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Original article

Expression of HBME-1 and CD56 in follicular variant of papillary carcinoma in children: An immunohistochemical study and their diagnostic utility

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ABSTRACT

Papillary thyroid carcinoma (PTC) is the most common differentiated thyroid cancer in children; and the follicular variant is the second most common variant after the classic subtype. The histological appearance of follicular variant of papillary thyroid cancer (FVPTC), can be mimicked by benign follicular nodules. Pediatric pathologists encountering such lesions with FVPTC-like appearance may err on diagnosing the benign lesions as malignant. In adult patients, several immunohistochemical markers have emerged recently as a useful adjunct to distinguish differentiated thyroid carcinomas from benign follicular lesions. We undertook an inter-institutional retrospective study to establish the diagnostic utility of immunohistochemical staining for HBME-1, Galectin-3 and CD56 in differentiating FVPTC from its benign mimics, follicular adenoma and adenomatoid nodules, in children. Our specific aim of the project was to define the sensitivity and specificity of the three antibodies in FVPTC. Based on institutional diagnoses, a total of 66 cases were obtained: 32 FVPTC and 34 benign follicular nodules that comprised of 23 follicular adenoma and 11 adenomatoid nodules. Five investigators, who were blinded to the original diagnoses, independently reviewed the slides following pre-determined criteria and semi-quantitatively scoring the immunohistochemical staining. The immunohistochemical staining revealed that a combination of positive HBME-1 and negative CD56 result gave 100% specificity and positive predictive value in distinguishing FVPTC from benign follicular nodules. However, the antibody combination suffered from a lower sensitivity (50%). We used a cutoff of 25% positivity of tumor cells in determining positivity of tumor cells to an antibody. In conclusion, our study found a very high specificity and strong positive predictive value for the combination of HBME-1 and CD56 immunohistochemical stains in distinguishing FVPTC from benign follicular lesions.

1. Introduction

Thyroid nodules in children occur at a low frequency; however, the incidence of malignancy appears to be increasing [1]. Thyroid neoplasms in children appear to have differences in biological behavior, because when histology and tumor sizes are controlled for, children present with higher stage disease and have higher risk of recurrence than adults, with a higher rate of distant metastases [2,3]. This raises the importance of diagnostic accuracy and early intervention in children. Papillary thyroid carcinoma is the most common differentiated thyroid cancer in children accounting for 90% or more of all childhood cases [4]. The World Health Organization (WHO) classification of PTC defines the "follicular variant" subtype as that having an exclusive or almost exclusive follicular growth pattern [5]. In one series, follicular variant of papillary thyroid carcinoma (FVPTC) comprised 23% of PTCs [6]. The diagnosis of FVPTC is straight-forward if the nuclear features are characteristic and uniform, and/or if there is infiltration of capsule. Distinguishing FVPTC from follicular adenoma (FA) and encapsulated adenomatous nodules, can be extremely difficult if nuclear features of papillary carcinoma are not well developed or are only focally expressed [7,8]. Not surprisingly, significant inter-observer and intra-observer variability in the diagnosis of FVPTC exists even among the experts [9–11].

Immunohistochemistry (IHC) has been shown to serve as a valuable

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adjunct to routine histology to improve the diagnostic accuracy of thyroid cancers in adults. Antibodies to HBME-1, Galectin-3, CD56, Galectin-7, BRAF, RET-PTC, CK19, CD15, CD44, Cyclin D, and E-cadherin have been employed in various combinations to support the diagnosis of difficult thyroid tumors. While HBME-1 and Galectin-3 are reportedly positive in papillary carcinoma of thyroid, CD56 is lost in papillary carcinoma. The utility of immunohistochemical markers to diagnose FVPTC in children has not been reported. We undertook this study in immunohistochemistry with the goal to see if there is a role for HBME-1, Galectin-3 and CD56 in differentiating FVPTC from its benign mimics of follicular patterned nodules, specifically FA and adenomatoid nodules (AN) in children. The findings of our study are described herein.

2. Materials and methods

2.1. Study design

Following approval from the institutional review Board of Children's Mercy Hospital - Kansas City (CMH), undertook this collaborative study with two other tertiary Children's Hospitals: Nationwide Children's Hospital (Columbus, OH) and Children's Healthcare of Atlanta. We did not seek to collect patient identifiable data and thus the IRB waived patient consent. The study is retrospective, and was performed on excised tissue of thyroid nodules that was received for pathological examination during the period of 2003–2013 from children aged between 1 to 17 years. Cases were searched in institutional pathology databases for the diagnosis terms "follicular variant of papillary thyroid carcinoma", "follicular adenoma" and "adenomatoid nodule." From each subject's thyroid nodule, one representative paraffin-embedded tissue block was identified by a pathologist (who was unrelated to the study) at each of the three institutions. Six unstained slides, with tissue cut at 4-micrometer thickness from the designated formalin-fixed paraffin-embedded (FFPE) tissue blocks were obtained.

2.2. Tissue processing

An independent coordinator located at CMH, received all the slides. Based on institutional diagnosis, the coordinator divided the cases into two groups: FVPTC and Benign Follicular Nodules (BFN). Tissue staining of all cases was performed at CMH under identical conditions. On one slide of each case, routine Hematoxylin and Eosin (H&E) staining was performed. Additionally, immunohistochemistry for HBME1, Galectin-3 and CD56 was performed on each case in an automated immunostainer (Leica Bond). The antibody source and dilutions used are shown in Table 1.

2.3. Evaluation of slides and consensus

The slides were independently evaluated by five investigators (four board-certified pathologists and one resident), who were blinded to the institutional diagnosis. As there is no gold standard for the diagnosis of FVPTC and its benign mimics, we decided to employ the consensus diagnosis obtained on independent review of H&E stained slides as a surrogate gold standard to establish the utility of immunohistochemical (IHC) markers in these lesions. The consensus diagnostic criteria to diagnose FVPTC were: exclusive or almost exclusive follicular growth pattern with no obvious papillae, nuclear features of PTC, presence of capsular invasion or an infiltrative pattern. For our study, we defined consensus diagnosis as the diagnosis reached by four or more pathologists independently reviewing the histology slides of a case.

Table 1
Primary antibodies showing clonality, dilution and supplier.

Antibody	Dilution	Manufacturer/Supplier	Clonality
HBME1	1:25	Cell Marque	Mouse monoclonal
Galectin-3	1:200	Novocastra (Leica)	Mouse monoclonal
CD56	1:200	ThermoFisher Scientific	Mouse monoclonal

The IHC stains were semi-quantitatively scored by each investigator. Membranous staining of HBME-1 and CD56 was quantified and scored as percentage, while nuclear and cytoplasmic staining of tumor cells was similarly scored for Galectin-3. The proportion of positively stained tumor cells within the nodule were scored as, absent (no positively stained tumor cells), rare (> 0–25% tumor cells), focal (> 25 – 75%), diffuse (> 75%). The data was tabulated in a spreadsheet by each investigator. To report a consensus interpretation of an IHC stain, we compared the semi-quantitative score provided by the investigators for each case, and accepted the score reported by a majority (three or more) of investigators. Cases with absent and rare IHC scores were grouped as 'negative' (N), and those with focal and diffuse scores were grouped as 'positive' (P). Thus, the negative cases had less than 25% of tumor cells staining for an antibody whereas the positive cases had more than 25% positively stained tumor cells.

2.4. Statistical analyses

The number of cases used to determine the sensitivity (> 50%) and specificity (> 50%) of the three antibodies had a power of > 90%. The consensus diagnoses and the consensus IHC scores of positive or negative (two-tiered scoring) were utilized for statistical analysis. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of the IHC stains (individually and in combination) in the two consensus determined study groups were derived from 2 × 2 contingency tables.

Inter-reader agreement of IHC scores (two-tier) was measured using Fleiss Kappa statistic and SAS%MAGREE macro that is based on methodology presented by Fleiss et al, while that of four-tiered IHC scores was estimated using Krippendorff's alpha reliability and SAS% KALPHA macro which is based on methodology from Hayes and Krippendorff [12,13]. The measure of agreement/ reliability was interpreted as follows; less than 0.20 - poor, 0.20 to 0.40 - fair, 0.40 to 0.60 - moderate 0.60 to 0.80 - good and 0.80 to 1.00 - very good agreement [14].

All statistical tests were two-sided and conducted at the alpha = 0.05 level. Statistical analysis was done using The SAS software v 9.4 (Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 66 cases were obtained, which based on original institutional diagnosis comprised 32 FVPTC and 34 BFN (23 FA and 11 AN). The five investigators independently reviewing only the H&E stained slides of the 32 cases carrying the institutional diagnosis of FVPTC concurred with the diagnosis of FVPTC on 20 cases. On the other hand, the independent review of the 34 cases carrying the institutional diagnosis of BFN, resulted in a concurring diagnosis of BFN on all 34 cases. Interestingly, five cases carrying the institutional diagnosis of FVPTC were classified as BFN by consensus diagnosis following independent review! Whether this discrepancy indicates a true error of the original diagnosis or an artifact because of the selection error of the representative section of the tumor remains unknown. In order to target tumors with unequivocal diagnoses, we eliminated 12 cases of FVPTC on which consensus diagnosis could not be achieved. The consensus agreement with the institutional diagnoses yielded a total of 20 cases of consensus-determined FVPTC (CFVPTC) and 34 cases of consensus-determined BFN (CBFN) which had diagnostic features of either FVPTC or FA/AN, respectively on the single representative slide. Considering the nomenclature revision in 2016, which followed the commencement of

Table 2
IHC staining of HBME-1, Galectin-3 and CD56 in CFVPTC and CBFN.

A. CFVPTC (Total number of cases = 20)					
HBME-1		Galectin-3		CD56	
Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)
18 (90)	2 (10)	15 (75)	5 (25)	10 (50)	10 (50)
B. CBFN (Total number of cases = 34)					
HBME-1		Galectin-3		CD56	
Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)
1 (2.9)	33 (97.1)	11 (32.3)	23 (67.6)	32 (94.1)	2 (5.9)

Abbreviations: N, number of cases; CFVPT, Cconsensus determined follicular variant of papillary thyroid carcinoma; CBFN, consensus determined benign follicular nodules.

our study in 2015, two investigators reviewed the slides to determine if any of the 20 CFVPTC cases would be diagnosed as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). The CFVPTC cases showed one or more of the following features: invasion of capsule or focal necrosis or increased mitoses (> 3 per 10 high power fields), which precluded them from being labeled as NIFTP. Further, we attempted to sub-classify the CFVPTC cases into "encapsulated with invasion" versus "infiltrative" subtypes. It was determined that 12 of 20 CFVPTC (60%) were infiltrative subtype and 8 of 20 CFVPTC (40%) could be "encapsulated with invasion" subtype.

3.1. Immunohistochemical staining

The IHC staining of HBME-1, Galectin-3 and CD56 antibodies on the two groups of thyroid tumors (CFVPTC and CBFN) was scored as described in the Methods section. Result of the IHC scoring and its statistical analysis for agreement between the five investigators revealed the interobserver agreement to be good ($\kappa = 0.696$) for HBME-1, fair ($\kappa = 0.399$) for Galectin-3 and good ($\kappa = 0.632$) for CD56. The result of the IHC staining for the two groups of thyroid tumors utilizing the 3 antibodies is shown in Table 2.

The pattern of IHC staining of all three antibodies in 3 cases each of CFVPTC and CBFN are shown in Fig. 1.

3.2. IHC staining of CFVPTC

The HBME-1 IHC stain was positive in 18/20 (90%) CFVPTCs, while it was negative in 33/34 (97.1%) CBFNs. Galectin-3 was also positive in a majority (75%) of CFVPTCs, but a significant proportion (25%) of them were negative. The IHC staining of CD56 was not distinctive in CFVPTCs. The typical pattern of IHC staining of HBME-1 and CD56 in two cases of CFVPTC is shown in Fig. 1.

3.3. IHC staining of CBFN

The CD56 IHC stain was positive in 32/34 CBFN (94.1%), but was also positive in 10/20 CFVPTC (50%), which decreases its specificity in the diagnosis of benign follicular nodules. Significantly, HBME-1 was negative in 33/34 (97.1%) CBFN. Again, Galectin-3 IHC stain was not helpful in discriminating between the two groups of thyroid tumors. The typical pattern of IHC staining of HBME-1 and CD56 in two cases of CBFN is shown in Fig. 2.

3.4. Combination versus single antibody sensitivity and specificity

Result of the statistical analysis of IHC staining with regard to sensitivity and specificity of the antibodies is shown in Table 3. Notably, in our case series, the positive IHC result of HBME-1 by itself had the highest sensitivity and specificity for the diagnosis of FVPTC among the three antibodies. Also, the negative IHC result of CD56 had a high negative predictive value (94.1) for the diagnosis of FVPTC among the three antibodies. The combination of HBME-1 and CD56 had 100% specificity and 100% positive predictive value in distinguishing FVPTC from BFN. The interobserver agreement for the interpretation of IHC staining was good for both HBME-1 ($\kappa = 0.696$) and CD56 ($\kappa = 0.632$).

4. Discussion

Several studies in adults have demonstrated the utility of immunohistochemical markers in the diagnosis of follicular variant of papillary thyroid carcinoma. We undertook this inter-institutional study to determine if a panel of immunohistochemical stains could be employed to distinguish FVPTCs from its benign mimics in childhood thyroid tumors. We narrowed the antibody panel to 3 antibodies based on the adult literature. Our results of IHC staining for FVPTC and BFN are congruent with those reported in adults.

Hector Battifora mesothelial–1 (HBME-1) is a membrane antigen found in the microvilli of mesothelial cells and other epithelial cells. Studies suggest that overexpression of HBME-1 in thyroid tumors indicate malignancy, especially PTC, whereas thyroid adenomas are generally negative [15–18]. Galectin-3 is a member of a family of Beta-galactoside binding lectins, and its overexpression has been reported in several cancers and especially well-differentiated follicular-derived thyroid carcinomas [19]. Normal thyroid tissue is generally negative for Galectin-3. CD56 is a neural cell adhesion molecule that is expressed in normal thyroid tissue and several follicular lesions, but it is frequently lost in PTC [20].

Studies of immunohistochemical markers in adult FVPTC tumors demonstrate that HBME-1 has a higher sensitivity when compared to Galectin-3, ranging between 81.1% and 100% [21–25]. Some of these studies used a cut-off percentage of positively staining tumor cells at > 10% whereas some used a > 25% cut-off to label a case as positive. We used a cut-off of > 25% tumor cell staining and the sensitivity for HBME-1 was 94.7% in our study, which is consistent with the published studies. Nechifor-Boilaa et al studied 90 cases of FVPTC and showed a sensitivity of 81.1% for HBME-1, 27.8% for Galectin-3 and 64.4% for CD56 [21]. In their study, Galectin-3 had a high sensitivity for classic variant of papillary thyroid carcinoma (94.9%), but much lower sensitivity for FVPTC (27.8%). Torregrossa et al compared Galectin-3 and HBME-1 IHC staining in 133 cases of FVPTC [23]. In their study, Galectin-3 was positive in 99.7%, but only 48.8% tumor cells had > 25% positive cells whereas 50.9% tumor cells showed < 25% positivity. Papotti et al also studied Galectin-3 and HBME-1 IHC staining in 14 cases of FVPTC, and a sensitivity of 86.6% for Galectin-3 in the FVPTC cases [25]. However, they revealed that 30.7% of cases had < 25% positive tumor cells, and 69.2% cases showed > 25% positive tumor cells. Employing a cut-off of > 25% tumor cell staining, the sensitivity of Galectin-3 for FVPTC was 57.7% in our study. Interpretation of IHC staining in thyroid tumors may risk becoming subjective and less amenable to comparison between institutions, unless specific criteria are followed in its interpretation. Our study suggests that the cut-off percentage of positive tumor cells to deem an antibody as positive has important implication in the interpretation of immunohistochemical result.

With regard to CD56, Nechifor-Boilaa et al using a cut-off of 10% tumor cell staining, found that 66 of 90 cases (73.3%) of FVPTC were negative for CD56. Similarly, Alshenawy using a cut-off of 10% tumor cell staining, found that 7 of 8 cases (87.5%) of FVPTC to be negative for CD56 [22]. Rasha et al. using a cut-off of 10% tumor cell staining

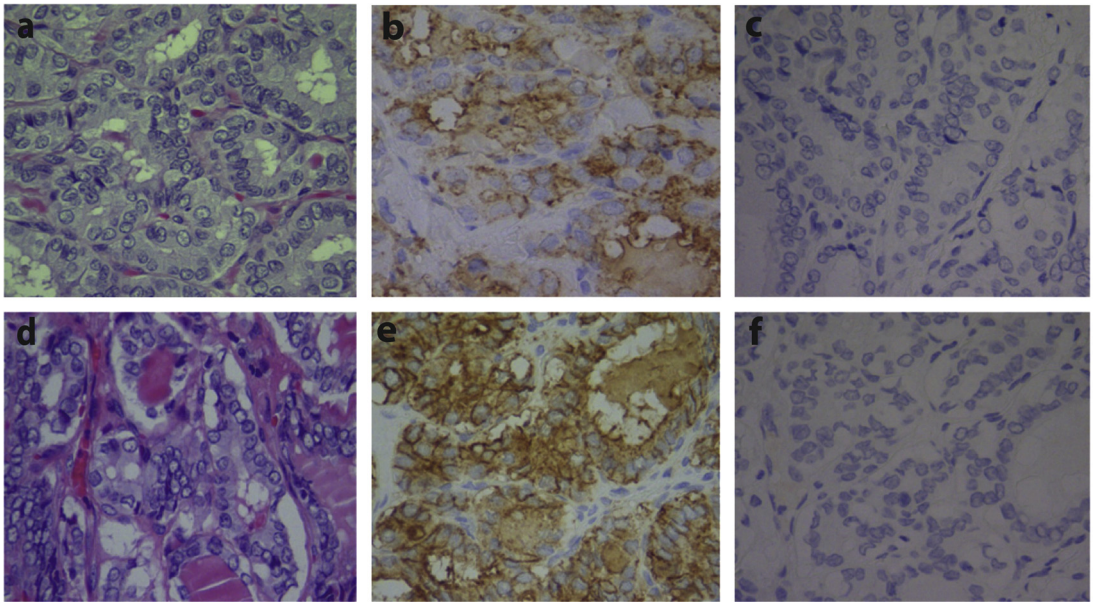

Fig. 1. H&E stain and immunostains of consensus determined follicular variant of papillary thyroid carcinoma. A,D: H&E stains; B,E: HBME-1 immunostain; C,F: CD56 immunostain (Magnification of all figures x400).

found that 13 of 16 FVPTC cases (81.3%) were negative [26]. Using a cut-off of > 25% tumor cell staining, CD56 was negative in 50% of FVPTC cases. Thus, our study found lower proportion of FVPTC cases to be negative for CD56. We are unable to provide an explanation for this variation of CD56 IHC staining between our pediatric FVPTC tumors versus adult FVPTC tumors. Comparing adult data with our study for the BFN cases with respect to CD56 IHC staining, positive staining for CD56 occurs in 85.7% cases (reference 22), 89.4% cases (reference 26) and 94.1% cases (our study) of BFN.

In order to support the diagnosis of FVPTC and exclude the differential diagnostic consideration of BFN, a combination of two or more antibodies would be gainful. In our study of 3 antibodies, the interpretation of IHC staining of Galectin-3 suffered from lower inter-observer agreement, and the staining pattern indicated that it would not be positive in approximately one-quarter of FVPTC. A combination of HBME-1 and CD56 demonstrated 100% specificity and 100% positive predictive value in the diagnosis of FVPTC (p = < 0.0001 and 0.002, respectively).

Table 3
Statistical analysis of HBME-1, Galectin-3 and CD56 IHC staining in CFVPTC.

IHC STAINS	SN (%)	SP (%)	PPV (%)	NPV (%)
HBME-1 (P)	94.7	94.2	90	97.1
Galectin-3 (P)	57.7	82.1	75	67.6
CD56 (N)	83.3	76.2	50	94.1
HBME1 (P) CD56 (N)	50	100	100	77.3

Abbreviations: P, positive; N, negative; SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV: negative predictive value.

The diagnosis of PTC in children is significant because at clinical presentation, one-half of patients tend to have extra-thyroidal extension

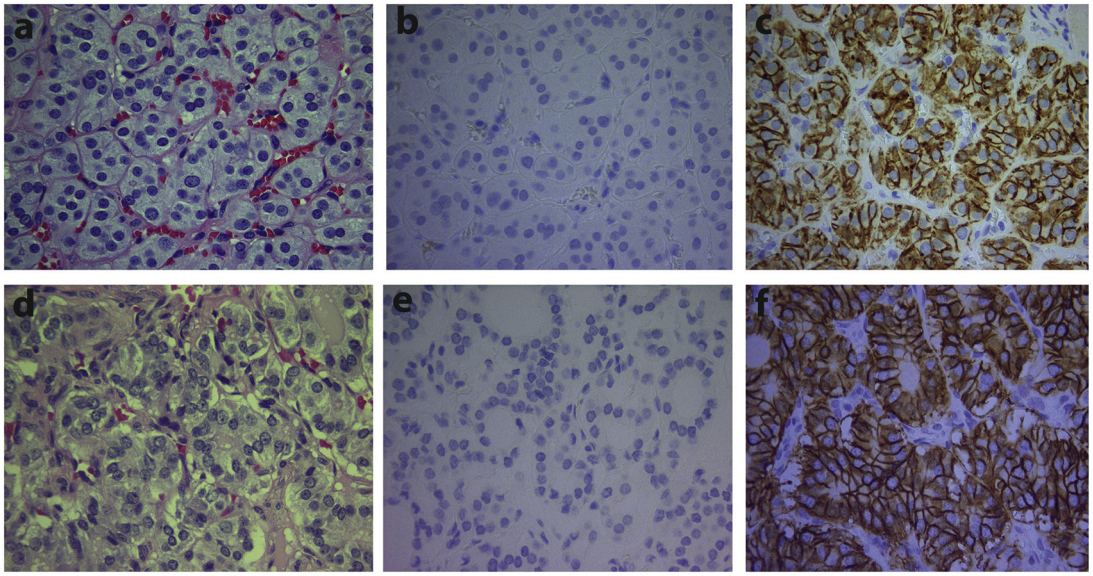

Fig. 2. H&E stain and immunostains of consensus determined benign follicular nodules. A,D: H&E stains; B,E: HBME-1 immunostain; C,F: CD56 immunostain (Magnification of all figures x400).

of disease and about three-quarters have nodal positivity [27]. The surgical management of PTC has been a subject of debate regarding the extent of resection as not removing the entire thyroid has been associated with recurrent disease, whereas extensive surgery could be complicated by hypoparathyroidism and or recurrent laryngeal nerve damage [28]. While the above-mentioned clinical outcome studies refer to PTC as a group, there are no studies specifically addressing FVPTC tumors in children.

One of the limitations of our study was non-retention of patient identifiers, which precludes us from returning to an individual case to perform additional study or gather follow-up data. Another limitation is the nature of FFPE tissue available for the study. Since, the samples originated from 3 different institutions, the variation in formalin fixation, materials used in block preparation and storage of archived material could not be controlled. We tried to mitigate further variability by performing H&E staining and IHC staining in identical conditions at one institution. The performance characteristics of the three antibodies as reported here could serve as a resource for individual institutions if they intend to validate these antibodies at their own institution. Some of the variables, such as histological processing techniques and paraffin block storage, as encountered in the study would not be a factor for validated antibodies at any one institution. At the outset of our study, the archival cases were not subcategorized into encapsulated or invasive subtypes of FVPTC, since the focus of our study was to establish the utility of immunohistochemical markers in discriminating FVPTC from its benign mimics. Nikiforov et al defined specific criteria to designate thyroid tumors as NIFTP and noted that most patients presented in fourth to sixth decades [29]. Even though NIFTP is expected to be an infrequent tumor in children, it is a differential diagnostic consideration of FVPTC and therefore it would be valuable to know the immunohistochemical profile of NIFTP tumors occurring in children. As this entity has only been recently described; in the future, when significant number of cases become available such an immunohistochemical study could be undertaken.

The strength of our study is in inter-institutional collaboration that provided enough material from a rare pediatric tumor to complete the study. Also, the independent review by five investigators comprising four board-certified pediatric pathologists and one final year pathology Resident, simulated the variation seen in the practice of diagnostic pathology. Based on the results of this study, we infer that a combination of HBME-1 (> 25% tumor cell positivity) and CD56 (< 25% tumor cell positivity) IHC staining pattern has a strong positive predictive value in the diagnosis of FVPTC. However, it has to be noted that the lower sensitivity of this combination (50%) may impact a case that is being worked up by immunohistochemistry. The above practice, implemented following the study at one of the three Institutions, has significantly reduced the number of “send outs” for consultation of thyroid tumors in children. In conclusion, we recognize that while the majority of FVPTC, FA and AN diagnoses may not require immunohistochemical work up, and in those few instances where an FVPTC diagnosis is being considered, a positive staining of HBME-1 in combination with a negative staining of CD56 could provide ancillary support to rule in the diagnosis. It is also possible that despite the use of the immunohistochemical staining, some follicular patterned lesions may be difficult to classify and may require expert consultation.

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Conflict of interest

All authors report that they have no conflict of interest.

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References

[1] L.B. Vergamini, A.L. Frazier, F.L. Abrantes, et al., Increase in the incidence of differentiated thyroid carcinoma in children, adolescents, and young adults: a population-based study, J. Pediatr. 164 (2014) 1481–1485.
[2] M. Silva-Vieira, R. Santos, V. Leite, et al., Review of clinical and pathological features of 93 cases of well differentiated thyroid carcinoma in pediatric age at the Lisbon Centre of the Portuguese Institute of Oncology between 1964 and 2006, Int. J. Pediatr. Otorhinolaryngol. (79) (2015) 1324–1329.
[3] S.G. Waguespack, G. Francis, Initial management and follow-up of differentiated thyroid cancer in children, J. Compr. Canc. Netw. 8 (2010) 1289–1300.
[4] I. Halac, D. Zimmerman, Thyroid nodules and cancers in children, Endocrinol. Metab. Clin. North Am. 34 (2005) 725–744.
[5] J. Rosai, J. Alores Saavedra, S. Asioli, et al., Papillary thyroid carcinoma, in: R.V. Lloyd, R.Y. Osamura, G. Kloppel, J. Rosai (Eds.), WHO Classification of Tumors of Endocrine Organs, International Agency for Research on Cancer, Lyon, 2017, pp. 81–91.
[6] A.R. Hogan, Y. Zhuge, E.A. Perez, et al., Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients, J. Surg. Res. (156) (2009) 167–172.
[7] Z.W. Baloch, V.A. Livolsi, Our approach to follicular-patterned lesions of the thyroid, J. Clin. Pathol. 60 (2007) 244–250.
[8] C. Kragel, T.M. Shattuck, The follicular variant of papillary thyroid carcinoma as a source of false negative cytopathology: a report of four cases with an emphasis on the multifocality of nuclear changes, Diagn. Cytopathol. 43 (2015) 174–177.
[9] M. Hirokawa, J.A. Carney, J.R. Goellner, et al., Observer variation of encapsulated follicular lesions of the thyroid gland, Am. J. Surg. Pathol. 26 (2002) 1508–1514.
[10] R.V. Lloyd, L.A. Erickson, M.B. Casey, et al., Observer variation in the diagnosis of follicular variant of papillary thyroid carcinoma, Am. J. Surg. Pathol. 28 (2004) 1336–1340.
[11] T.M. Elsheikh, S.L. Asa, J.K. Chan, et al., Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma, Am. J. Clin. Pathol. 130 (2008) 736–744.
[12] A.F. Hayes, K. Krippendorff, Answering the call for a standard reliability measure for coding data, Commun. Methods Meas. 1 (2007) 77–89.
[13] J.R. Landis, G.G. Koch, The measurement of observer agreement for categorical data, Biometrics 33 (1977) 159–174.
[14] J.L. Fleiss, J.C.M. Nee, J.R. Landis, Large sample variance of kappa in the case of different sets of raters, Psychol. Bull. 86 (1979) 974–977.
[15] M.B. Casey, C.M. Lohse, R.V. Lloyd, Distinction between papillary thyroid hyperplasia and papillary thyroid carcinoma by immunohistochemical staining for cytokeratin19, galectin-3, and HBME-1, Endocr. Pathol. 14 (2003) 55–60.
[16] M. Miettinen, P. Karkkainen, Differential reactivity of HBME-1 and CD15 antibodies in benign and malignant thyroid tumours. Preferential reactivity with malignant tumours, Virchows Arch. 429 (1996) 213–219.
[17] M.J. Sack, C. Astengo-Osuna, B.T. Lin, et al., HBME-1 immunostaining in thyroid fine-needle aspirations: a useful marker in the diagnosis of carcinoma, Mod. Pathol. 10 (1997) 668–674.
[18] C.C. Cheung, S. Ezzat, J.L. Freeman, et al., Immunohistochemical diagnosis of papillary thyroid carcinoma, Mod. Pathol. 14 (2001) 338–342.
[19] E. Saggiorato, S. Cappia, P. De Giuli, et al., Galectin-3 as a presurgical immunocytodiagnostic marker of minimally invasive follicular thyroid carcinoma, J. Clin. Endocrinol. Metab. 86 (2001) 5152–5158.
[20] A.B. Ceyran, S. Senol, B.C. Simsek, et al., Role of CD56 and e-cadherin expression in the differential diagnosis of papillary thyroid carcinoma and suspected follicular-patterned lesions of the thyroid: the prognostic importance of e-cadherin, Int. J. Clin. Exp. Pathol. 8 (2015) 3670–3680.
[21] A. Nechifor-Boilaa, A. Borda, G. Sassolas, et al., Immunohistochemical markers in the diagnosis of papillary thyroid carcinomas: The promising role of combined immunostaining using HBME-1 and CD56, Pathol. Res. Pract. 209 (2013) 585–592.
[22] H.A. Alshenawy, Utility of immunohistochemical markers in diagnosis of follicular cell derived thyroid lesions, Pathol. Oncol. Res. 20 (2014) 819–828.
[23] L. Torregrossa, P. Faviana, T. Camacci, et al., Galectin-3 is highly expressed in nonencapsulated papillary thyroid carcinoma but weakly expressed in encapsulated type; comparison with Hector Battifora mesothelial cell 1 immunoreactivity, Hum. Pathol. 38 (2007) 1482–1488.
[24] M.L. Prasad, N.S. Pellegata, Y. Huang, et al., Galectin-3, fibronectin-1, CITED-1, HBME1 and cytokeratin-19 immunohistochemistry is useful for the differential diagnosis of thyroid tumors, Mod. Pathol. 18 (2005) 48–57.
[25] M. Papotti, J. Rodriguez, R. De Pompa, et al., Galectin-3 and HBME-1 expression in well-differentiated thyroid tumors with follicular architecture of uncertain malignant potential, Mod. Pathol. 18 (2005) 541–546.
[26] R.M. Abd El Atti, L.S. Shash, Potential diagnostic utility of CD56 and claudin-1 in papillary thyroid carcinoma and solitary follicular thyroid nodules, J. Egypt. Canc. Inst. 24 (2012) 175–184.
[27] R. Palaniappan, A. Krishnamurthy, S.S. Rajaraman, R.K. Kumar, Management outcomes of pediatric and adolescent papillary thyroid cancers with a brief review of literature, Indian J. Cancer 55 (2018) 105–110.
[28] F.A. Verburg, H.M. Van Santen, M. Luster, Pediatric papillary thyroid cancer: current management challenges, Oncol. Ther. 10 (2017) 165–175.
[29] Y.E. Nikiforov, R.A. Gosssein, K. Kakudo, V. LiVolsi, M. Papotti, et al., Non-invasive follicular thyroid neoplasm with papillary-like nuclear features, in: R.V. Lloyd, R.Y. Osamura, G. Kloppel, J. Rosai (Eds.), WHO Classification of Tumors of Endocrine Organs, International Agency for Research on Cancer, Lyon, 2017, pp. 78–80.