Original Contribution

Benign vascular anomalies: A transition from morphological to etiological classification

Kanika Rastogi[a], Lavleen Singh[a,*], Niyaz A. Khan[b], Surbhi Goyal[a], Arti Khatri[a], Natasha Gupta[c]

[a] Department of Pathology, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi 110031, India
[b] Department of Pediatric Surgery, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi 110031, India
[c] Department of Radiodiagnosis, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi 110031, India

ARTICLE INFO

ABSTRACT

The International Society for the Study of Vascular Anomalies (ISSVA) devised a multidisciplinary etiopathogenesis based approach to classify benign vascular anomalies into tumors and malformations. This classification scheme has major therapeutic and prognostic implications as treatment modalities differ for both the categories. Inappropriate usage of the term "hemangioma" for etiopathogenetically distinct entities is commonly seen in clinical practice leading to delivery of incorrect treatment to the patients. We aimed to study the histomorphological and immunohistochemical features of benign vascular anomalies for their precise histopathological classification. A total of 48 cases diagnosed over a period of 3.5 years were reviewed and reclassified into vascular tumors and malformations based on ISSVA classification and prototypical histopathological features. Biopsies were reviewed based on 5 histopathological criteria viz. endothelial morphology, mitotic activity, intralesional nerve bundles, intralesional inflammation, and prominent vessel type. A panel of GLUT-1, WT-1, and Ki-67 was performed in each case. Seven cases of infantile hemangioma, 4 cases each of non-involuting congenital hemangioma and pyogenic granuloma, and 33 cases of vascular malformations were diagnosed. Endothelial cell morphology (p < 0.001), mitotic activity (p < 0.001), and intralesional nerve bundles (p < 0.001) were found to be statistically significant in differentiating hemangioma from malformations. GLUT-1 (p < 0.001) and Ki-67 labeling index (p < 0.001) were useful to distinguish infantile hemangioma from vascular malformations. To conclude, the ISSVA classification of benign vascular anomalies can be reliably done on histopathology. However, every case must be interpreted in the light of clinical and radiological features.

1. Introduction

The benign vascular anomalies (benign vascular tumors and malformations) are commonly encountered lesions in infancy and childhood accounting for 20–30% of all pediatric soft tissue tumors [1]. The International Society for the Study of Vascular Anomalies (ISSVA) devised a multidisciplinary etiopathogenesis based approach to classify benign vascular anomalies into tumors and malformations [2]. This classification system is based on the concept pioneered by Mulliken and Glowacki in 1982 [3] where hemangiomas were considered the proliferative vascular lesions and malformations were considered a defect of embryonal vascular morphogenesis. The etiopathogenesis based classification has major therapeutic and prognostic implications. Surgical resection, embolization or sclerotherapy are preferred treatment modalities for vascular malformations (VM), while beta-blockers and steroids have a curative role in proliferative endothelial tumor like hemangioma [4]. Despite the acceptance of ISSVA classification for more than two decades, there is still a lack of usage of uniform nomenclature amongst both clinicians and histopathologists regarding the appropriate subclassification of benign vascular anomalies. It is often seen that the etiopathogenetically distinct entities are lumped under the generic term "hemangioma", owing to which patients often end up receiving improper treatment [5]. The current WHO classification of benign vascular tumors includes entities like synovial hemangioma, intramuscular angioma, venous hemangioma, and arteriovenous malformation/hemangioma, without taking into consideration their malformation or neoplastic nature [6]. We aimed to study and analyze the morphological features of endothelial cells, characteristics in the surrounding stroma and immunohistochemical expression of endothelium associated markers and proliferation markers for precise histopathological classification of benign vascular anomalies into tumors and malformations.

---

* Corresponding author.
  E-mail address: singhlavleen04@gmail.com (L. Singh).

Table 1

Overview of benign vascular anomalies cases diagnosed in accordance with ISSVA and compared with the previous diagnosis.

Lesion	ISSVA classification (n)	Previous diagnosis
Lymphatic-venous malformation	14	Lymphangioma, n = 6
		Hemangioma, n = 2
		Cavernous hemangioma, n = 3
		Lymphatic-venous malformation, n = 3
Capillary-venous malformation	3	Hemangioma, n = 1
		Capillary-venous malformation, n = 2
Capillary-lymphatic-arteriovenous malformation	1	Lymphangioma, n = 1
Venous malformation	8	Hemangioma, n = 3
		Venous malformation, n = 5
Lymphatic malformation	6	Lymphatic malformation, n = 6
Capillary malformation	1	Hemangioma, n = 1
IH, proliferative phase	3	Hemangioma, n = 1
		IH, proliferative phase, n = 2
IH, involutional phase	4	Hemangioma, n = 2
		Veno capillary malformation, n = 1
		IH, involutional phase, n = 1
NICH	4	Hemangioma, n = 4
Pyogenic granuloma	4	Pyogenic granuloma, n = 4

IH - infantile hemangioma. NICH - noninvoluting congenital hemangioma.

2. Materials & methods

The study included all consecutive cases of benign vascular anomalies (n = 48) received in the Department of histopathology over a period of 3.5 years (January 2016–June 2019) in a tertiary care pediatric hospital. Hematoxylin & eosin-stained slides were retrieved, reviewed, and reclassified into vascular tumors and malformations based on ISSVA classification and prototypical histopathological features. The clinical details of the patients with respect to the age of presentation, presence/absence at birth, the natural course and results of imaging studies were recorded from the case files, wherever available. Clinico-pathological case definitions were devised. The lesion occurring between 2 and 8 weeks of life, progressing rapidly for 6–12 months followed by an involution phase and showing lobules of poorly canalized capillaries with an admixture of endothelial and pericytic cells was considered infantile hemangioma (IH) [7]. A lesion present since birth showing a progressive increase with the size of the baby with the presence of capillaries, veins, lymphatics, arteries or an admixture thereof was considered malformation. A lesion present since birth with a natural course showing static course or regression with the size of the baby and displaying lobules of capillaries with prominent draining veins separated by fibrotic stroma was considered congenital hemangioma (CH) [6]. An exophytic lesion showing lobules in which a larger vessel is surrounded by small capillaries accompanied with inflammatory infiltrate was considered pyogenic granuloma (PG) [7]. A protocol for reviewing the biopsies was formulated based on 5 histopathological criteria viz. endothelial morphology, mitotic activity, intralesional nerve bundles (INBs), intralesional inflammation, and prominent vessel type. A panel of GLUT-1 (Thermo Scientific, USA), WT-1(Thermo Scientific, USA), and Ki-67 (Thermo Scientific, USA) was performed in each case using standard immunohistochemistry protocol and bound antibody was detected using a streptavidin-biotin complex technique (Biogenex, USA). Immunostaining results for GLUT-1 and WT-1 were evaluated semiquantitatively according to the percentage of cells showing cytoplasmic positivity, i.e., < 1% (score 0), 1% to 10% (score 1), 11% to 50% (score 2), and > 50% (score 3) and whether immunoreactive cells showed mild (score 1), moderate (score 2) or intense (score 3) immunostaining. The percentage positivity and intensity scores were added to get a total score which ranged from 0 to 6. To exclude equivocal reactions, a total score of 3 or more was considered as a diagnostically relevant positive reaction [8]. For Ki-67 staining, distinct nuclear staining of the lesional endothelial cells was recorded as positive. The Ki-67 labeling index was defined as the percentage of immunoreactive lesional endothelial cells in the evaluated area. All counts were performed at a magnification of 400× (field size = 0.1735 mm^2). Five viable fields from the area of maximal labeling were chosen for counting and the average was taken as MIB labeling index. For the ease of estimation, the Ki-67 was divided into two groups 0–2%, and > 2%. The presence of these 5 criteria was compared between two major groups i.e., tumors (infantile hemangioma, congenital hemangioma, pyogenic granuloma) and VM, and the statistical significance was tested by Fisher exact test, a p-value < 0.01 was considered significant. The research was conducted in accordance with the Helsinki Declaration and the ethical clearance was obtained from the institutional ethical committee.

3. Results

A total of 48 cases of benign vascular anomalies diagnosed over a period of 3.5 years were studied. Age ranged from 11 months to 12 years. The male to female ratio was 0.8:1. Based on ISSVA classification, 18 cases of combined vascular malformation (CM), 15 cases of simple malformation (SM), 7 cases of infantile hemangioma (3 cases in proliferative phase and 4 cases in involuting phase), and 4 cases each of noninvoluting congenital hemangioma (NICH) and pyogenic granuloma were diagnosed. Out of 18 cases of combined malformations, only 5 were previously labeled correctly, rest being signed out as either hemangioma or simple malformation. Four cases of simple malformation were labeled as hemangiomas previously. Three cases of IH were termed simply hemangioma previously and one was labeled as capillary-venous malformation. All cases of NICH were signed out as hemangioma previously. None of the pyogenic granuloma cases was reclassified (Table 1).

3.1. Histopathological and immunohistochemical features of hemangioma

In IH, endothelial cells were mainly plump in both proliferative and involutional phase, with focal areas of flat endothelium also seen in the latter (Fig. 1A). 2–4 mitoses/HPF were seen in the proliferative phase and none in the involutional phase. Intralesional nerve bundles were seen in 2 cases of involuting IH (Fig. 1B). No significant inflammation was noted in any of the cases. All 4 cases of congenital hemangioma were noninvoluting type and showed plump to flattened endothelium with 2–3 mitoses/HPF in all but one case (Fig. 1C). Intralesional nerve bundles were not identified. Few mast cells were seen in 2 cases. GLUT-1 positivity in the endothelial cells was seen in IH (Fig. 2A) but not in CH. However, the reactivity was focal in most cases of IH in the involutional phase (n = 3) (Fig. 2B). WT-1 was positive in all the cases of
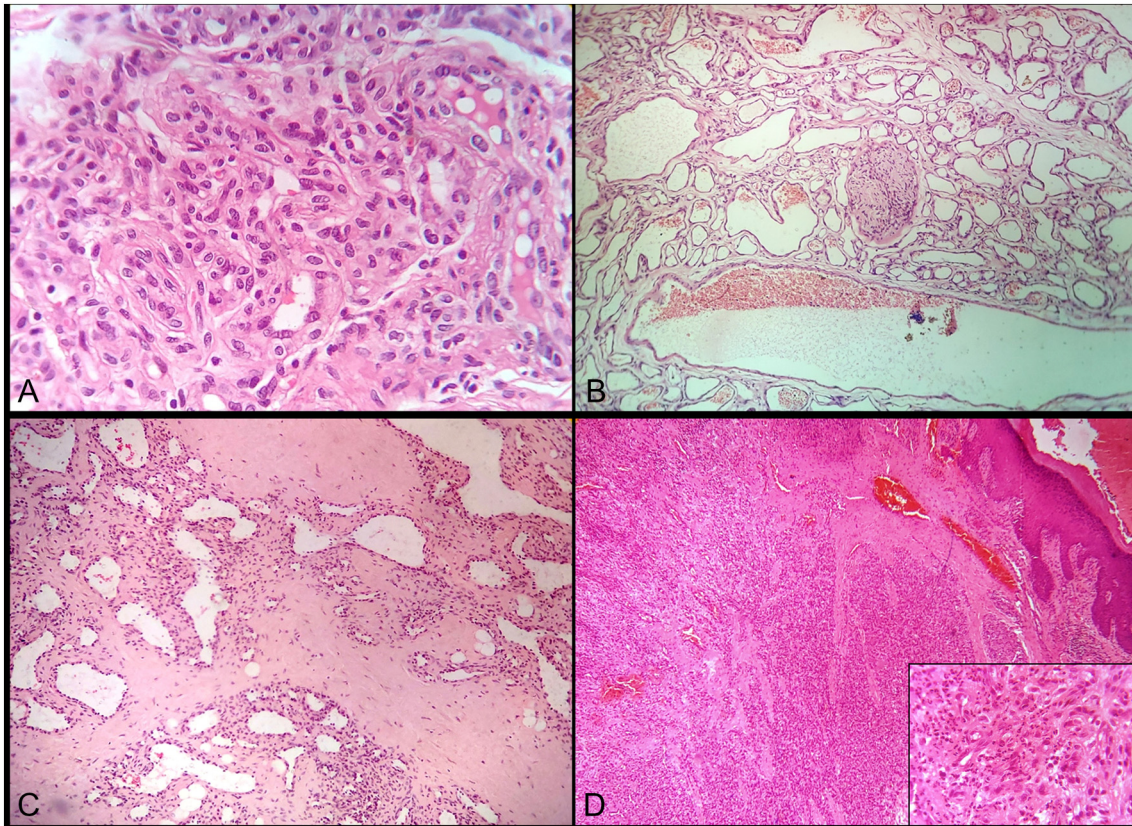
Fig. 1. (A) Infantile haemangioma showing both well canalized and poorly canalized capillaries lined by plump endothelial cells (400×, H&E). (B) Intralesional nerve bundle seen in involutional infantile hemangioma (100×, H&E). (C) Noninvoluting congenital hemangioma showing lobules of capillaries separated by densely sclerotic stroma. Capillaries are lined by plump to flattened endothelial cells (100×, H&E). (D) Pyogenic granuloma showing the lobular arrangement of blood vessels (40×, H&E). Inset shows capillaries lined by plump endothelial cells along with acute inflammatory infiltrate (400×, H&E).

both IH and CH (Fig. 2D). IH (proliferative phase) and CH showed the Ki-67 labeling index in the range of 2–10% with a median of 4% (Fig. 2C).

3.2. Histopathological and immunohistochemical features of pyogenic granuloma

Pyogenic granuloma showed an exophytic lesion composed of lobules of capillaries. The vessels were lined by plump endothelial cells displaying 5–10 mitoses/HPF. Intralesional nerve bundles were not seen. Both acute and chronic inflammatory cells were noted in all cases (Fig. 1D). The lesion was nonreactive for GLUT-1, however, showed bright positivity for WT-1 in the cytoplasm of endothelial cells as well as in the stromal cells. Ki-67 labeling index was high in all the cases and ranged from 4 to 10%.

3.3. Histopathological and immunohistochemical features of vascular malformations

The simple malformations encountered were venous type (n = 8, 53.3%) followed by lymphatic type (n = 6, 40%) and capillary malformation (n = 1, 6.7%). The combined malformations included lymphatic-venous (n = 14, 77.8%), followed by capillary-venous (n = 3, 16.7%) and capillary-lymphatic-arteriovenous (n = 1, 5.5%) type. The endothelial cells were flat and did not show any mitotic activity Fig. 3A. Intralesional bundles were seen in 26 (78.8%) cases. No significant inflammation was noted. GLUT-1 was negative in all cases and proved useful in distinguishing capillary predominant malformations from infantile hemangioma. In addition, GLUT-1 highlighted INBs by showing crisp positivity in perineurial cells, thus obviating the need to use an

additional neural stain Fig. 3C. At least focal cytoplasmic WT-1 reactivity was seen in the endothelial cells of 7 (21%) VMs (3 in lymphatic venous type and 4 in simple venous type) Fig. 3D. However, the tunica media of vessels in all cases showed WT-1 positivity. All the malformations consistently showed the Ki-67 labeling index < 2%.

3.4. Comparison between benign vascular tumors and vascular malformations (Table 2)

For comparing the histomorphological features, infantile hemangioma, congenital hemangioma, and pyogenic granuloma were grouped together as vascular tumors and compared with the malformations. It was found that plump endothelial cell morphology (p < 0.001), presence of mitotic activity (p < 0.001) and absence of intralesional nerve bundles (p < 0.001) were statistically significant in differentiating hemangioma from malformations. GLUT-1 (p < 0.001) and Ki-67 labeling index (p < 0.001) were useful immunohistochemical markers to distinguish IH from VM. Even though WT-1 was statistically significant in differentiating tumors from malformations, its positivity does not rule out the possibility of latter (positive in 21% VM). It was also noted that the number of vessel density was higher in tumors than in malformations and this was an important feature that aided in making the distinction between the two, particularly in capillary predominant lesions Fig. 3B.

4. Discussion

Based on the biological behavior and multidisciplinary approach, the ISSVA classification provides a consistent terminology and clinically relevant information to serve as a guide for pathologists, clinicians, and
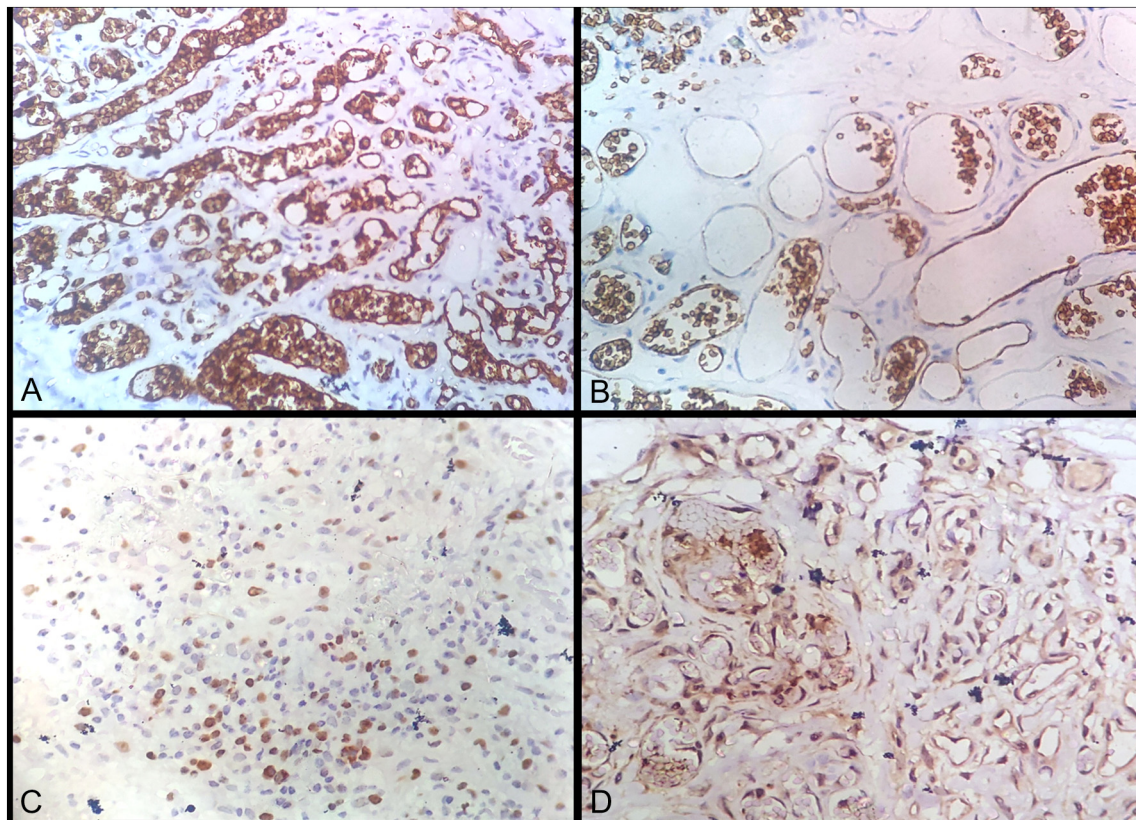
Fig. 2. (A) Endothelial cells and erythrocytes showing strong and diffuse GLUT-1 immunostaining in the proliferative phase of infantile hemangioma (400×). (B) Involuting infantile hemangioma showing focal GLUT-1 reactivity in the endothelial cells (400×). (C) High Ki-67 labeling index seen in the proliferative phase of infantile hemangioma (400×). (D) Lesional endothelial cells show WT-1 positivity in congenital hemangioma (400×).

researchers. The management of vascular anomalies has been evolving continuously. There has been a shift from surgery to pharmacotherapy in the treatment of hemangiomas. Beta-blockers are now the first-line modality for treating infantile hemangiomas requiring systemic therapy [9]. For congenital hemangiomas, a wait and watch is often the best treatment and surgery and laser are used for problematic cases only. Surgical excision with or without embolization, sclerotherapy, and pulsed dye laser is the common therapy used to manage malformations [4].

Deciding the appropriate line of treatment needs accurate diagnosis and terminology. Despite being accepted for more than two decades, ISSVA classification is still grossly underutilized by clinicians and histopathologists alike. One of the recent studies done over a period of two years found that 60.5% of British publications used incorrect terminology as per the 2018 ISSVA classification [10]. In another American review of 1-year literature of articles containing the term hemangioma, 71.3% of investigators used hemangioma wrongly to describe another vascular anomaly. It was also found that patients whose lesions were mislabelled were more likely to receive incorrect treatment when compared with patients whose anomalies were correctly classified using ISSVA terminology [5].

With appropriate and adequate clinical history most of the vascular anomalies can be correctly subclassified. The clinical growth pattern of the lesion generally allows the distinction to be made [11]. However, adequate or clear history is not always available and lesions may have an atypical appearance (i.e., the diagnosis is uncertain) or behave in a manner that is inconsistent with the expected proliferative and involution phases within the expected time frame [8,9]. For such cases, imaging and histopathology serve as adjunctive tools for reaching a correct diagnosis. Plump endothelial morphology, absence of INBs and presence of endothelial mitoses are important histopathological features to differentiate hemangiomas from VMs. Adegboyega et al. [12]

reported the presence of INBs in 91% arteriovenous malformations (n = 76) while none of the hemangioma cases showed this feature (n = 91). In contrast, we found INBs in 2 cases (28.6%) of IH. Though the above discussed histopathological features are helpful in the diagnosis, every case should be interpreted in the light of clinical and radiological features.

Histopathological examination alone may also be misleading, e.g. the distinction between infantile hemangioma and congenital hemangioma may be difficult [13], vascular malformations may be confused with involuting IH and CH due to the persistence of large draining vessels in the latter two [14]. Immunohistochemistry helps in resolving such difficult cases. The human glucose transporter protein isoform-1 (GLUT-1) is a member of glucose transporters facilitating the passive transport of glucose into the cell. GLUT-1 is highly expressed in the endothelium of barrier tissues where selective glucose transfer from the blood to tissues is crucial, such as in the central nervous system, retina, iris, ciliary muscle, endoneurium and in the placenta. The expression is also seen in erythrocytes. The protein is not expressed in the vasculature of any other normal tissue [15]. North et al. reported endothelial immunoreactivity for GLUT-1 to be a specific feature of juvenile hemangiomas during all phases of these lesions [16]. Later on, it was found that congenital nonprogressive hemangiomas were histologically and immunophenotypically distinct from infantile hemangiomas and that these were GLUT-1 negative [17]. Since then various studies have been done [13,15,18] and GLUT-1 is now considered a sensitive and specific marker for the diagnosis of IH. It serves as an important tool in differentiating IHs from close differentials like CH, capillary malformation and capillary-venous malformation. One of the practical pitfalls in the interpretation of GLUT-1 is in the capillaries filled with blood where positivity of GLUT-1 in peripheral erythrocytes gives a false impression of positivity in the endothelial cells.

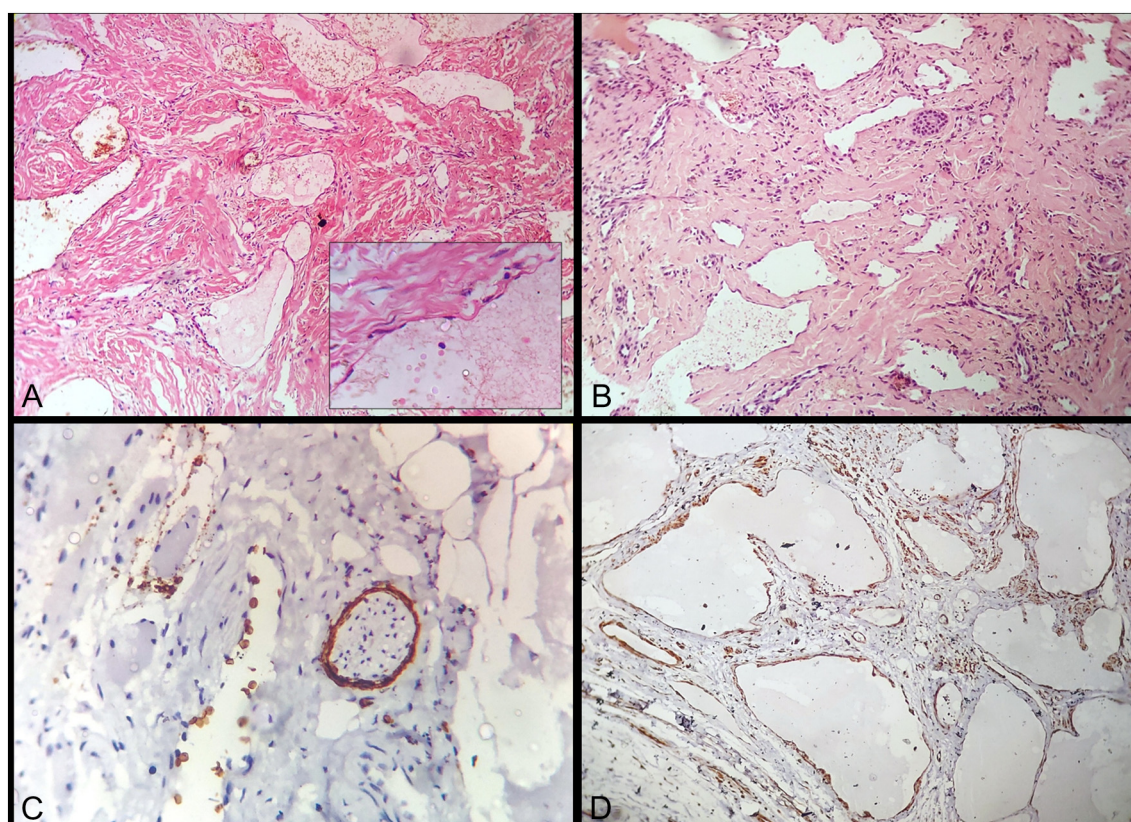WT-1 is a tumor suppressor gene encoding for a transcription factor

Fig. 3. (A) Simple venous malformation (100, H&E). Inset shows flattened endothelium of the lesional vessels (400×, H&E). (B) Capillary malformation. Note the low density of vessels in the lesion (100×, H&E). (C) GLUT-1 immunostain highlighting an intralesional nerve bundle in venous malformation (400×). (D) Focal WT-1 positivity seen in the endothelial cells of vessels in venous malformation (100×).

that contains 4 zinc-finger motifs at the C-terminus and a proline/glutamine-rich DNA-binding domain at the N-terminus [19]. In addition to being involved in the normal development of the genitourinary system, it plays an important role in regulating hematopoiesis and angiogenesis. Bone marrow stem cells show constitutive expression of *WT-1* which is maintained during their differentiation into endothelial cells [20]. Nuclear WT-1 positivity is seen in various tumors like Wilms tumor, desmoplastic small round cell tumor, and mesothelioma. Cytoplasmic immunoreaction for WT-1 has been described in vascular tumors, including hemangiomas, but not in malformations [21]. Trindade et al., however, reported WT-1 positivity in all their cases of arteriovenous malformations but not in capillary, venous or lymphatic malformations [18]. Galfione et al. also found low to intermediate positivity in 10 out of 13 vascular malformation cases. They, however, did not categorize the malformations nor classified vascular tumors based on ISSVA classification [22]. Background normal vessels, both in hemangiomas and

malformations, also stain positively for WT-1 [18,21]. In our study, lymphatic venous and simple venous malformations showed focal WT-1 positivity in the endothelial cells. Needless to say, both GLUT-1 and WT-1 immunostaining need to be done in capillary predominant lesions to differentiate between IH, CH, and VMs. Ki-67 is a well-known proliferation marker and hence is expected to be high in tumors and not in malformations.

The advances in molecular genetics have given new insights into the genetic basis of vascular anomalies, providing potential molecular targets for the development of new pharmacotherapy. Somatic mutations involving the tyrosine kinase receptor signaling through RAS or PIK3CA pathways are the commonest genetic aberrations identified in the vascular anomalies [23]. *PIK3CA* mutations have been detected in malformations and studies have shown rapamycin (mTOR inhibitor) to be effective in complicated or refractory cases [24,25]. Mutations in the same gene have been noted in biologically distinct entities, e.g., both

Table 2
Important histopathological and immunohistochemical features seen in vascular tumors and malformations.

Histopathological criteria	IH (n = 7)	NICH (n = 4)	PG (n = 4)	Tumors (IH + NICH + PG) (n = 15)	VM (n = 33)	P value*
Plump endothelial cells	6 (85.7%)	4 (100%)	4 (100%)	13 (86.6%)	0(0%)	< 0.001
Mitoses present	4 (57.1%)	3 (75%)	4 (100%)	11 (73.3%)	0 (0%)	< 0.001
INBs present	2 (28.6%)	0 (0%)	0 (0%)	2 (13.3%)	26 (78.8%)	< 0.001
Inflammation present	0 (0%)	0 (0%)	4 (100%)	4 (26.6%)	0 (0%)	0.007
WT-1 +	7 (100%)	4(100%)	4(100%)	15 (100%)	7 (21.2%)	< 0.001
GLUT-1 +	7 (66%)	0 (0%)	0(100%)	7 (46.6%)	0 (0%)	< 0.001ᵃ
Ki-67 > 2%	4 (57.1%)	3 (75%)	4(100%)	11 (73.3%)	0 (100%)	< 0.001

CH – congenital hemangioma, GLUT-1 – glucose transporter protein isoform-1, IH – infantile hemangioma, INBs – intralesional nerve bundles, PG – pyogenic granuloma, VM – vascular malformation, WT-1 – Wilms tumor-1.
 * P-value is calculated for columns 5 and 6, i.e. tumors and malformations.
 ᵃ GLUT-1 immunopositivity was noted only in infantile hemangioma amongst all the hemangiomas.

congenital hemangioma and capillary malformation show *GNAQ* or *GNA11* mutations [26-29]. Moreover, the mutant allele frequency detected in these cases is low and there are no hotspots, making the detection of these mutations possible only by high through-put techniques like next-generation sequencing which are not cost-effective for routine histopathology laboratory. Though the genetic/epigenetic landscape of these lesions is continuously evolving, in the present scenario, the clinical-radiological and histopathological diagnosis remains the basis of management for these lesions.

5. Conclusions

An etiopathogenesis based ISSVA classification of benign vascular anomalies can be reliably done on histopathology. Endothelial cell characteristics, endothelial mitotic activity, and INBs are important morphological features for their subclassification. Every case must be interpreted in the light of clinical and radiological features. GLUT-1 stain is highly sensitive and specific in differentiating IH from other benign vascular anomalies and it also highlights the INBs, an important morphological feature of VMs.

Source of funding

None.

Declaration of competing interest

None.

References

[1] Dehner LP. Stocker and Dehner's pediatric pathology. 3rd ed PA: Lippincott Williams and Wilkins; 2011 Chapter 24. Soft tissues.

[2] ISSVA Classification of Vascular Anomalies. International Society for the Study of Vascular Anomalies Available at issva.org/classification; 2018, Accessed date: 14 February 2019.

[3] Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982;69:412–22.

[4] Eivazi B, Werner JA. Management of vascular malformations and hemangiomas of the head and neck – an update. Curr Opin Otolaryngol Head Neck Surg 2013;21:157–63.

[5] Hassanein AH, Mulliken JB, Fishman SJ, Greene AK. Evaluation of terminology for vascular anomalies in current literature. Plast Reconstr Surg 2011;127:347–51.

[6] Calonje JE. Hemangiomas. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO classification of tumors of soft tissue and bone. Lyon: IARC; 2013. p. 138–40.

[7] Weiss SW, Goldblum JR. Enzinger and Weiss's soft tissue tumors. 6th ed Philadelphia, PA: Elsevier; 2014 Chapter 21. Benign vascular tumors and malformations.

[8] Singh L, Ranjan R, Arava S, Singh MK. Role of p40 and cytokeratin 5/6 in the differential diagnosis of sinonasal undifferentiated carcinoma. Ann Diagn Pathol 2014;18:261–5.

[9] Krowchuk DP, Frieden IJ, Mancini AJ, et al. Clinical practice guideline for the management of infantile hemangiomas. Pediatrics 2019;143:e20183475.

[10] Steele L, Zbeidy S, Thomson J, Flohr C. How is the term haemangioma used in the literature? An evaluation against the revised ISSVA classification. Pediatr Dermatol 2019;0:1–6.

[11] Lee BB, Antignani PL, Baraldini V, et al. ISVI-IUA consensus document diagnostic guidelines of vascular anomalies: vascular malformations and hemangiomas. Int Angiol 2015;34:333–74.

[12] Adegboyega PA, Qiu S. Hemangioma versus vascular malformation: presence of nerve bundle is a diagnostic clue for vascular malformation. Arch Pathol Lab Med 2005;129:772–5.

[13] Al-Adnani M, Williams S, Rampling D, Ashworth M, Malone M, Sebire NJ. Histopathological reporting of paediatric cutaneous vascular anomalies in relation to proposed multidisciplinary classification system. J Clin Pathol 2006;59:1278–82.

[14] North PE. Pediatric vascular tumors and malformations. Surg Pathol Clin 2010;3:455–94.

[15] Filho TJD, Oliveira DHIP, Moura ID, et al. Importance of GLUT-1 in the differential diagnosis of vascular anomalies. J Vasc Bras 2015;14:168–76.

[16] North PE, Waner M, Mizeracki A, Mihm Jr. MC. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 2000;31:11–22.

[17] North PE, Waner M, James CA, Mizeracki A, Frieden IJ, Mihm Jr. MC. Congenital nonprogressive hemangioma: a distinct clinicopathologic entity unlike infantile hemangioma. Arch Dermatol 2001;137:1607–20.

[18] Leon-Villapalos J, Wolfe K, Kangesu L. GLUT-1: an extra diagnostic tool to differentiate between haemangiomas and vascular malformations. Br J Plast Surg 2005;58:348–52.

[19] Trindade F, Tellechea O, Torrelo A, Requena L, Colmenero I. Wilms tumor 1 expression in vascular neoplasms and vascular malformations. Am J Dermatopathol 2011;33:569–72.

[20] Timar J, Meszaros L, Orosz Z, Albini A, Raso E. WT1 expression in angiogenic tumors of the skin. Histopathology 2005;47:67–73.

[21] Lawley LP, Cerimele F, Weiss SW, North P, Cohen C, Kozakewich HP, et al. Expression of Wilms tumor 1 gene distinguishes vascular malformations from proliferative endothelial lesions. Arch Dermatol 2005;141:1297–300.

[22] Galfione SK, Ro JY, Ayala AG, Ge Y. Diagnostic utility of WT-1 cytoplasmic stain in variety of vascular lesions. Int J Clin Exp Pathol 2014;7:2536–43.

[23] Greene AK, Goss JA. Vascular anomalies: from a clinicohistologic to a genetic framework. Plast Reconstr Surg 2018;141:709e–17e.

[24] Vlahovic AM, Vlahovic NS, Haxhija EQ. Sirolimus for the treatment of a massive capillary-lymphatic-venous malformation: a case report. Pediatrics 2015;136:e513–6.

[25] Triana P, Dore M, Cerezo VN, et al. Sirolimus in the treatment of vascular anomalies. Eur J Pediatr Surg 2017;27:86–90.

[26] Ayturk UM, Couto JA, Hann S, et al. Somatic activating mutations in *GNAQ* and *GNA11* are associated with congenital hemangioma. Am J Hum Genet 2016;98:789–95.

[27] Shirley MD, Tang H, Gallione CJ, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in *GNAQ*. N Engl J Med 2013;368:1971–9.

[28] Couto JA, Huang L, Vivero MP, et al. Endothelial cells from capillary malformations are enriched for somatic GNAQ mutations. Plast Reconstr Surg 2016;137:77e–82e.

[29] Couto JA, Ayturk UM, Konczyk DJ, et al. A somatic *GNA11* mutation is associated with extremity capillary malformation and overgrowth. Angiogenesis 2017;20:303–6.