Multifocal Lymphangioendotheliomatosis With Thrombocytopenia
A Newly Recognized Clinicopathological Entity

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Background: Severe thrombocytopenic coagulopathy may complicate platelet-trapping vascular tumors such as kaposiform hemangioendothelioma and tufted angioma. Low-grade, chronic consumptive coagulopathy may occur with extensive venous and lymphatic malformations. We have also observed patients with rare multifocal, congenital skin and gastrointestinal (GI) tract vascular anomalies of distinctive and remarkably similar appearance, all associated with coagulopathy. We studied the clinical and histopathologic features of 3 patients demonstrating this previously uninvestigated phenomenon.

Observations: All 3 patients presented with hundreds of congenital red-brown skin plaques as large as a few centimeters, with similar lesions throughout the GI tract and severe GI tract bleeding. One patient had synovial involvement. All had significant thrombocytopenia, with prothrombin and partial thromboplastin times and fibrinogen levels near the reference range. Corticosteroids and/or interferon alfa treatment resulted in equivocal or no improvement. Skin lesions from all 3 patients were histologically distinctive and similar, including dilated, thin-walled vessels in the dermis and subcutis lined by hobnailed, proliferative endothelial cells (10%-15% immunoreactive for Ki-67), most displaying intraluminal papillary projections. Immunoreaction for the lymphatic marker LYVE-1 was uniformly present.

Conclusions: We propose the term multifocal lymphangioendotheliomatosis with thrombocytopenia to distinguish this newly recognized clinicopathological entity. These congenital lesions, like tufted angioma and kaposiform hemangioendothelioma, show lymphatic differentiation, strengthening the association between abnormal lymphatic endothelium and coagulopathy.

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MULTIFOCAL VASCULAR tumors and malformations are relatively unusual among vascular anomalies, but are characteristic of several well-defined disorders. These include so-called neonatal hemangiomatosis (benign and disseminated),1 blue rubber bleb nevus syndrome,2 glomuvenous malformations,3,4 Maffucci syndrome,5 hereditary hemorrhagic telangiectasia,6,8 familial cutaneous capillary malformations,9,10 and familial multiple mucocutaneous venous malformations.11,12 We herein describe 3 patients with an entirely different disorder, characterized by multiple congenital and progressive cutaneous and gastrointestinal (GI) tract vascular lesions with occasional involvement of other anatomic sites, coagulopathy, and distinctive histopathologic features resembling those of solitary acquired lesions recently classified as benign lymphangioendothelioma13 and previously as acquired progressive lymphangiomia.14 We propose the term multifocal lymphangioendotheliomatosis with thrombocytopenia to describe this unique and potentially life-threatening condition.

METHODS

Three patients with an unusual and remarkably similar clinical presentation characterized by multiple discrete cutaneous and GI tract vascular anomalies associated with coagulopathy were identified independently at 3 different institutions. Medical records were reviewed, and hematoxylin-eosin-stained tissue sections were reviewed and compared by one of us (P.E.N.). Biopsy specimens included skin samples of the lower back and right hip synovium (patient 1, aged 3-6 years), a punch biopsy specimen from a left buttock lesion (patient 2, aged 6 years), and a resection specimen from the chest (patient 3, aged 13 years 9 months). Histochemical, immunohistochemical, and immunofluorescent studies, including evaluation for expression of the lymphatic marker LYVE-1,15 were performed.

For immunofluorescent microscopy, paraffin-embedded sections (6-µm thickness) were deparaffinized, rehydrated, and treated with 0.01% protease XXIV (Sigma-Aldrich Corp,
StLouis, Mo) in phosphate-buffered saline solution for 20 minutes at 37°C. Sections were double-stained using a rabbit polyclonal antibody against human LYVE-1 (1:600) (a generous gift from D. Jackson, PhD, John Radcliffe Hospital, Oxford, England), and a mouse monoclonal anti–human CD31 antibody (1:40; DAKO Corporation, Carpinteria, Calif), followed by incubation with respective secondary antibodies labeled with Texas (Jackson Immunoresearch Laboratories, Inc, West Grove, Pa) (1:50) or fluorescein isothiocyanate (1:50) as described. Cell nuclei were counterstained with Hoechst bisbenzimide (Sigma-Aldrich Corp) at 20 mg/mL. For immunohistochemistry, paraffin-embedded sections were deparaffinized, rehydrated, and subjected to antigen retrieval using a steamer method. Sections for CD31 immunoreaction were pre-treated with pronase (S2013; DAKO Corporation) for 6 minutes before antigen retrieval. Sections were protein blocked before incubation with primary antibodies under optimal conditions (Table 1). Bound antibody was detected using an LSAB+ (DAKO Corporation) peroxidase kit and DAB+ (DAKO Corporation) chromagem. Negative controls were processed in parallel without primary antibody.

Table 1. Antibodies and Conditions Used for Immunoperoxidase Immunohistochemistry*

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigen Recognized</th>
<th>Type</th>
<th>Dilution and Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYM</td>
<td>12-Amino acid C terminal of human GLUT1</td>
<td>Polyclonal rabbit</td>
<td>1:500; 30 min (RT)</td>
</tr>
<tr>
<td>1A4</td>
<td>α-Smooth muscle actin</td>
<td>Monoclonal mouse, IgG2a</td>
<td>1:100; 30 min (RT)</td>
</tr>
<tr>
<td>JC/70A</td>
<td>CD31 (PECAM)</td>
<td>Monoclonal mouse, IgG1</td>
<td>1:100; Overnight</td>
</tr>
<tr>
<td>MIB-1</td>
<td>Ki-67</td>
<td>Monoclonal mouse, IgG1</td>
<td>1:100; 30 min (RT)</td>
</tr>
<tr>
<td>h-CD1</td>
<td>h-Caldesmon</td>
<td>Monoclonal mouse, IgG1</td>
<td>1:100; 30 min (RT)</td>
</tr>
</tbody>
</table>

Abbreviations: GLUT1, glucose transporter protein isoform 1; PECAM, platelet/endothelial cell adhesion molecule; RT, room temperature. *All antibodies were supplied by DAKO Corporation, Carpinteria, Calif. All tissue sections were paraffin embedded.

RESULTS

PATIENT 1

A boy, the product of an uncomplicated 35-week pregnancy, was born with hundreds of cutaneous vascular lesions. There was no family history of similar lesions. Results of a skin biopsy reportedly showed dilated capillaries, without evidence of a vascular tumor. His platelet count at birth was $33 \times 10^9/\mu L$, but increased with oral prednisone therapy. Two weeks postnatally, he was readmitted with GI tract bleeding, and endoscopy revealed diffusely distributed mucosal vascular lesions in the stomach and sigmoid colon. Continued GI tract bleeding and thrombocytopenia necessitated approximately 250 transfusions. His thrombocytopenia fluctuated from 10 $\times 10^9/\mu L$ to reference levels, but was most commonly $30 \times 10^9/\mu L$ to $50 \times 10^9/\mu L$. He did not respond to therapy consisting of systemic corticosteroids or interferon alfa-2a. At 3 months of age, he underwent gastrostomy and suture ligation of multiple gastric hemangiomas, followed by partial colectomy at 1 year of age to remove profusely bleeding vascular lesions, resulting in resolution of intestinal bleeding. He did well until 5 years of age, when he was referred to the University of California–San Francisco for severe right hip pain, a limp, a leg length difference of 2 cm, flexion contracture of the right hip, and persistent skin lesions.

Examination revealed a healthy-appearing boy with hundreds of skin lesions varying in diameter from a few millimeters to several centimeters (Figure 1). The lesions were red-brown to burgundy in color, round to oval in shape, some with a slightly scaly surface (Figure 1C). Although most were superficial, several were indurated, suggesting deeper dermal or subcutaneous involvement.

An incisional biopsy specimen from a truncal lesion demonstrated an abnormal complement of small, ectatic, thin-walled vessels scattered throughout the reticular dermis and subcutis. These vessels, largely devoid of intraluminal erythrocytes, were lined by a monolayer of slightly hobnail endothelial cells that focally formed intraluminal papillary projections (Figure 2). Most lesional vessels had 1 or more simple, fingerlike projections, and some displayed moderately complex papillary tufts appearing to float freely in the luminal plane of section. Thrombi were not evident. Papillary stromal cores and cells lining the papillae showed strongly positive periodic acid–Schiff reaction, consistent with basement membrane material. These areas were immunonegative for $\alpha$-light chains (not shown), ruling out accumulation of immunoglobulins. Cells lining the component vessels and papillae were endothelial in nature, as evidenced by CD31 immunoreactivity. A small number of cells closely apposed to endothelial cells lining the vessels and papillary fronds were immunopositive for $\alpha$-smooth muscle actin (SMA); these were immunonegative for the well-differentiated smooth muscle marker h-caldesmon. Although no mitotic figures were evident, approximately 15% of the lesional vascular cells were positive for the cell proliferation marker Ki-67. Lesional endothelial cells strongly expressed the lymphatic marker LYVE-1 and the panendothelial marker CD31 (Figure 3A). Findings were negative for the infantile hemangioma–associated marker GLUT1.

A biopsy specimen from the right hip synovium at 6 years of age revealed a relatively sparse proliferation of small vessels, lined by a single layer of endothelial cells rimmed by a few loosely arranged stromal cells. The perivascular stroma was notably myxoid with scattered hemosiderin deposits, a few extravasated red blood cells, and a scant chronic inflammatory infiltrate. During the next 2 years, skin lesions continued to increase in number and size, particularly on the torso. Bone scan findings demonstrated increased uptake in the right hip and left calcaneus, but were otherwise negative. The patient continues to be seen for chronic orthopedic problems, with mild, intermittent coagulopathy.
PATIENT 2

A white girl presented to The Cleveland Clinic dermatology service, Cleveland, Ohio, at 6 years of age (Figure 4) with a history of hundreds of congenital brown-red papules and nodules, ranging in size from 0.5 to 6 cm, on her trunk and extremities. Episodic severe GI tract bleeding requiring transfusion had begun in the neonatal period and continued into childhood. Family history was negative for similar disorders. Endoscopy demonstrated multifocal mucosal vascular lesions in the stomach and intestines. She was treated with corticosteroids for continuing episodes of GI tract bleeding, with equivocal response. Her platelet count ranged from $33 \times 10^3/\mu L$ to $75 \times 10^3/\mu L$. Her medical history was further remarkable for vesicoureteral reflux and recurrent urinary tract infections. “Moth-eaten” bone lesions throughout the skeleton were attributed to long-term corticosteroid therapy. Over time, new subcutaneous skin lesions developed, prompting dermatology referral at 6 years of age.

Results of a punch biopsy of a skin lesion on the back revealed isolated groupings of small, delicate vessels containing intraluminal papillary projections, clustered primarily at the dermal-subcutaneous junction, but also present in the midreticular dermis. As in patient 1, the endothelial cells lining these vessels were immunopositive for LYVE-1 as well as CD31 (Figure 3B); approximately 10% showed nuclear Ki-67 immunoreactivity.

PATIENT 3

A boy who was the full-term product of an uncomplicated pregnancy displayed hundreds of small cutaneous vascular papules and plaques similar to those of patients 1 and 2 at birth. Family history was negative for similar disorders. At 1 month of age, he was admitted to the Hopital Nacional de Pediatría in Buenos Aires, Argentina, with acute GI tract bleeding. In addition to many small cutaneous lesions, a large segmental lesion involving the maxillary division of the left cranial nerve V dermatome was noted. Endoscopic evaluation revealed lesions of similar appearance in the gastric antrum and the small and large intestines. He required multiple blood transfusions as an infant and received systemic corticosteroids. At 1 year of age he had recurrent intestinal bleeding, increased number of skin lesions, decreased platelet level ($18 \times 10^3/\mu L$) with a fibrinogen level in the reference range, and prothrombin and partial thromboplastin times that varied from the reference range to mildly elevated. His intestinal bleeding stabilized, and he had no further episodes of bleeding after 3 years of age.

By 11 years of age, he had additional cutaneous lesions (Figure 5) and was significantly disfigured by a large congenital facial lesion. A portion of the large nasal/cheek lesion was removed at the age of 13 years 9 months, revealing an extensive dermal network of dilated, angulated vascular spaces with the appearance of lymphatics, dissecting the dermal collagen and creating stromal and adnexal islands surrounded by thin-walled vascular spaces containing endothelium-lined papillary projections (Figure 6A and B). Cells lining these vessels and papillae were strongly immunopositive for the panendothelial marker CD31 (Figure 6C) and were associated with a variable complement of SMA-positive/h-caldesmon–negative pericytes (Figure 6D). As in the lesions from patients 1 and 2, lesional endothelial cells coexpressed LYVE-1 and CD31, consistent with lymphatic differentiation (Figure 3C).

COMMENT

We herein report the clinical and histopathologic features of 3 patients with remarkably similar patterns of congenital and progressive disease, characterized by multifocal cutaneous and GI tract vascular lesions resulting in severe GI tract bleeding beginning in early infancy. Sy-
Novial involvement is additionally present in one of these patients. All 3 have chronic, albeit fluctuating thrombocytenia, and their vascular lesions display distinctive histological features consistent with lymphatic endothelial origin and low-grade proliferative activity. The lesional vessels in these patients are immunoreactive for LYVE-1, a lymphatic endothelial cell-specific marker in normal tissues, including skin,15,16,19 and in tumor-associated lymphatic vessels.17,20,21 On the basis of this striking and previously unrecognized constellation of clinical and pathological features, including positive findings for LYVE-1 and lymphatic morphologic features, we suggest the name multifocal lymphangioendotheliomatosis with thrombocytopenia for this rare disorder.

One previously reported case had clinical features similar to those described herein. In 1987, Odell et al22...
described a patient with infantile hemorrhagic angiodyplasia. This neonate presented with multiple congenital skin lesions, severe thrombocytopenia, and GI tract hemorrhage that did not respond to corticosteroid therapy. She died at 7 months of age as a result of GI tract hemorrhage and sepsis. Autopsy showed no other areas of visceral involvement. Published photographs show cutaneous lesions virtually identical to those seen in our patients. The pathological characteristics of this case, with limited photomicrographic documentation, were described as “congeries of dilated capillaries, arterioles, and postcapillary venules,” but in all other aspects this patient is similar to ours.

A number of other multifocal vascular skin disorders presenting at birth, in infancy, or in childhood have been described (Table 2). The skin lesions in our 3 patients, however, are unique in their clinical and histological appearance, and far more numerous than would be typical in any of these conditions except for diffuse infantile hemangiomatosis. The morphologic characteristics of cutaneous lesions in multifocal lymphangiendotheliosis with thrombocytopenia are quite distinctive, characterized by flat or indurated papules and plaques with a red-brown to burgundy color. Many have central pallor, and in some cases central scarlike areas. Slowly progressive onset of new lesions was observed in all cases, without clinical evidence of regression. Multifocal infantile hemangiomas, by contrast, are typically bright red and dome-shaped or nodular in clinical appearance. They typically present in the first few weeks of life and disappear or involute significantly by 5 years of age. Blue rubber bleb nevus syndrome is characterized by multiple venous malformations involving the skin and GI tract, blue in color, and usually very compressible, with clinical appearances including classic nipple-like lesions, small punctate papules, and larger disfiguring lesions. These lesions may slowly increase in number over time (as in our patients), but remain far fewer in total number. Multifocal venous malformations with glomus cells (eg, glomuvenous malformations and glomangiomas) are clinically similar to but distinguishable from venous malformations, typically involving a large cutaneous area as multiple, soft, red-to-blue nodules that may be widely distributed or confluent, or as pink to deep blue, cobblestonelike plaques that typically thicken with time. Maffucci syndrome is usually not congenitally evident, but develops during childhood as multiple bulging, firm, blue-to-purple vascular lesions that are most prominent on the distal extremities. These lie deeper in the dermis and subcutis than the lesions in our patients; patients with Maffucci syndrome develop further in showing lytic bone lesions, whereas GI tract involvement is absent. Hereditary hemorrhagic telangiectasia only rarely presents in early infancy; mucocutaneous lesions typically present first on the tongue and oral mucosa, and later involve the face and extremities during adulthood, most often as small red-to-purple papules with radiating peripheral telangiectasias.

The distinctive histological appearance of the lesions we have observed are also quite different from those described for other conditions characterized by multiple vascular lesions presenting at birth, with or without GI tract involvement. Multiple infantile hemangiomas are vascular tumors composed of microvessels that strongly express a number of unusual antigens, including GLUT1 and Lewis Y antigen, that are also expressed by placental chorionic villus capillaries. Histological examination of blue rubber bleb nevus syndrome reveals lesions composed of gaping, thin-walled veins (venous malformations), often containing thrombi at various stages of organization. Glomangiomas resemble the venous malformations of blue rubber bleb nevus syndrome in consisting of large, dilated, thin-walled veins in the dermis and subcutaneous tissue, but differ from the latter in their added component of 1 or more layers of uniform, cuboidal glomus cells around the lesional veins. Both of these histological appearances are unlike the delicate vessels with papillary endothelial projections and evidence of lymphatic differentiation that we describe. Patients with Maffucci syndrome have venous malformations and so-called spindle-cell hemangiomas (spindle-cell hemangioendotheliomas), the latter also probably a form of vascular malformation that has been altered by the effects of vascular collapse and thrombosis with a histological appearance different from the lymphatic lesions we have described. The lesions of hereditary hemorrhagic telangiectasia consist of dilated venules and arterioles, not vessels of lymphatic differentiation, with fully developed lesions demonstrating features of arteriovenous malformation.

The distinctive histological appearance of the lesions in our patients, with dilated LYVE-1–positive ves-

Figure 4. Hundreds of brown-red papules and nodules, ranging in size from 0.5 to 6 cm, are seen on the extremities (A) and trunk (B) of patient 2, a white girl. The lesions were present since birth.

Figure 5. Patient 3 at 11 years of age. Hundreds of small cutaneous vascular lesions on the extremities and abdomen (A) and back (B), as well as a large facial lesion (not shown) were present at birth. Congenital lesions did not regress, and new lesions appeared throughout childhood.
sels that contain characteristic endothelium-lined intraluminal projections, are similar to those of the recently described lesion known as benign lymphangioendothelioma, but this is typically solitary. This latter entity, originally termed acquired progressive lymphangioma, is an uncommon, benign lesion that typically appears as a singular lesion in adult patients; to our knowledge, there are only 9 reported cases with childhood onset, including 1 patient with a single congenital lesion. All reported cases have involved skin or, less commonly, oral mucosa. Three patients have had multiple lesions, but none had widespread numerous skin lesions or the GI tract involvement and thrombocytopenia that we observed in our 3 patients. Another histologically related lesion is papillary intralymphatic angioendothelioma (PILA). Tumors of this type are solitary lesions of uncertain biological potential that resemble and are probably equivalent to 6 childhood tumors described by Dabska in 1969 as malignant endovascular papillary angioendothelioma. Two of the cases originally reported by Dabska metastasized, causing death after a long interval; but others to date have behaved in a benign fashion. Like benign lymphangioendothelioma and the lesions we describe herein, PILA tumors show papillary intravascular proliferation and histological or immunophenotypic evidence of lymphatic vessels. The lesions we describe, however, lack the well-developed and matchsticklike, columnar intraluminal proliferation of endothelial cells seen in PILA. Thus, while sharing evidence of lymphatic differentiation, PILA and multifocal lymphangioendotheliomatosis with coagulopathy differ significantly not only in clinical behavior, association with coagulopathy, gross appearance, and growth pattern, but also in histological architecture.

The nature of the coagulopathy in our patients deserves comment. Two major types of coagulopathy are seen in association with vascular anomalies. Large segmental vascular malformations, and occasionally multifocal vascular malformations, can be complicated by a chronic disseminated intravascular coagulopathy thought to be due to chronic intraleisional clotting leading to the consumption of clotting factors, elevated D-dimer levels and prothrombin and partial thromboplastin times, and modest decreases in platelet and fibrinogen levels.

Figure 6. Hemotoxylin-eosin–stained sections of tissue resected from the large cheek lesion in patient 3, shown at low- (A) and middle-power (B) magnification, demonstrate an arborizing network of delicate, angular vessels within the dermis, filled with papillary, endothelium-lined intraluminal projections. Cells lining the vessels and their papillae were immunopositive for the panendothelial cell marker CD31 (C) and were associated with a smaller number of pericytes that were immunopositive for α-smooth muscle actin (SMA) (D) and immunonegative for h-caldesmon (not shown) (original magnifications: A, ×100; B, ×200; and C and D, ×400.)
A second type of coagulopathy is the Kasabach-Merritt phenomenon (KMP), seen in association with certain types of vascular tumors, usually solitary but very rarely multifocal. It is primarily characterized by platelet trapping with a more marked decrease in platelet and fibrinogen levels, and some elevation of D-dimer levels, with prothrombin and partial thromboplastin times that are mildly elevated or within the reference range. It is now recognized that KMP occurs almost exclusively as a complication of 2 rare types of vascular tumors that demonstrate a significant degree of histological overlap, kaposiform hemangioendothelioma and tufted angioma; very rare cases have also been reported with hemangiopericytoma, including one multifocal case. Kasabach-Merritt phenomenon often presents within the first year of life, and although the tumors causing it may persist, the coagulopathy itself nearly always resolves (with treatment) during infancy, rather than continuing into childhood, as was the case in our patients. The coagulopathy in our patients did not resolve with time, but became chronic and fluctuating. In other respects, however, it more closely resembles KMP than the coagulopathy found in association with vascular malformations.

Interestingly, abnormal lymphatic vessels appear to be an intrinsic feature of kaposiform hemangioendothelioma and tufted angioma. Furthermore, recent studies have demonstrated diffuse immunoreactivity for the vascular endothelial growth factor receptor 3, a tyrosine kinase expressed on normal lymphatic endothelial cells in normal tissues, including the skin, and in tumor-associated lymphatic vessels. In our own experience (P.E.N., S.S.D., and M.D., unpublished data, December 2003), this specificity is well preserved in lymphatic and blood vascular malformations.

The International Society for the Study of Vascular Anomalies has sanctioned an updated classification that divides vascular anomalies into 2 basic groups, vascular tumors and vascular malformations, based on biological behavior and clinical and histological characteristics. We find the entity we describe herein to be not easily classified by this approach. Although many of the lesions are present at birth (typical of malformations), some continue to expand slowly, new ones appear, and at least some show significant endothelial mitotic activity as evidenced by positive findings for Ki-67 (more characteristic with a tumor). The overall histological architecture, however, is that of a malformation, with lesional hypercellularity largely limited to intraluminal proliferations.

Since our initial description of these patients, additional patients of similar clinical presentation and histological features were described in abstract form by Prasad et al. using the term congenital cutaneovisceral angiomatosis with thrombocytopenia. Results of LYVE-1 staining were not available for those cases. Two of the patients in this additional series had lung involvement as well as skin and GI tract involvement. It seems likely that these patients are equivalent to those we have described. We prefer the term multifocal lymphangioendotheliomatosis with thrombocytopenia in light of (1) the synovial involvement, in addition to cutaneous visceral involvement, among our cases, (2) the consistent presence of proliferative vessels with positive findings for LYVE-1 within lesions, (3) the histological similarity of individual lesions in this disorder to the well-described benign lymphangioendothelioma most commonly seen as an acquired solitary lesion in adults, and (4) the universal presence of thrombocytopenia. Although most cases of this distinct entity appear to be evident at birth, lesions are progressive and increase in number with time.

Table 2. Multivocal Vascular Anomalies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Type of Vascular Anomaly</th>
<th>Source(s)</th>
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<tbody>
<tr>
<td>Neonatal hemangiomas</td>
<td>Infantile hemangiomas</td>
<td>Metry and Hebert, 2000</td>
</tr>
<tr>
<td>Blue rubber bleb nevus syndrome</td>
<td>Venous malformations</td>
<td>Boente et al, 1999</td>
</tr>
<tr>
<td>Multifocal (autosomal dominant) glomuvenous malformations (glomangiomas)</td>
<td>Venous malformations with glomus cells</td>
<td>Wood and Dimnick, 1977; Boon et al, 1999</td>
</tr>
<tr>
<td>Maffucci syndrome</td>
<td>Arteriovenous malformations, dilated arterioles, venules</td>
<td>Kaplan et al, 1993</td>
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<tr>
<td>Hereditary hemorrhagic telangiectasia</td>
<td>Venous malformations and spindle-cell hemangiomas</td>
<td>Peery, 1987; Braverman et al, 1990; Azuma, 2000</td>
</tr>
<tr>
<td>Familial (autosomal dominant) cerebrocutaneous capillary malformations</td>
<td>Cerebral capillary-venous malformations, some combined with cutaneous hyperkeratotic capillary-venous malformations</td>
<td>Labaube et al, 1999; Eerola et al, 2000</td>
</tr>
<tr>
<td>Familial (autosomal dominant) mucocutaneous venous malformations</td>
<td>Venous malformations</td>
<td>Calvert et al, 1999; Viskula et al, 1996</td>
</tr>
<tr>
<td>Multifocal lymphangioendotheliomatosis with thrombocytopenia</td>
<td>Lymphangioendotheliomatosis</td>
<td>Frieden et al, 2002; Frieden et al, 2003; present report</td>
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</table>
Thus we cannot exclude the possibility some otherwise identical cases may present later in life.

Since the acceptance of this manuscript, an additional 15-year-old patient with multiple cutaneous and gastrointestinal “hemangiomas” of clinical appearance and behavior remarkably similar to those we have described, also complicated by chronic thrombocytopenia and gastrointestinal bleeding, has been reported by Mukhtar and Letts.\(^4\) Although lesional histological characteristics were not documented for this patient, the authors choosing instead to use the generic term “hemangioma,” we believe this patient probably also exemplifies multifocal lymphangioendotheliomatosis with thrombocytopenia. It is of interest that this latter patient had bony as well as cutaneous visceral involvement, supporting the concept of a truly multifocal phenomenon.

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