studied biomarkers, Hector Battifora Mesothelial-1 (HBME-1) is noted to be potentially helpful in diagnosing thyroid lesions.

HBME-1 is a membrane antigen that is seen within normal tracheal epithelia, the microvilli of mesothelial cells as well as in some carcinomas of the pancreas, lung and breast (Sack et al. 1997). Initially, HBME-1 was recognized as a mesothelial marker. It was also seen to be expressed in some normal and neoplastic tissues including thyroid carcinoma. Few studies were carried out to explore this marker's expression in various thyroid lesions, especially in malignancy. Miettinen and Kärkkäinen described a strong and dispersed HBME-1 expression in PTC and FC cases, while

benign lesions and normal thyroid parenchyma were either negative or showed only focal and weak positivity (Miettinen & Karkkainen 1996). Mase et al. reported that HBME-1 showed 84.6% positivity in FC and 97.2% in PTC in 205 specimens excised (Mase et al. 2003). Another meta-analysis conducted showed that increased expression of HBME-1 in a thyroid nodule is suggestive of malignancy, and this is particularly true for PTC. This analysis also showed HBME-1 sensitivity of 78.8% for thyroid malignancy, 87.3% for PTC and 65.2% for FC, with a specificity of 82.1% (Haiyan & Fan 2015).

The purpose of this study is to determine the utility of HBME-1 in distinguishing benign and malignant thyroid lesions and to support the use of HBME-1 as a routine immunohistochemistry panel to aid the diagnosis of thyroid neoplasms.

MATERIALS AND METHODS

Tissue Specimens

The study approval was obtained from the Ethical Committee of Universiti Kebangsaan Malaysia (Ref No. UKM FPR.4/244/FF-2017-101). Altogether 108 thyroidectomy specimens were included in the study, which comprised 54 malignant and 54 benign thyroid lesions. The malignant lesions include PTC (31 cases), FC (11 cases), MC (seven cases), poorly differentiated carcinoma (one case) and anaplastic carcinoma (four cases). The benign lesions include hyperplastic nodule/goiter (28 cases), follicular adenoma (14 cases), lymphocytic thyroiditis (11 cases) and a hyalinising trabecular tumour. These cases were all diagnosed at the Universiti Kebangsaan Malaysia Medical Centre within a period of seven years. The classification of the malignant cases was based on the WHO Classification Tumours of Endocrine Organs (fourth edition). All cases were reviewed by three independent observers, i.e., one trainee and two pathologists under light microscopy. Subsequently, the most representative section and its corresponding paraffin block were selected for each case for immunohistochemical staining with HBME-1.

Immunohistochemical Staining Method

Monoclonal Mouse Anti-Human Mesothelial Cell, clone HBME-1 (Code M3505, Dako Denmark) was used as the primary antibody, at a dilution of 1:100. The positive control used was a mesothelioma tissue.

The immunohistochemistry was carried out on formalin-fixed paraffin embedded (FFPE) tissue sections using the protocol from EnVision™ FLEX+, Mouse, High pH (Code No. K8012, Dako Denmark). The primary antibody dilution was performed to achieve optimal concentration using Antibody Diluent, Dako REAL™ (Code No. S2022, Dako Denmark). The washing steps were done between each reagent, using EnVision™ FLEX Wash Buffer 20x (Code No. DM831, Dako Denmark). The 1X DAB-containing Substrate Working Solution was prepared by diluting the 50X

concentrated EnVision™ FLEX DAB+ Chromogen (Code No. DM827, Dako Denmark) with Envision™ FLEX ™ Substrate Buffer (Code No. DM823, Dako Denmark).

The FFPE tissue was sectioned to about 3 µm thickness and mounted on an adhesive glass slide, then it was left to be air-dried overnight at room temperature. Subsequently, the slides were incubated on a hot plate (60˚C) for an hour. An initial deparaffinization and pre-treatment step were then performed in the Decloaking Chamber™ NxGen (Ref. No: DC2012-220V, Biocare Medical California) using the EnVision™ FLEX Target Retrieval Solution, High pH (Code No. DM828, Dako Denmark), with the temperature of 110˚C for 30 minutes. Later, the slides were cooled at room temperature for 30 minutes and subsequently rinsed with running tap water for three minutes. Subsequently, the slides were incubated with EnVision™ FLEX Peroxidase-Blocking Reagent (Code No. DM821, Dako Denmark) for five minutes. This is followed by another washing step.

The next step was incubation with primary antibody for 30 minutes at room temperature, followed by incubation with EnVision™ FLEX/HRP (Code No. DM822, Dako Denmark) for 20 minutes. Then, the slides were incubated with 1X DAB-containing Substrate Working Solution for 10 mins. Following that, the tissues were counterstained with Hematoxylin 2 (REF 7231, Thermo Scientific, USA) for 15 seconds, followed by dehydration steps using increasing alcohol solutions (80%, 90%, 100% and 100%) and two times Xylene. Finally, the slides were mounted using DPX mounting medium (Cat. No.: 100579, Merck Millipore, Germany).

HBME-1 Immunohistochemical Staining Evaluation

The staining was evaluated by three observers independently and they were blinded from the initial diagnosis. The consensus of the majority (2/3 or 3/3) was taken as the final result. The cases were considered as positive if immunoreactivity was seen at the cell cytoplasm and/or cytoplasmic membrane of the lesional cells. Each case was semiquantitatively evaluated for the proportion score on a 4-point scale as either 0 (less than 10% positivity), 1+ (10-25% positivity), 2+ (26-50% positivity) and 3+ (more than 50 % positivity). This scoring system was based on a previously published study (Alshenawy 2014). In cases where there were staining of the colloid but no staining seen on the thyroid epithelial cells, it was considered negative.

Statistical Analysis

The data obtained were analysed using the "Statistical Package for the Social Sciences (SPSS) for Windows" software (version 20.0) (IBM Corp. Armonk, NY, USA). The Chi-Square test was used to assess the null hypothesis. The p-value of <0.05 was considered to be statistically significant. The categorical data were presented in frequency. The sensitivity, specificity, positive predictive value and negative predictive value were assessed in both

Table 1: Demographics and clinicopathological data of study groups.

Variables	Benign cases	Malignant cases
Mean age (SD)	45.8 (14.7)	49.17 (14.17)
Gender		
Male	12 (22.2%)	20 (37%)
Female	42 (77.8%)	34 (63%)
Ethnicity		
Malay	32 (59.3%)	32 (59.3%)
Chinese	13 (24.1%)	12 (22.2%)
Indian	5 (9.3%)	6 (11.1%)
Others	4 (7.4%)	4 (7.4%)
Size of lesion		
≤ 2cm	1 (1.9%)	13 (24.1%)
2- 4 cm	10 (18.5%)	20 (37.0%)
> 4cm	39 (66.7%)	18 (33.3%)
Not available	4 (7.4%)	3 (5.6%)
Extrathyroidal extension		
Present	-	10 (18.5%)
Absent	-	44 (81.5%)
Nodal metastasis		
Present	-	18 (33.3%)
Absent	-	36 (66.7%)
Distant metastasis		
Present	-	3 (5.6%)
Absent	-	51 (94.4%)

benign and malignant thyroid lesions.

RESULTS

Epidemiology and Clinicopathological Data

Altogether, 54 malignant and 54 benign cases were included in the study. Both benign and malignant lesions showed female predilection. The incidence of thyroid cancer was the highest among the Malay ethnicity (59.2%), followed by Chinese (22.2%) and Indians (11.1%). The extrathyroidal extension was noted in 10/54 (18.5%) malignant cases, and 18/54 (33.3%) cases showed nodal metastasis. Distant metastasis was observed in three malignant cases. Baseline demographic characteristics of both benign and malignant groups are shown in Table 1.

HBME-1 Expression

HBME-1 expression was significantly

Table 2: Comparison of HBME-1 staining pattern between malignant and benign cases

HBME-1 Pattern	Malignant	Benign	p-value
0	23 (42.6%)	52 (96.3%)	< 0.001
1+	8 (14.8%)	2 (3.7 %)	
2+	2 (3.7%)	0 (0%)	
3+	21 (38.9%)	0 (0%)	

Table 3: HBME-1 staining pattern in different subtypes of thyroid malignancies.

HBME-1 staining pattern	Papillary carcinoma	Follicular carcinoma	Medullary carcinoma	Poorly differentiated carcinoma	Anaplastic carcinoma	Total
0	4 (12.9%)	9 (81.8%)	6 (85.7%)	1 (100%)	3 (75%)	23
1+	5 (16.1%)	1 (9.1%)	1 (14.3%)	0 (0%)	1 (25%)	8
2+	2 (6.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2
3+	20 (64.5%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	21
Total	31(100.0%)	11(100.0%)	7(100.0%)	1(100.0%)	4(100.0%)	54

higher in malignant compared to benign lesions (P<0.001) (Table 2). Positive staining was observed predominantly in malignant cases (31/54, 57.4%), while only two benign cases were positive (2/54, 3.7%). Out of the 31 positive cases, 21 cases (38.9%) showed score 3+, while none of the benign lesions showed more than 50% positivity. The two benign cases showed only score 1+. The rest of the benign lesions (52/54, 96.3%) were negative (Table 2). The positive malignant cases mostly demonstrated score 2+ and 3+ (23/31), while the benign lesions were either negative (52/54, 96.3%) or showed score 1+ (2/54, 3.7%).

Further analysis of the 31 malignant cases revealed the highest HBME-1 positivity in PTC (27/31, 87.1%), followed by anaplastic carcinoma (1/4, 25%), follicular carcinoma (2/11, 18.2%) and medullary carcinoma (1/7, 14.3%). The PTC cases mostly showed the score 3+ (20/31, 64.5%). Both medullary and anaplastic carcinoma scored only 1+. The only case of poorly differentiated carcinoma included in this study was negative (Table 3).

Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of HBME-1 in Malignant Thyroid Neoplasms

The analysis showed that HBME-1 had a sensitivity of 57.4% and specificity of 96.3%, with a high PPV (93.9%) in distinguishing malignant from benign thyroid lesions. The NPV was 69.3%.

Correlation of HBME-1 Expression with Pathological Tumour Stage (pT), Nodal and Distant Metastasis

Further analysis showed no significant

Table 4: Correlation between HBME-1 staining patterns in malignant cases with their pathological tumour stage (pT)

HBME-1 Pattern	pT1	pT2	pT3	pT4	p-value
0	5 (33.3)	7 (53.8%)	8 (36.4%)	3 (75.0%)	0.462
1+	2 (13.3%)	0 (0.0%)	5 (22.7%)	1 (25.0%)	
2+	0 (0.0%)	1 (7.7%)	1 (4.5%)	0 (0.0%)	
3+	8 (53.3%)	5 (38.5%)	8 (36.4%)	0 (0.0%)	

Table 5: Correlation between HBME-1 staining pattern in papillary thyroid carcinoma with their pathological tumour stage (pT)

HBME-1 Pattern	pT1	pT2	pT3	pT4	p-value
0	0 (0.0%)	0 (0.0%)	4 (23.5%)	0 (0.0%)	0.08
1+	0 (0.0%)	0 (0.0%)	4 (23.5%)	1 (100.0%)	
2+	0 (0.0%)	1 (20.0%)	1 (5.9%)	0 (0.0%)	
3+	8 (100.0%)	4 (80.0%)	8 (47.1%)	0 (0.0%)	

correlation between HBME-1 expression and the pathological TNM primary tumour stage (P=0.462) (Table 4). A similar finding was shown when only PTC cases were analysed according to their pathological tumour stage (P=0.08) (Table 5). Further analysis also indicated no correlation between HBME-1 expression with nodal status (P=0.91) and distant metastasis (P=0.79) (Table 6).

DISCUSSION

The diagnosis of thyroid neoplasms depends mainly on their specific morphological features, which at times can be challenging. Studies have shown intra-observer and inter-observer variability among the pathologists in diagnosing thyroid neoplasms, especially in follicular variant PTC and the FC (Franc et al. 2003; Lloyd et al. 2004). Recent advances in molecular technologies have enhanced our awareness and understanding of the genetic basis of many thyroid tumours. However, molecular testing for classification of thyroid neoplasm is impossible, impractical and rather costly. Thus, the diagnosis of thyroid lesions still depends mainly on morphological classification.

PTC is the most common subtypes of thyroid cancer and consisted 80% of all thyroid carcinoma (Lloyd et al. 2017; Nosé 2018). Local data published in 2002 by Abdullah showed a slightly different percentage, i.e., PTC (69%), FC (21%), MC (7%) and other malignancies such as anaplastic carcinoma and Hurtle cell carcinoma (3%) (Abdullah 2002). Another local published data also reported PTC as the most common type for thyroid carcinoma (76.6%) (Nor Hayati et al. 2009). A review article on thyroid malignancy of hospital-based studies

Table 6: Correlation between HBME-1 staining pattern in malignant cases with their nodal and distant metastasis

HBME-1 Pattern	Nodal Metastasis			Distant Metastasis		
	Present	Absent	p-value	Present	Absent	p-value
0	8 (44.4%)	15 (41.7%)	0.91	2 (66.7%)	21 (41.2%)	0.79
1+	3 (16.7%)	5 (13.9%)		0 (0.0%)	8 (15.7%)	
2+	1 (5.65)	1 (2.8%)		0 (0.0%)	2 (3.9%)	
3+	6 (33.3%)	15 (41.7%)		1 (33.3%)	20 (39.2%)	

in Malaysia and Myanmar also showed PTC as the commonest histological type of thyroid carcinoma ranging from 57.5-76.6% (Htwe 2012). In our study, PTC comprised 57.4% of all thyroid cancers.

We analysed 108 cases of thyroid lesions and the demographics show a slightly older median age at diagnosis of malignant neoplasms (49.17 years) compared to benign lesions (45.8 years). However, our local cancer registry showed that the highest age-specific incidence rate for thyroid malignancies for both males and females was 65 years (Azizah et al. 2016). In this study, the female to male ratio was 1.7:1 compared to 3.3:1 for global incidence and 3.13:1 for national incidence (Azizah et al. 2016; Bray et al. 2018).

Many immunohistochemical markers were studied previously to assist in the diagnosis of malignant thyroid neoplasms. HBME-1 is one of the promising immunomarkers that have been analysed (Alshenawy 2014; Cochand-Priollet et al. 2011; Nga et al. 2008). HBME-1 is a membrane antigen seen in the mesothelial cells, normal tracheal epithelium and in the carcinoma of the lung, pancreas and breast (Bateman et al. 1997; Sack et al. 1997).

Previously published studies have shown that HBME-1 expression is generally increased in malignant thyroid lesions (Dunderovic et al. 2015; Ohta et al. 2015). In this study, the percentage of HBME-1 positivity was highest in PTC (87.1%) compared to other tumour subtypes. This finding coincided with other published studies that reported a high percentage of positivity in PTC, ranging from 55-97% (Alshenawy 2014; Cheung et al. 2001; Dunderovic et al. 2015; Haiyan & Fan 2015). We postulated that higher HBME-1 expression seen in PTC might be related to the BRAFV600E point mutation, as this somatic mutation was found in up to 90% of PTC cases (Nosé 2018). However, further studies are needed to clarify this hypothesis.

Normal or benign thyroid lesions were generally negative for HBME-1, as demonstrated by earlier studies (Alshenawy 2014; Erdogan-Durmus et al. 2016). This study is in agreement with those studies, as there is a high percentage of negativity for benign lesions (96.3%, 52/54). However, 1+ staining pattern was only observed in two out of 14 cases of follicular adenoma (3.7%). This was also seen in another study that showed weak and focal expression of HBME-1 in follicular adenoma (Haiyan & Fan 2015). From these findings, we can presume that when HBME-1 is negative or showing focal or weak positivity, the diagnosis of benign lesions is favoured. When a benign lesion, such as follicular adenoma, shows strong or moderate HBME-1 expression, a more thorough evaluation of the nuclear features to exclude PTC or presence of capsular or vascular invasion to exclude FC must be done. A study done by Mase et al. (2003) reported a strong HBME-1 expression in follicular adenoma cases and surprisingly, some of those cases were re-diagnosed as FC and PTC after the thorough histological examination was conducted.

In terms of HBME-1 sensitivity and

specificity, Alshenawy (2014) reported the sensitivity and specificity of 80% and 84% respectively in distinguishing malignant from benign thyroid lesions. Another study showed 84% sensitivity and 98% specificity with a PPV of 98% and a NPV of 83% (Zargari & Mokhtari 2019). However, our study only demonstrated a sensitivity of 57.4% and specificity of 96.3%, with PPV of 93.6% and NPV of 69.3%. Of note, a marker with high specificity and PPV is needed for diagnostic purposes especially in malignant lesions. With the findings of high specificity and PPV for HBME-1 expression in malignant cases, we highly recommend this marker to be included as one of the immunohistochemical panels for distinguishing benign from malignant thyroid neoplasms.

Our study found no correlation between HBME-1 expression and the clinical outcome (i.e. tumour stage, nodal status and distant metastasis). The result is comparable to a recent study published by Cho et al. (2018), which does not support the role of HBME-1 as a prognostic marker in thyroid lesions.

CONCLUSION

Our study concluded that HBME-1 might be a useful marker in distinguishing malignant from benign thyroid lesions, particularly for cases of PTC. When the morphological features are equivocal (between benign and malignant) and the HBME-1 is diffusely positive, then a malignancy should be considered. However, HBME-1 expression may not be so helpful in cases of other thyroid malignancies such as poorly differentiated carcinoma, anaplastic carcinoma and medullary carcinoma, as demonstrated in our study. On the contrary, negative HBME-1 staining strongly suggests a benign condition in a correct morphological setting. Our study also showed that HBME-1 has high specificity and PPV in discriminating between benign and malignant thyroid lesions.

ACKNOWLEDGEMENT

The preliminary results of this study were presented as a poster in the 5th Annual Scientific Meeting 2018 of the International Academy of Pathology (Malaysian Division) in Sabah, Malaysia in October 2018. This research was conducted with the support of a grant from the Universiti Kebangsaan Malaysia Medical Centre (Project code: FF-2017-101).

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Received: 20 Dec 2019
Accepted: 12 Apr 2020