Vascular Tumors in Infants: Case Report and Review of Clinical, Histopathologic, and Immunohistochemical Characteristics of Infantile Hemangioma, Pyogenic Granuloma, Noninvoluting Congenital Hemangioma, Tufted Angioma, and Kaposiform Hemangioendothelioma

Emma F. Johnson, MD, Dawn M. Davis, MD,†‡§ Megha M. Tollefson, MD,†‡ Karen Fritchie, MD,¶ and Lawrence E. Gibson, MD‖***

Abstract: Vascular tumors in infants present a diagnostic and treatment dilemma for both clinicians and pathologists. Infantile hemangioma, the most common vascular tumor in infants, can be confused for other less common vascular tumors in infants. Correct and timely diagnosis is important, as some vascular tumors can be associated with life-threatening coagulopathy. We present the cases of 5 vascular tumors that have clinical and histologic overlap: infantile hemangioma, pyogenic granuloma, noninvoluting congenital hemangioma, tufted angioma, and kaposiform hemangioendothelioma. Typical clinical and histopathologic features of each lesion are summarized. We review the utility and characteristic immunohistochemistry including CD31, CD34, GLUT-1, D2-40, LYVE-1, Prox-1, and WT-1. Collaboration between the clinician and the dermatopathologist correlating the clinical history and histopathologic features can lead to the correct diagnosis, whereas the utility of immunohistochemistry remains in question.

Key Words: vascular tumors, pediatrics, immunohistochemistry, infantile hemangioma, pyogenic granuloma, tufted angioma, kaposiform hemangioendothelioma

(*Am J Dermatopathol* 2018;40:231–239)

LEARNING OBJECTIVES

After participating in this activity, physicians should be better able to:

1. Select an appropriate clinical and histopathologic approach to work-up and diagnosis of vascular tumors in infants.
2. Assess the utility of immunohistochemical staining.
3. Evaluate the clinicopathologic correlation for correct and timely diagnosis.

From the *PGY-4 Dermatology Resident, Department of Dermatology, Mayo Clinic, Rochester, MN; †Associate Professor, Department of Dermatology, Mayo Clinic, Rochester, MN; ‡Associate Professor, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN; §Fellowship Director, Pediatric Dermatology Fellowship, Department of Dermatology, Mayo Clinic, Rochester, MN; ¶Associate Professor, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; ‖Professor, Department of Dermatology, Mayo Clinic, Rochester, MN; and **Professor, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

All authors and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organizations pertaining to this educational activity

Correspondence: Lawrence E. Gibson, MD, 200 First Street SW, Rochester, MN 55905 (e-mail: gibson.lawrence@mayo.edu).

INTRODUCTION

The correct and timely diagnosis of vascular tumors in infants can present difficulties for clinicians and dermatopathologists alike. These tumors must be differentiated both from infantile hemangiomas (IHs) and each other, as clinical course and treatment varies significantly.

Vascular anomalies can be subdivided into vascular tumors and vascular malformations. Vascular tumors are proliferative rather than static and have the potential for spontaneous resolution, whereas vascular malformations do not demonstrate proliferation nor spontaneous regression.[1] IHs are the most commonly encountered vascular tumors in infants, seen in approximately 2%–4.5% of infants.[2,3] Several vascular tumors can mimic the clinical presentation of IH. Differentiation between vascular tumors is important as clinical course can range from benign self-resolving lesions to those associated with life-threatening coagulopathy known as Kasabach–Merritt phenomenon.

We present cases of 5 vascular tumors in infants: IH, pyogenic granuloma, noninvoluting congenital hemangioma (NICH), tufted angioma (TA), and kaposiform hemangioendothelioma (KHE) to demonstrate the clinical, histopathologic, and immunohistochemical features of each.

CASE 1: INFANTILE HEMANGIOMA

A 6-month-old girl presented with an ovoid, violaceous, and telangiectatic patch on the right buttock (Fig. 1). This lesion was faintly present at birth and had begun to rapidly increase in size over the past 2 months. There was no bruit, overlying hair and the patient was otherwise well. Given the lesion was growing out of proportion to the patient's growth, a 4-mm punch biopsy was obtained. Biopsy showed uniform intradermal proliferation of small vascular spaces lined by plump endothelial cells (Fig. 1). CD31 and GLUT-1 highlighted the

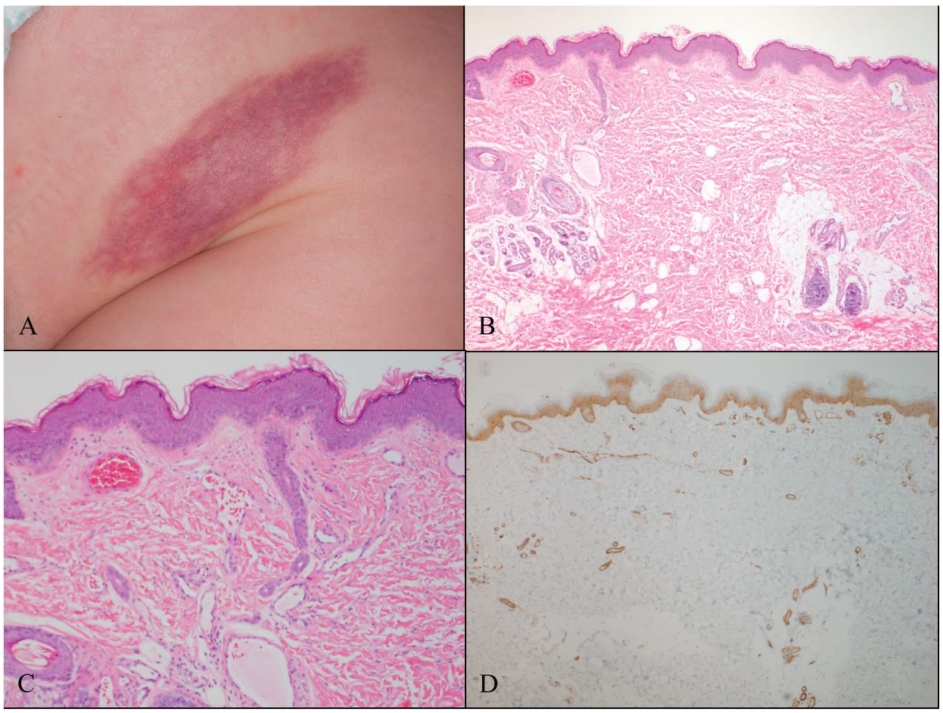

FIGURE 1. IH. A, Violaceous, vascular plaque on the right lower buttock of a 6-month-old girl. B, Dermal sheets of capillary-sized vascular channels (hematoxylin–eosin, original magnification ×40). C, Proliferation of capillaries with large lumen and thickened capillary basement membranes (hematoxylin–eosin, original magnification ×100). D, GLUT-1 immunostain highlighting the lesional capillary endothelial cells (GLUT-1 immunostain, original magnification ×40).

endothelial cells within the dermal vascular proliferation, confirming the diagnosis of IH. Clinical observation was recommended.

CASE 2: PYOGENIC GRANULOMA

A 14-month-old boy presented with a raised, erythematous papule with overlying ulceration on the right cheek (Fig. 2). This lesion developed at age 12 months and had spontaneously bled on several occasions. Given the symptomatic nature of the lesion, treatment with excision was performed. Histopathology demonstrated a pedunculated lesion of numerous small capillaries with bland endothelial cells in loose edematous, collagenous matrix (Fig. 2). Immunohistochemistry showed lesional cells to be positive for CD34 and negative for WT-1 (clone WT49) and D2-40 (podophilin).

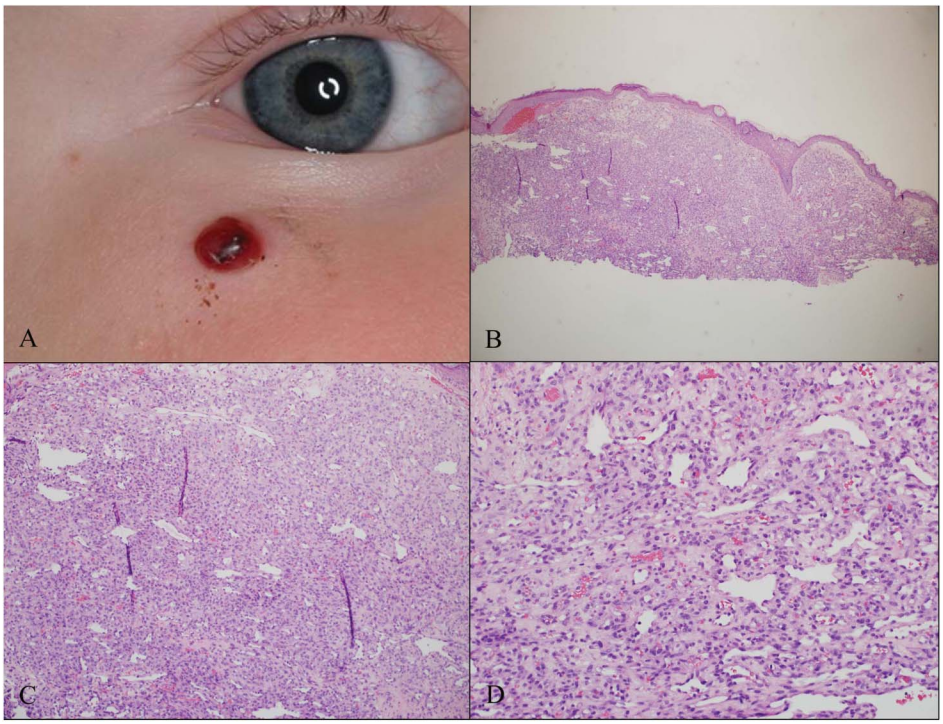

FIGURE 2. Pyogenic granuloma. A, Discrete vascular papule on the face of a 13-month-old. B, Lobular proliferation of capillary-sized vessels within the superficial dermis (hematoxylin–eosin, original magnification ×40). C, Lobules with distinct capillaries with branching lumina (hematoxylin–eosin, original magnification ×100). D, Closely packed capillary-sized vessels (hematoxylin–eosin, original magnification ×200).

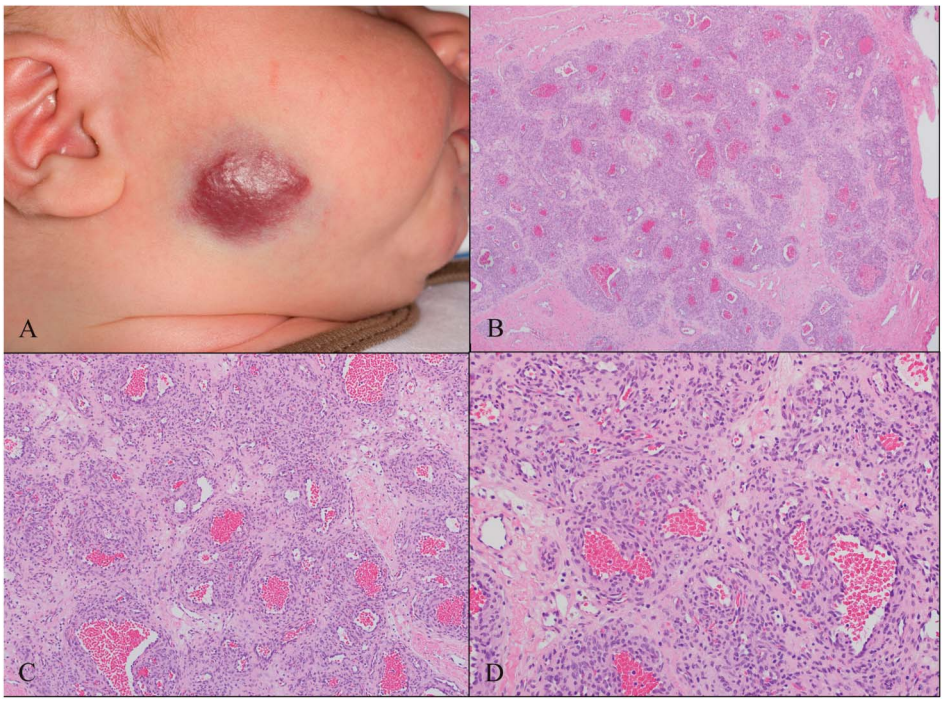

FIGURE 3. NICH. A, Indurated, vascular plaque on the lateral face of a 4-month-old infant. B, Lobular infiltration of vascular proliferation in the dermis (hematoxylin–eosin, original magnification ×40). C, Lobules of congested capillaries separated by bands of fibrosis (hematoxylin–eosin, original magnification ×100). D, Dilated capillaries surrounded by layer of pericytes (hematoxylin–eosin, original magnification ×200).

CASE 3: NONINVOLUTING CONGENITAL HEMANGIOMA

A 9-day-old male infant presented with a lesion on the left cheek present since birth. Clinical examination demonstrated an indurated, vascular plaque with a white-to-blue halo without ulceration (Fig. 3). The lesion persisted and spontaneously bled on several occasions. As the lesion was symptomatic for the patient, an excisional biopsy was performed at age 4 months. Histopathology showed lobules of congested capillaries with intervening fibrous stroma involving the mid to deep dermis (Fig. 3). Immunohistochemical staining demonstrated CD34 positivity and GLUT-1, WT-1, and D2-40 negativity.

CASE 4: TUFTED ANGIOMA

An 8-day-old male infant presented with a deeply erythematous, slightly raised plaque with a vascular halo along the ischium

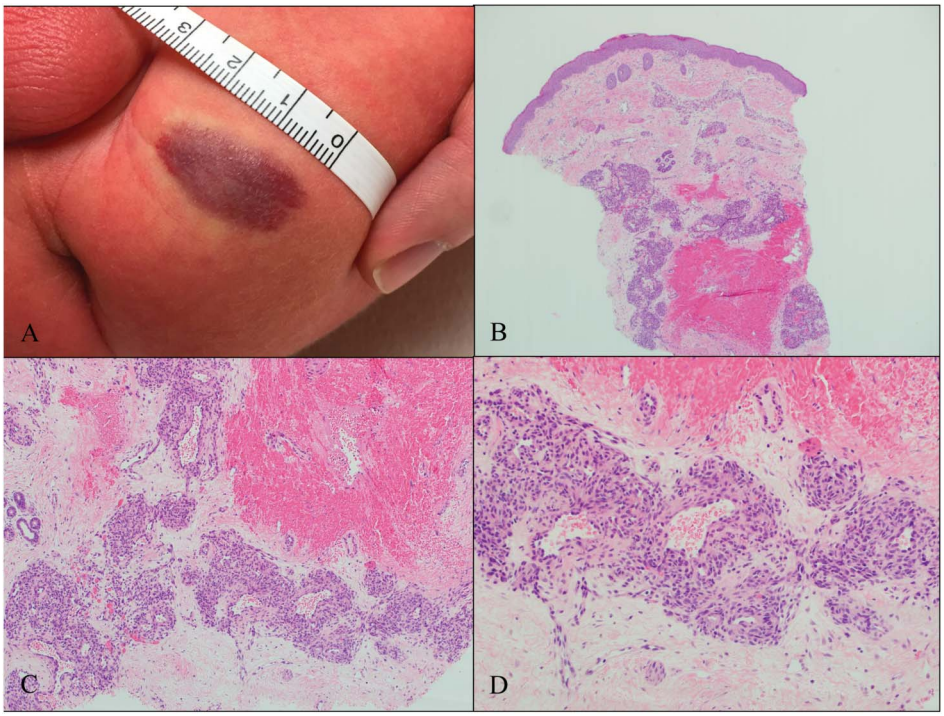

FIGURE 4. TA. A, Red-to-blue, vascular plaque on the proximal lower extremity of a 8-day-old male infant. B, Typical "cannonball" infiltration of the mid and deep dermis (hematoxylin–eosin, original magnification ×40). C, Lobules of closely packed, poorly canalized capillaries (hematoxylin–eosin, original magnification ×100). D, Capillaries lined with bland, plump endothelial cells (hematoxylin–eosin, original magnification ×200).

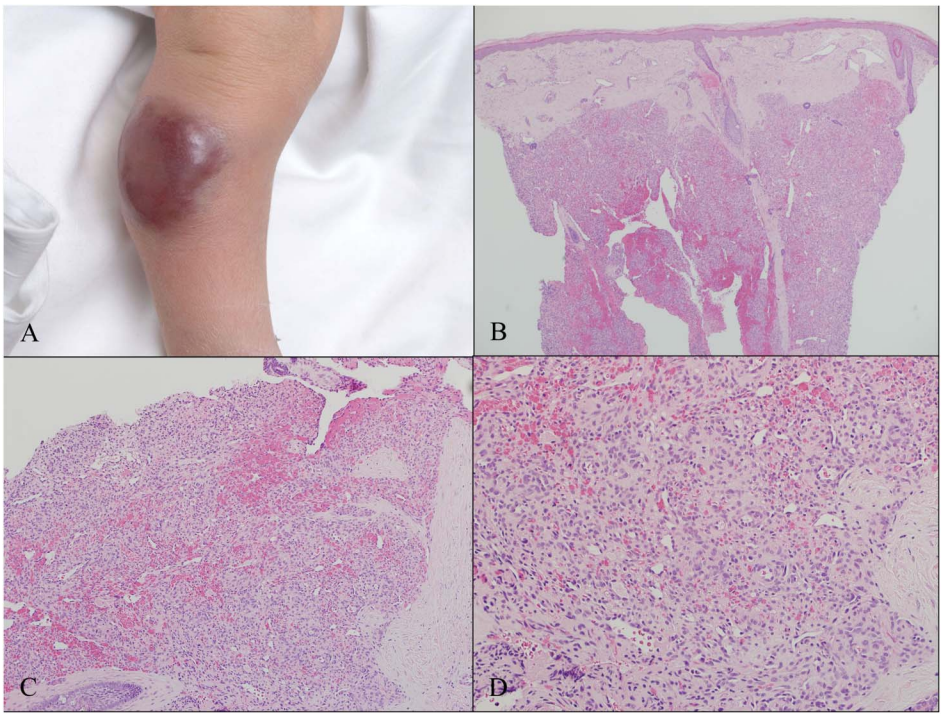

FIGURE 5. KHE. A, Indurated, violaceous vascular plaque on the lower extremity of a newbord infant. B, Dense vascular proliferation infiltrating the mid and deep dermis (hematoxylin–eosin, original magnification ×40). C, Infiltration of endothelial cells, congested capillaries and slit-like vascular spaces (hematoxylin–eosin, original magnification ×100). D, Varying sizes of vascular spaces, some capillaries show thrombosis (hematoxylin–eosin, original magnification ×200).

present since birth (Fig. 4). Biopsy was taken to confirm a diagnosis and showed typical "cannonball" distribution of lobules of closely packed and poorly canalized capillaries (Fig. 4). Immunohistochemistry showed lesional cells positive for CD34 and negative for GLUT-1, WT-1, and D2-40. Clinical observation was recommended and no coagulopathy has subsequently developed.

CASE 5: KAPOSIFORM HEMANGIOENDOTHELIOMA

A newborn baby girl was found to have a firm, nonblanchable, purple plaque on the right lateral lower leg (Fig. 5). Given the induration, size, and clinical appearance, an excisional biopsy was performed. Histopathology showed a dense, deep infiltrate of endothelial cells, congestive capillaries, and slit-like vascular spaces. Peripheral capillaries showed rare thrombosis (Fig. 5). Immunohistochemistry showed lesional cells positive for CD31 positivity, focally positive for D2-40, and negative for GLUT-1 and WT-1. Complete blood count and coagulation studies were obtained to rule out a consumptive coagulopathy. Laboratory results were within normal limits. The patient's family was instructed to monitor for any changes in firmness, size, associated pain, or color which could portend a coagulopathy. Serial clinical and laboratory monitoring every 3 months was recommended.

DISCUSSION

Vascular tumors in infants present a diagnostic challenge for both clinicians and dermatopathologists. The

TABLE 1. Clinical Features of Selected Vascular Tumors in Infants

	IH	Pyogenic Granuloma	NICH	TA	KHE
Present at birth (congenital)	15%–60% present at birth, generally become apparent in the first few weeks of life	9% diagnosed between 1 and 12 months of age	Yes	15% present at birth, acquired early in infancy	60% present at or within 1 month of birth
Location predilection	50% occur on head and neck	Cheek and forehead	Extremities, postauricular	Upper trunk, neck/shoulders	Extremities, trunk
Evolution	Early rapid increase in size, continued slow growth, and plateau and involution during first years of life	Tendency of contact bleeding, do not involute spontaneously	Proportionate postnatal growth	Variable: spontaneous regression, no change, or enlargement and progression	Enlarging mass, pain, swelling
Painful	No	Variable	No	Variable	Variable
Associated with Kasabach–Merritt Phenomena	No	No	No	Less frequent than KHE, up to 38%	Up to 71% develop KMP

KMP, Kasabach–Merritt phenomena.

TABLE 2. Histopathology and Immunohistochemistry of Selected Vascular Tumors in Infancy

Entity	Histopathology
IH	Dermal proliferation of lobules and sheets of tightly packed, capillary-sized vessels lined with plump endothelial cells. Moderate mitotic figures are present. Mast cells and dermal dendrocyte frequent within stroma.
Pyogenic granuloma	Exophytic, lobulated, dermal mass. Numerous small capillaries with bland endothelial cells in well-developed lobular architecture, variable superficial acute and chronic inflammatory cells.
NICH/RICH	Lobules of congested capillaries surrounded by layer of pericytes separated by bands of fibrosis. Variably atrophic epidermis and adnexal structure. Involving subcutaneous tissue and dermis.
TA	Typical "cannonball" distribution of lobules of closely packed poorly canalized capillaries lined with bland endothelial cells and surrounded by pericytes. Involving the dermis and superficial subcutis. Dilated crescent-shaped/semilunar lymphatic channels at periphery.
KHE	Lobular, infiltrative fascicles of endothelial cells, congested capillaries, slit-like vascular spaces, and epithelioid endothelial cells. Capillary may show thrombosis.

Entity	GLUT-1	WT-1	CD31	CD34	D2-40	LYVE-1	Prox-1
IH	+	+	+	+	−	+	−
Pyogenic granuloma	−	+	+	+	−	−	−
NICH	−	+	+	+	−	−	−
TA	−	+	+	+	+ (focally)	+ (focally)	+
KHE	−	NR	+	+ (focally)	+	+ (focally)	+

NR, not reported.

clinical picture is often very similar, presenting as a vascular plaque or nodule at birth or shortly thereafter. Histopathologically the lesions demonstrate considerable overlap. Correct diagnosis is important as work-up, treatment, and monitoring for these lesions vary. Although IHs and rapidly involuting congenital hemangiomas (RICHs) generally demonstrate spontaneous involution, TA and KHE can be associated with serious systemic complications, such as Kasabach–Merritt syndrome. To differentiate between the vascular tumors in infancy, a multidisciplinary approach, including clinical and histopathologic examination are of utmost importance.

Classic clinical characteristics for each entity are summarized in Table 1. Specifically, worrisome signs and symptoms of a more serious vascular tumor is tumor location, impact on functionality, larger tumor size, localized tenderness, and the presence of increased hair growth.[4] Observation for enlargement, change in color, tenderness, or induration is important diagnostically and in forming a treatment plan as this can portend a coagulopathy.

Although these vascular tumors often show morphologic similarities, there are some helpful features that may aid in correct diagnosis (Table 2). IH is commonly diagnosed clinically, but histopathology demonstrating dermally based, lobular capillary-sized vascular channels lined with plump endothelial cells can help make the diagnosis. The lobular and well-developed nature of pyogenic granuloma helps to differentiate from other vascular tumors. Although NICH also demonstrates a lobular architecture, this lesion often shows the presence of bands of fibrosis around tumor lobules, variability in the size of vascular channels, and presence of arteriovenous fistulae.[5] TA and KHE are both characterized by the presence of scattered, rounded lobules of closely packed capillaries in typical "cannonball" distribution in the dermis, and superficial subcutis. This histopathologic overlap suggests that the 2 tumors represent a spectrum rather than distinct tumors.[6,7] This overlap is further demonstrated by the similar immunophenotypes and potential for both tumors to induce Kasabach–Merritt syndrome, a potentially life-threatening consumptive coagulopathy defined by clinically significant thrombocytopenia in association with a rapidly enlarging vascular tumor.[8]

Taken in concert with clinical and histopathologic characteristics, immunohistochemistry can be a helpful ancillary tool in the classification of vascular tumors (Table 2). IHs can be differentiated from other vascular tumors by glucose transporter (GLUT) 1 expression which is present in IH but not other vascular tumors seen in infants.[1] Immunohistochemistry staining demonstrates D2-40, Prox-1, and LYVE-1 expression in KHE and TA and is negative in PG, NICH, and RICH.[7,9] Authors have suggested TA is characterized by more focal expression and restriction of staining to the periphery of lymphatic markers (Prox1, D2-40, and LYVE-1) compared with KHE.[7,10]

Finally, WT-1 has been reported to be helpful in differentiating vascular neoplasms from vascular malformations.[11–13] WT-1 is reported to be positive in RICH, TA, and PG.[11,12,14] However, there are 2 clones commercially available, WT 49 (used in our cases) and WT 6F-H2 (used in cases reported in literature). All of the vascular tumors in the cases presented stained negatively for WT-1 (WT 49 clone). We hypothesize that these 2 clones cannot be used interchangeably for the staining of vascular tumors. Further studies with additional cases would be necessary to validate this theory.

In conclusion, we provide a clinical, pathological, and immunophenotypic review of select vascular tumors in infants. These tumors exhibit many overlapping clinical and histopathologic features leading to diagnostic challenges. Immunohistologic profiles are helpful but cannot be relied on in isolation to render a diagnosis. Consequently, clinicopathologic correlation is of utmost importance for acute diagnosis and appropriate treatment.

REFERENCES

1. Hoeger PH, Colmenero I. Vascular tumours in infants. Part I: benign vascular tumours other than infantile haemangioma. *Br J Dermatol.* 2014;171:466–473.
2. Sidbury R. Update on vascular tumors of infancy. *Curr Opin Pediatr.* 2010;22:432–437.
3. Anderson KR, Schoch JJ, Lohse CM, et al. Increasing incidence of infantile hemangiomas (IH) over the past 35 years: correlation with decreasing gestational age at birth and birth weight. *J Am Acad Dermatol.* 2016;74:120–126.
4. Frieden IJ, Rogers M, Garzon MC. Conditions masquerading as infantile haemangioma: part 1. *Australas J Dermatol.* 2009;50:77–97.
5. Lee PW, Frieden IJ, Streicher JL, et al. Characteristics of noninvoluting congenital hemangioma: a retrospective review. *J Am Acad Dermatol.* 2014;70:899–903.
6. Chu CY, Hsiao CH, Chiu HC. Transformation between Kaposiform hemangioendothelioma and tufted angioma. *Dermatology*. 2003;206: 334–337.
7. Le Huu AR, Jokinen CH, Rubin BP, et al. Expression of prox1, lymphatic endothelial nuclear transcription factor, in Kaposiform hemangioendothelioma and tufted angioma. *Am J Surg Pathol.* 2010;34: 1563–1573.
8. Chan S, Cassarino DS. Rapidly enlarging "bruise" on the back of an infant. Kaposiform hemangioendothelioma complicated by Kasabach-Merritt syndrome. *JAMA Dermatol.* 2013;149:1337–1338.
9. Debelenko LV, Perez-Atayde AR, Mulliken JB, et al. D2-40 immunohistochemical analysis of pediatric vascular tumors reveals positivity in kaposiform hemangioendothelioma. *Mod Pathol.* 2005;18:1454–1460.
10. Arai E, Kuramochi A, Tsuchida T, et al. Usefulness of D2-40 immunohistochemistry for differentiation between kaposiform hemangioendothelioma and tufted angioma. *J Cutan Pathol.* 2006;33:492–497.
11. Trindade F, Tellechea O, Torrelo A, et al. Wilms tumor 1 expression in vascular neoplasms and vascular malformations. *Am J Dermatopathol.* 2011;33:569–572.
12. Lawley LP, Cerimele F, Weiss SW, et al. Expression of Wilms tumor 1 gene distinguishes vascular malformations from proliferative endothelial lesions. *Arch Dermatol.* 2005;141:1297–1300.
13. Tsuta K, Kato Y, Tochigi N, et al. Comparison of different clones (WT49 versus 6F-H2) of WT-1 antibodies for immunohistochemical diagnosis of malignant pleural mesothelioma. *Appl Immunohistochem Mol Morphol.* 2009;17:126–130.
14. Funk T, Lim Y, Kulungowski AM, et al. Symptomatic congenital hemangioma and congenital hemangiomatosis associated with a somatic activating mutation in GNA11. *JAMA Dermatol.* 2016;152:1015–1020.

CME EXAM
INSTRUCTIONS FOR OBTAINING *AMA PRA CATEGORY 1 CREDITS*™

The American Journal of Dermatopathology includes CME-certified content that is designed to meet the educational needs of its readers.

An annual total of *12 AMA PRA Category 1 Credits*™ is available through the twelve 2018 issues of The American Journal of Dermatopathology. This activity is available for credit through March 31, 2019.

Accreditation Statement

Lippincott Continuing Medical Education Institute, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation Statement

Lippincott Continuing Medical Education Institute, Inc., designates this journal-based CME activity for a maximum of one (1) *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

To earn CME credit, you must read the article in The American Journal of Dermatopathology and complete the quiz, answering at least 80 percent of the questions correctly. Mail the Answer Sheet along with a check or money order for the $15 processing fee, to Lippincott CME Institute, Inc., Wolters Kluwer Health, Two Commerce Square, 2001 Market Street, 3rd Floor, Philadelphia, PA 19103. Only the first entry will be considered for credit, and must be postmarked by the expiration date. Answer sheets will be graded and certificates will be mailed to each participant within 6 to 8 weeks of participation. Visit http://cme.lww.com for immediate results, other CME activities, and your personalized CME planner tool.

CME EXAMINATION
April 2018

Please mark your answers on the ANSWER SHEET.

After participating in this activity, physicians should be better able to achieve the following: Improved clinical and histopathologic approach to the work-up and diagnosis of vascular tumors in infants. Increased understanding of the utility of immunohistochemical staining in the diagnosis of vascular tumors in infants. Appreciation of the necessity for clinicopathologic correlation for the correct and timely diagnosis of vascular tumors in infants.

1. A newborn boy presents with a rapidly enlarging, indurated, vascular plaque on the arm. What is the boy at risk for?
   a. Platelet consumptive disorder (Kasabach-Merritt Phenomenon)
   b. Underlying malignancy
   c. Blindness
   d. Congestive heart failure
2. A four-month-old child has a vascular appearing lesion on the temple. Biopsy shows GLUT-1 positivity. What is the most likely diagnosis?
   a. Non-involuting congenital hemangioma
   b. Pyogenic granuloma
   c. Infantile hemangioma
   d. Tufted angioma
3. Which of the following is most commonly associated with Kasabach-Merritt Phenomenon?
   a. Infantile hemangioma
   b. Non-involuting congenital hemangioma
   c. Tufted angioma
   d. Kaposiform Hemangioendothelioma
4. Which of the following immunohistochemical stains is most helpful differentiating Kaposiform Hemangioendothelioma from other vascular tumors in infants?
   a. GLUT-1
   b. WT-1
   c. CD-34
   d. Prox-1

5. A seven-month-old male has a reddish-blue vascular plaque on the lower extremity. Biopsy demonstrates lobules of capillaries in a "cannonball" distribution within the dermis. Immunohistochemistry demonstrates negative GLUT-1 staining and positive WT-1, CD-31, CD-34, Prox-1 staining with focal positivity of D2-40 and LYVE-1. What is the most likely diagnosis?
   a. Infantile hemangioma
   b. Kaposiform hemangioendothelioma
   c. Tufted angioma
   d. Non-involuting congenital hemangioma

ANSWER SHEET FOR THE AMERICAN JOURNAL OF DERMATOPHATHOLOGY
CME PROGRAM EXAM
April 2018

Please answer the questions on pages 237-238 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): _____
Street Address _____
City/State/Zip _____
Daytime Phone _____
Specialty _____

1. (A) (B) (C) (D)
2. (A) (B) (C) (D)
3. (A) (B) (C) (D)
4. (A) (B) (C) (D)
5. (A) (B) (C) (D)

Your evaluation of this CME activity will help guide future planning. Please respond to the following questions below.

Please rate these activities (1 — minimally, 5 — completely)	1 2 3 4 5
These activities were effective in meeting the educational objectives	O O O O O
These activities were appropriately evidence-based	O O O O O
These activities were relevant to my practice	O O O O O

Please rate your ability to achieve the following objectives, both before and after this activity: 1 (minimally) to 5 (completely)

After participating in this CME activity participants should be able to:	Pre 1 2 3 4 5	Post 1 2 3 4 5
1. Select an appropriate clinical and histopathologic approach to work-up and diagnosis of vascular tumors in infants.	O O O O O	O O O O O
2. Assess the utility of immunohistochemical staining.	O O O O O	O O O O O
3. Evaluate the clinicopathologic correlation for correct and timely diagnosis.	O O O O O	O O O O O

Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 — definitely will not change, 5 — definitely will change)	1 2 3 4 5
	O O O O O

4. How many patients are likely to be impacted by what you learned from this activity?
o <20% o 20-40% o 40-60% o 60-80% o >80%

5. Please list at least one (1) change you will make to your practice as a result of this activity: _____

6. How will you apply what you learned from these activities (mark all that apply):

- o In diagnosing patients
- o In monitoring patients
- o In educating students and colleagues
- o As part of the quality or performance improvement project
- o For maintenance of board certification
- o In making treatment decisions
- o As a foundation to learn more
- o In educating patients and their caregivers
- o To confirm current practice
- o For maintenance of licensure

7. How committed are you to applying this activity to your practice in the ways you indicated above? 1 2 3 4 5
(1 —definitely will not change, 5 — definitely will change) o o o o o

8. Did you perceive any bias for or against any commercial products or devices? **Yes** **No**
If yes, please explain: o o

9. How long did it take you to complete these activities? _____hours _____minutes

What are your biggest clinical challenges related to dermatopathology?

[ ] Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box)

Mail the completed Answer Sheet and a check or money order for the $15 processing fee by March 31, 2019 to:
Lippincott CME Institute, Inc.
Wolters Kluwer Health
Two Commerce Square
2001 Market Street, 3rd Floor
Philadelphia, PA 19103