Congenital Nonprogressive Hemangioma

A Distinct Clinicopathologic Entity Unlike Infantile Hemangioma

Paula E. North, MD, PhD; Milton Waner, MD; Charles A. James, MD; Adam Mizeracki, BS; Ilona J. Frieden, MD; Martin C. Mihm, Jr, MD

Background: Infantile hemangiomas are common tumors, distinctive for their perinatal presentation, rapid growth during the first year of life, and subsequent involution—and for their expression of a unique immunophenotype shared by placental microvessels. Occasional “hemangiomas” differ from the classic form in presenting fully formed at birth, then following a static or rapidly involuting course. These congenitally fully developed lesions have generally been assumed to be clinical variants of more typical, postnatally developing hemangiomas. This assumption has not been tested by rigorous histologic and immunophenotypic comparisons.

Objective: To compare the histologic and immunohistochemical features of congenital nonprogressive hemangiomas with those of typical, postnatally proliferating, hemangiomas.

Design: All cellular vascular tumors resected from infants younger than 4 months at Arkansas Children’s Hospital, Little Rock, over the past 20 years (43 lesions from 36 patients) were first characterized histologically and immunohistochemically, then clinically by chart review.

Setting: A university-affiliated pediatric hospital.

Main Outcome Measures: Histologic appearance, immunoreactivity for the infantile hemangioma–associated antigens GLUT1 and LeY, and clinical behavior.

Results: Congenital nonprogressive hemangiomas differed from postnatally proliferating infantile hemangiomas in histologic appearance and immunohistochemical profile. Distinguishing pathologic features of these tumors were lobules of capillaries set within densely fibrotic stroma containing hemosiderin deposits; focal lobular thrombosis and sclerosis; frequent association with multiple thin-walled vessels; absence of “intermingling” of the neovasculature with normal tissue elements; and lack of immunoreactivity for GLUT1 and LeY.

Conclusion: Congenital nonprogressive hemangiomas are histologically and immunophenotypically distinct from classically presenting hemangiomas of infancy, unlikely to be related to the latter in pathogenesis.

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INFANTILE (JUVENILE) hemangiomas are the most common tumors of infancy, affecting approximately 10% of children.1 These benign vascular tumors vary in location and extent of tissue involvement, and thus in clinical impact, but share a remarkably predictable biological behavior. Lesions generally appear within weeks after birth, proliferate rapidly during the first year of life, and then spontaneously involute over a period of several years. Most begin as relatively inconspicuous blanched or blushed macules, in some cases evident at birth, that then dramatically expand as tumorlike masses. A minority of infantile hemangiomas, perhaps 15%, are relatively prominent at birth, usually presenting as diffuse, plaquelike lesions that grow rapidly prior to their characteristic period of involution. Members of our group2 have reported recently that these congenital examples of otherwise typical, postnatally proliferating, infantile hemangiomas are histologically indistinguishable from classic, postnatally presenting examples, including expression of an unusual set of tissue-specific vascular antigens uniquely shared by placental microvessels.3 These antigens are not expressed by the normal vasculature of skin or subcutis; or by a variety of benign vascular tumors that are histologically similar to hemangioma (including pyogranuloma, tufted angioma, and infantile kaposiform hemangioendothelioma); or by vascular malformations.3 Two of these antigens, the erythrocyte-type glucose transporter protein GLUT1, and Lewis Y antigen (LeY), can be detected by immunohistochemical analysis using formalin-fixed, paraffin-embedded tissue speci-
METHODS

SPECIMENS

We performed an initial database review, searching for all surgical specimen archived at Arkansas Children’s Hospital, Little Rock, between January 1980 and December 2000, for which the diagnosis contained the suffix “angioma” (903 cases). These were then restricted to examples resected from patients younger than 4 months to exclude most noncongenital lesions and enrich for “alarming” congenital lesions, yielding a more manageable and focused group of 59 lesions from 50 patients. Hematoxylin-eosin–stained tissue sections from these cases were then reviewed, and all vascular and lymphatic malformations were excluded (15 cases). This process yielded 44 cellular vascular lesions composed of proliferative, mitotically active vascular elements resected from infants younger than 4 months. One case, histologically consistent with infantile hemangioma, showed poor preservation of tissue antigenicity (GLUT1-positive internal controls were nonreactive) and was subsequently excluded, leaving a final total of 43 lesions from 36 patients (1 patient had multiple lesions resected).

During review of the hematoxylin-eosin–stained sections, the lesions were comparatively evaluated by investigators blind to clinical history for a variety of general histologic features relevant to vascular proliferations, including lobularity, endoneurial pseudoinvasion, lesional mitotic activity, endothelial cell atypia (eg, spindled or epithelioid shape and/or abnormal mitotic figures), epithelial collarate formation, planes of tissue involvement, characteristics of the accompanying larger vasculature, and the presence or absence of ulceration, thrombosis, hemorrhage, hemosiderin deposition, fibrosis, calcification, or necrosis. Histopathologic diagnoses were rendered during the course of these reviews and/or abnormal mitotic figures), epithelial collarate formation, planes of tissue involvement, characteristics of the accompanying larger vasculature, and the presence or absence of ulceration, thrombosis, hemorrhage, hemosiderin deposition, fibrosis, calcification, or necrosis. Histopathologic diagnoses were rendered during the course of these reviews based on published criteria for infantile hemangioma, pyogenic granuloma, vascular and lymphatic malformations, tufted angioma, and infantile kaposiform hemangioendothelioma.38 No examples of infantile myofibromatosis (infantile hemangiopericytoma), as defined by Mentzel et al,11 were identified. Lesions that did not fit well into established diagnostic categories were initially grouped as other.

Diagnoses, including other, were then correlated with GLUT1 and LeY immunoreactivities, and with selected clinical features determined (when available) by subsequent medical record review. These clinical features included patient sex and race; gestational history; age at resection; age when lesion was first noticed; biological behavior (whether the lesion grew, regressed, or remained static postnataally); whether multiple lesions were present; gross configuration of the lesion (eg, bulging tumor mass vs exophytic polyp vs diffuse infiltration or plaquelike expansion); and whether the patient experienced complicating conditions such as Kasabach-Merritt syndrome, heart failure, or ulceration.

IMMUNOHISTOCHEMICAL ANALYSIS

Paraffin sections were deparaffinized, rehydrated, and subjected to citrate buffer antigen retrieval, then protein-blocked before incubation with primary antibodies to GLUT1 or LeY as previously described.3,4 Bound primary antibody was detected using a DAKO Corp (Carpinteria, Calif) LSAB+ peroxidase kit using DAB+ chromagen.4 Immunoreactions for CD34 and a smooth muscle actin were performed similarly, but without antigen retrieval, using monoclonal antibodies directed against CD34 (clone QBEnd/10, prediluted; Biogenex, San Ramon, Calif) or a smooth muscle actin (clone 1A4, DAKO N1584). Negative controls were processed in parallel without primary antibody. Normal tissue immunoreactivities (perineurium and erythrocytes) provided internal positive controls for GLUT1. For LeY, sections of LeY-immunopositive oral mucosa were included in each run as positive controls. Immunoreactivities were scored blindly by the first author (P.E.N.) as none, weak, moderate, or intense (≥ controls). For LeY, occasional weak immunoreactivity in a perinuclear, hof-type pattern was discounted. Only membranous and/or diffuse cytoplasmic-membranous LeY immunoreactivity was scored as positive.

RADIOGRAPHIC ANALYSIS

Subsequent to the pathologic examinations, available radiographic imaging studies (ultrasound, computed tomography, and magnetic resonance imaging) of all congenital nonprogressive lesions included in the study were reviewed. Findings were compared with those characteristic of well-established vascular tumors and anomalies, including infantile hemangiomas and vascular and lymphatic malformations, based on published criteria.12

RESULTS

Based on histopathologic and immunohistochemical findings, all 43 congenital and early neonatal cellular vascular lesions could be classified into 5 coherent categories
(Table 1). For 4 of these categories, accounting for 37 of the 43 lesions, subsequent chart review revealed postnatal lesional growth (Table 1). These 4 categories were (1) infantile hemangioma (GLUT1/LeY immunopositive), (2) pyogenic granuloma, (3) infantile kaposiform hemangioendothelioma, and (4) tufted angiomata. The fifth histologic category (originally classified as hemangioendothelioma, and (4) tufted angioma. The fifth histologic category (originally classified as other) consisted of 6 GLUT1/LeY–immunonegative lesions (from 6 patients) that shared a singular, but previously undescribed, histologic appearance. Subsequent chart review showed that all 6 of these lesions were fully formed at birth and did not enlarge postnatally. We therefore re-named this category congenital nonprogressive hemangioma. The differential clinical, histologic, and immunophenotypic findings that define these 5 distinctive lesional types are described below.

**CONGENITAL NONPROGRESSIVE HEMANGIOMAS**

These lesions, initially grouped in the other category until their remarkably similar histologic appearance was recognized, were cellular lesions consisting of multiple well-defined lobules of proliferating capillaries, often flowing into one another to form ribbons within subcutaneous tissue and, in some cases, overlying dermis. None invaded underlying skeletal muscle. High-magnification views of these proliferative lobules, considered without reference to their greater context within the tissue, revealed features reminiscent of infantile hemangioma (Figure 1A): plump endothelial cells forming small capillary lumina and surrounded by pericytes, moderate numbers of normal mitotic figures among both component cell types, and no alarming nuclear or cytoplasmic atypia. Not surprisingly, all of these lesions had originally received pathologic diagnoses of cellular, capillary, or juvenile hemangioma, reflecting various terminologies used between 1980 and 1997. However, low-magnification views (eg, Figure 1B) revealed clear distinguishing features for these lesions.

In contrast to infantile hemangiomas, in which the tumor lobules are separated by normal-appearing tissue elements, the tumor nodules of congenital nonprogressive hemangiomas were separated by bands of abnormal, dense fibrous tissue (Figure 1B–D; Figure 2A–B), with epidermal atrophy and loss of dermal adnexal appendages in overlying skin. In contrast, the epidermis covering infantile hemangiomas is, in our experience, atrophic only in involuted lesions, and is normal or hyperplastic in proliferative lesions. This latter observation is confirmed by a recent study by Bielenberg et al, who found that the growth phase of infantile cutaneous hemangiomas correlated with hyperplasia and angiogenesis in the adjacent epidermis. Congenital nonprogressive hemangiomas were further distinguished by occasional sclerosis of capillary lobules, either peripherally or globally (Figure 2A), and acute fibrin thrombi were seen in 3 of the 6 lesions (Figures 2B). Hemosiderin granules (Figure 1C and Figure 2C) and occasional small foci of dystrophic calcification (Figure 1D) were also invariant findings, within both the proliferating lobules and the fibrous septi of congenital nonprogressive hemangiomas, further suggesting a role for past hemorrhage or thrombosis in the evolution of these lesions. No well-formed, hyalinized, or calcified phleboliths were present.

The cells comprising the cellular lobules within these lesions were confirmed to be endothelial and pericytic by CD34 and α smooth muscle actin immunoreactions, respectively (Figure 3). Mast cells were only occasionally evident in hematoxylin–eosin–stained sections of these congenital lesions. Neither GLUT1 nor LeY expression was immunohistochemically detectable in any of these 6 lesions, despite consistently strong immunoreaction of internal positive controls (Figure 4). Small foci of ex-
tramedullary hematopoiesis were observed in 5 of 6 cases, and these immunoreacted positively for GLUT1 (Figure 5). All examples showed an irregular, sparse infiltrate of chronic inflammatory cells including occasional eosinophils.

Some of these congenital lesions (in patients 4 and 5) contained large, thin-walled vascular structures compressed between multiple tumor lobules (some of which were several millimeters in diameter [Figure 6]). These vessels were typically collapsed and consequently easily overlooked on casual examination. In some sections, lobules of capillary growth invaginated into these collapsed lumina from broad, murally based pedicles (Figure 6A), or appeared to “float” in their lumina (Figure 6B). In other sections from these same lesions, capillary lobules were not associated with vessels (Figure 6C). For the patient whose lesion is depicted in Figure 6 (patient 5), the surgeon’s operative note described a grossly lymphangiomatous lesion with cystic, fluid-filled spaces and what looked like lymph nodes, which proved on microscopic examination to be capillary lobules. In other cases (patients 1, 3, and 6), smaller-caliber vascular structures, consistent with veins or lymphatic vessels, were dispersed between lobules in numbers that appeared abnormally high (Figure 1B-C). Small arterial feeders were evident in many lesions, but showed no clear connection to individual capillary lobules, in contrast to the lobules of infantile hemangioma that commonly show a central feeding artery in histologic sections (Figure 7B). A significant negative finding was the absence of intraneuronal involvement by the neoplastic growths, in contrast to the frequent intraneuronal involvement in infantile hemangiomas (Figure 8). The strongly lobular pattern of capillary growth in some congenital nonprogressive hemangiomas was reminiscent of the “cannonball” pattern of tufted angioma (Figure 1B). However, the densely packed capillary tufts with small, peripherally located crescentic vascular clefts, characteristic of tufted angioma (Figure 9B), were absent. Spindled endothelial cell reminiscent of kaposiform hemangioendothelioma were also notably absent. None of these lesions showed histologic evidence of ulceration or epithelial collarette formation.

Retrospective review of patient medical records revealed that all of the lesions placed into this histologic category were clinically unusual (Table 1 and Table 2). They invariably presented fully formed at birth, and they invariably did not enlarge between birth and the time of resection. Because all of these lesions, as mandated by the design of the study, were resected before the patient reached age 4 months (Tables 1 and 2), information about their potential involutive behavior is limited. All of the 6 patients with lesions in this category had single, bulging, tumorlike lesions, all moderately large (2-5 cm); and 3 patients showed at least focal red discoloration of the

Figure 1. Congenital nonprogressive hemangioma. Hematoxylin-eosin–stained sections of a bulging subcutaneous mass, fully formed at birth, resected from the forehead of 2-month-old girl (patient 3). A, High-magnification view shows dense capillary proliferation similar in appearance to that of infantile hemangioma, with occasional mitotic figures (black arrow). B, Lower magnification view reveals the distinguishing features of these lesions: numerous distinct lobules of capillary growth (black arrow) admixed with numerous thin-walled vessels, many suggestive of lymphatic vessels (white arrow). C, Some areas show a more dominant pattern of small vessels, with less capillary proliferation; note the golden brown deposits of hemosiderin in the lower-right corner. D, Foci of calcification are also occasionally present (black arrow).
overlying skin. Patient photographs were available for 2 of these lesions. Both of these were bossed lesions with peripheral rims of skin pallor (Figure 10A and Figure 11A), remarkably similar to the clinical entity “congenital hemangioma” described by Boon et al6 and Martinez-Perez et al.5

The 6 examples of congenital nonprogressive hemangioma showed no obvious anatomic sites of predilection. The resected examples described here arose on the forehead, cheek, posterior neck, posterior auricular area, wrist, and labia majora. Based on history and histologic analysis, none of the lesions was ulcerated. Of the 6 affected infants, 4 were girls and 2 were boys; 5 were white, and 1 was African American.

Radiologic imaging studies were available for 3 of the 6 patients with congenital nonprogressive hemangioma. One of these (patient 3; Figure 10A) underwent head magnetic resonance imaging for a bulging subcutaneous lesion of the forehead to rule out intracranial involvement. The lesion showed diffuse loss of signal throughout the lesion on T2-weighted imaging compatible with diffuse hemosiderin deposition, a finding not associated with infantile hemangiomas (Figure 12). This large soft tissue mass also had internal high-signal hemorrhage on T1-weighted imaging, associated marked calvarial displacement at day 17 of life (implying intrauterine mass effect), and lack of a central arterial flow void (Figure 12). These findings are highly atypical for infantile hemangiomas. Two patients (patients 5 and 6) had only limited ultrasound imaging performed that showed small, nonspecific oval soft tissue masses. No Doppler interrogation was available for these 2 patients.

INFANTILE HEMANGIOMAS

Most of the cellular lesions in this study (25/43) met traditional, well-established histologic criteria for the diagnosis of proliferative-phase infantile hemangioma. These appeared as nearly solid masses of small capillaries consisting of plump endothelial cells and pericytes, admixed with numerous mast cells and grouped in delicately defined lobules separated by fine strands of connective tissue or by normal intervening tissue (Figure 7A). None of the lobules was encapsulated or fibrotic, and many contained normal tissue elements (Figure 7A) and a feeding artery (Figure 7B), in contrast to congenital nonprogressive hemangioma. All were subcutaneous or cutaneous, and 3 of the 25 lesions showed histologic evidence of active ulceration. Neural pseudoinvasion was a common feature (Figure 8B, Figure 13A), and occasional mitotic figures were present in all cases (Figure 7C). Hemosiderin deposition and thrombosis were rare (2 cases), and were limited to ulcerated, acutely inflammed areas.

Patient characteristics for the patients in the infantile hemangioma group are summarized in Table 1. Age at which these lesions were first evident (25 lesions from
25 patients) could be determined from available clinic notes or photographs for 16 of the 25. Four were present at birth, and all had appeared by age 1 month. The average age at presentation for these 16 patients was 10 days. For all 25 of these lesions, including the 4 known to be noticeable at birth, there was a well-documented history of marked postnatal enlargement. Of the 25 patients, 5 had multiple cutaneous hemangiomas by clinical history (1 of these had multiple hepatic lesions also, as evidenced by ultrasound), although each of these 5 had only a single lesion each (all cutaneous) resected for pathologic review and diagnosis.

Of the 4 congenitally evident lesions in this histologic category, 3 appeared at birth as inconspicuous, blushed macules that rapidly expanded postnatally to form much larger, tumorlike growths. The fourth of these congenitally evident lesions was a relatively flat lesion covering much of the right face at birth, with irregular bright red surface discoloration that grew rapidly in thickness thereafter. Patient photographs (not shown) document diffuse involvement of the right forehead, cheek, upper eyelid, chin, and lips. Magnetic resonance imaging revealed bilateral parotid gland involvement with extension into the pharyngeal space. This congenitally prominent, but nevertheless postnatally progressive lesion had been clinically diagnosed as infantile hemangioendothelioma or the diffuse or segmental type at the time of patient presentation and showed a good response to aggressive oral and intravenous steroid therapy begun at age 6 weeks. A small portion of this extensive lesion, described as an enlarging nodular area threatening the visual axis, was resected and included in this study. It was histologically indistinguishable from the other 24 more clinically typical infantile hemangiomas in our series.

All 25 infantile hemangiomas showed strong lesional endothelial immunoreactivity for GLUT1 and LeY (Table 1; Figure 13), including the extensive, diffusely distributed, right facial lesion described above, corroborating previous reports. Native dermal and subcutaneous capillaries, present at the margins of many of these specimens, were invariably immunonegative for both of these antigens.

**PYOGENIC GRANULOMAS**

Ten lesions, all immunonegative for GLUT1 and LeY (Table 1), displayed the histologic and immunohistochemical features of pyogenic granuloma, including proliferating lobules of capillaries set within edematous fibromyxoid stroma. Superficial, acute thrombosis was found in 3 of these, all of which were ulcerated and inflamed. Two lesions (from 2 patients) were typical, small, exophytic eruptions. Both were pedunculated, papillomatous upper-eyelid lesions, appearing between 2 weeks and 1 month after birth and growing rapidly. One blurred...
Tufted Angioma

A lesion resected from the thigh of a 2-month-old boy was histologically consistent with tufted angioma. The dermal portion of this lesion was composed of discrete vascular tufts of tightly packed capillaries with small, round lumina indenting peripheral, crescentic, thin-walled vessels suggestive of lymphatics (Figure 9B). The bulk of the tumor, which measured 5 cm in greatest dimension, was located in the subcutis where the vascular tufts were larger and frequently coalescent, again in association with dilated peripheral lymphatic-like vessels. The outer rims of the capillary nodules displayed focal spindled morphology similar to infantile kaposiform hemangioendothelioma. There was no lesional immunoreactivity for GLUT1 or LeY (Table 1).

The lesion first appeared at age 3 weeks as a dime-sized, bruiselike growth on the thigh that became tender and swelled to 5 cm by the time of resection at age 8 weeks. There was no evidence of coagulopathy. Preoperative magnetic resonance imaging results suggested a high-flow lesion, but the intraoperative gross appearance was that of a relatively discrete fibromyxoid mass, largely subcutaneous, invading adjacent skin and muscle. It did not recur.

INFANTILE KAPOSIIFORM HEMANGIOENDOTHELIOMA

A previously reported lesion3,4 was diagnosed as infantile kaposiform hemangioendothelioma. This tumor consisted of sheets and irregular lobules of relatively bland spindle cells defining slitlike spaces containing erythrocytes (Figure 9C) focally associated with lobules of better-differentiated capillaries and many abnormal collections of small, collapsed, thin-walled vessels suggestive of lymphatic channels. The lesion involved skin, subcutis, and underlying deep skeletal muscle. None of the vascular elements was immunoreactive for GLUT1 or LeY (Table 1). According to clinical history, this extensive facial lesion, analyzed by biopsy specimen at age 2 months, was prominent at birth and continued to grow rapidly postnatally. The patient had Kasabach-Merritt phenomenon and died at age 6 months from intracranial hemorrhage secondary to profound thrombocytopenia complicated by sepsis.

CONCLUSION

Congenital hemangiomas fully formed at birth have previously been considered clinical variants of infantile hemangioma, equivalent in the biological sense to more typical, postnatally presenting hemangiomas, and differing...
from these primarily in the time (relative to birth) at which “full bloom” is reached and in the rapidity of involution. This concept has been supported by histologic descriptions of biopsy specimens (and of rare resections) of these lesions as proliferations of capillaries, presumed to be diagnostic of infantile hemangioma.

We have tested this assumption by rigorous histologic and immunohistochemical analysis, with subsequent clinical and radiologic correlation, of a large series of cellular vascular lesions of infants collected over a 20-year period at Arkansas Children’s Hospital. We show here that congenital nonprogressive hemangiomas fully
formed at birth are histologically and immunophenotypically distinct from classically presenting hemangiomas of infancy, and thus are unlikely to be pathogenically related to them. The 6 congenital nonprogressive hemangiomas described here demonstrated a singular histologic appearance that differed from that of classic infantile hemangiomas in (1) striking lobularity, defined by a densely fibrotic stroma; (2) ubiquitous presence of stromal hemosiderin deposits; (3) focal thrombosis and sclerosis of capillary lobules; (4) absence of intermingling of the neovascularure with normal tissue elements such as nerve, adipose tissue, and salivary gland; (5) relatively scarce mast cells; and (6) common association of the proliferating capillary lobules with multiple, thin-walled vessels. In addition, all of these congenital, nonprogressive lesions showed complete lack of immunoreactivity for GLUT1 and LeY and thus were immunohistochemically distinct from typical infantile hemangiomas.

Magnetic resonance imaging findings, available for one of the patients with congenital nonprogressive hemangioma, were also distinctive, and included internal hemorrhage with signal loss on T2-weighted imaging consistent with diffuse hemosiderin deposition (also evident in histologic sections). In addition, this large facial lesion with calvarial displacement lacked a central arterial flow void. These are not expected findings in infantile hemangiomas, which typically demonstrate central flow voids and homogeneous, moderate to high signal on T2-weighted imaging. 

Recognition of congenital nonprogressive hemangioma as an entity biologically distinct from infantile hemangioma has important implications for patient management. Certainly the possibility of rapid involution in cases of this type should be considered, based on previous clinical reports that describe an unusually rapid course of involution for lesions that are grossly and clinically similar to those described here. 

Interestingly, other congenital lesions of similar clinical presentation have been described as persisting, and have been called noninvoluting congenital hemangiomas. Because all of the lesions in our study were resected before the patients reached age 4 months, it was not possible to correlate histologic findings with involutinal behavior, only with clinical appearance and lack of disproportionate postnatal growth. Future comparative studies of congenital nonprogressive hemangiomas of rapidly involuting and noninvoluting types should clarify whether these are closely related or inherently different entities distinguishable by biopsy findings.

Conservative management of congenital, fully formed hemangiomas may be indicated, at least until the involutional potential of a given lesion is clear. However, as pointed out by Boon et al, it may be wise early on to perform biopsies on unusually firm or otherwise atypical lesions to rule out more serious entities such as infantile sarcoma or myofibromatosis.

Distinction between true infantile hemangiomas and congenital nonprogressive hemangiomas is also important for any meaningful discussions of pathogenesis concerning these disparate lesional types. For instance, ultrasonographic detection of hemangiomas of the congenital nonprogressive type early in utero is not relevant to understanding temporal patterns of development for true, GLUT1-positive infantile hemangiomas. Awareness of this distinction will help avoid potential misinterpretations.

The distinctive histologic appearance of congenital nonprogressive hemangioma reported here superficially resembles that of both tufted angioma and pyogenic granuloma, clinically distinct entities that are also represented in the present study. In fact, the limited histologic overlap between tufted angioma and pyogenic granuloma has been noted; both of these entities, like congenital nonprogressive hemangiomas, are strongly lobular in appearance and are immunonegative for GLUT1 and LeY. Beyond these similarities, however, we found sufficient differences not only in clinical presentation, but also in histologic appearance, to confidently distinguish congenital nonprogressive hemangiomas from tufted angiomas and pyogenic granulomas.

Tufted angiomas present as infiltrative, slowly growing macules or plaques, most commonly in the first few years of life, although rare lesions present at birth or in adult life. Histologically, they show a widespread distribution of distinct capillary lobules within the dermis and subcutis, creating a cannonball pattern when viewed at low magnification. These capillary lobules consist of densely packed endothelial cells and pericytes forming tiny round lumina, and often display small, compressed vascular crescents at their periphery. Hemosiderin deposits are not
Figure 9. Pyogenic granuloma (A), tufted angioma (B), and infantile kaposiform hemangioendothelioma (C) were also represented in the study. A, The pyogenic granuloma shown was resected from the eyelid of a 3-month-old girl after appearing at age 1 month. Note the mildly edematous fibromyxoid stroma. B, This tufted angioma demonstrates the characteristic cannonball distribution of dense capillary lobules with peripheral vascular crescents (black arrows). C, A biopsy specimen taken at age 3 months revealed a proliferation of bland spindled cells forming slitlike spaces containing erythrocytes and occasional fibrin microthrombi. This infantile kaposiform hemangioendothelioma caused the patient’s death at age 6 months as a complication of Kasabach-Merritt syndrome.

Table 2. Summary of Clinical Data and Treatment for Patients With Congenital Nonprogressive Hemangiomas*

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Location of Lesion</th>
<th>Clinical Description of Lesion</th>
<th>Original Pathologic Diagnosis</th>
<th>Current Histologic Findings</th>
<th>Medical and Surgical Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>Midline posterior cervical</td>
<td>Moderately firm, freely movable 5 × 5 × 3-cm subcutaneous mass covered by discolored skin and hair</td>
<td>Hemangioma, capillary type, with dilated lymphatic channels</td>
<td>Cellular capillary lobules within fibrotic stroma containing numerous thin-walled vessels; overlarying skin atrophy; foci of hemosiderin, EMH†</td>
<td>Resection en toto at age 9 d</td>
</tr>
<tr>
<td>2/M</td>
<td>Radial aspect of wrist</td>
<td>2 × 2-cm bossed subcutaneous mass</td>
<td>Capillary hemangioma</td>
<td>Similar to patient 1, with addition of focal acute thrombosis within lobules</td>
<td>Resection en toto at age 2 mo 6 d</td>
</tr>
<tr>
<td>3/F</td>
<td>Forehead (see Figure 10A)</td>
<td>5 × 5 × 3-cm bulging, slightly pedunculated mass with peripheral rim of skin pallor; freely movable, subcutaneous</td>
<td>Hemangioma mixed, predominantly juvenile type</td>
<td>Similar to patient 1, without obvious EMH (see Figures 1 and 10)</td>
<td>Steroid trial, not tolerated; resection en toto at age 2 mo 18 d</td>
</tr>
<tr>
<td>4/F</td>
<td>Preauricular (see Figure 11A)</td>
<td>4 × 4 × 3-cm bulging subcutaneous mass with mottled, deep red skin discoloration and peripheral pallor</td>
<td>Capillary hemangioma</td>
<td>Similar to patient 1, with addition of large pseudosplanchitary capillary proliferations within large vascular spaces, and focal acute thrombosis (see Figure 11B-C); EMH and hemosiderin deposition marked; focal global hyalinizing sclerosis of lobules; skin atrophy</td>
<td>Resection en toto at age 2 mo 6 d</td>
</tr>
<tr>
<td>5/M</td>
<td>Postauricular</td>
<td>“Doughy” 3-cm, nodular subcutaneous mass with normal overlying skin</td>
<td>Cellular hemangioma</td>
<td>See Figure 6; similar to patient 1, with notable presence of very large lymphatic spaces intertwined with the capillary lobules; hemosiderin and EMH present</td>
<td>Resection en toto at age 2 mo 9 d</td>
</tr>
<tr>
<td>6/F</td>
<td>Labia majora</td>
<td>2.5-cm movable submucosal mass, moderately firm in consistency</td>
<td>Lobular capillary hemangioma</td>
<td>See Figure 2; similar to patient 1, with focal lobular sclerosis and acute thrombosis; hemosiderin and EMH present</td>
<td>Resection en toto at age 1 mo 9 d</td>
</tr>
</tbody>
</table>

*All of the hemangiomas were congenital lesions, fully formed at birth (see Table 1 and the text). None were complicated by ulceration, cardiac failure, or coagulopathy.
†EMH indicates extramedullary hematopoiesis.
common, and thrombosis is generally limited to micro-
thrombi within occasional capillary lumina. By contrast,
congenital nonprogressive hemangiomas, as represented
in the present study, present as bulging, tumorlike masses,
largely subcutaneous and fully formed at birth; they are
composed of capillary lobules and ribbons that vary widely
in size—many very large—without the peripheral cres-
cents of tufted angioma. Large thin-walled vessels, some
cystically dilated, are frequently present, and in some cases
contain invaginated lobules of dense capillary growth
within their lumina.

Hemosiderin granules are sprinkled throughout con-
genital nonprogressive hemangiomas, and thrombosis is
notably common, occasionally involving entire lobules,
some of which are sclerotic. Unlike congenital nonpro-
gressive hemangiomas, pyogenic granulomas (termed
lobular capillary hemangiomas by some pathologists in rec-
ognition of their strongly lobular histologic appearance8)
are relatively small, generally acquired lesions that lack a
widespread growth pattern; most are exophytic eruptions
of skin or mucosal surfaces, although rare subcuta-
neous27 and intravascular18,19 forms have been described.

Figure 10. Congenital nonprogressive hemangioma. This subcutaneous forehead lesion was fully formed at birth and did not change in size prior to its resection
at age 2.5 months (patient 3; hematoxylin-eosin–stained sections shown in Figure 1). A, Note the central skin discoloration and peripheral rim of skin pallor.
B, This lesion, like all 6 congenital nonprogressive hemangiomas in this study, was immunonegative for glucose transporter protein isoform 1(GLUT1). Again,
note the normal GLUT1 immunopositivity of luminal erythrocytes.

Figure 11. Congenital nonprogressive hemangioma. A, This preauricular mass (patient 4), like the forehead mass shown in Figure 10A, showed red skin
discoloration with a peripheral rim of pallor. It was resected at age 2 months. B, A hematoxylin-eosin–stained section revealed lobules of capillaries surrounding
and within the lumen of a large, ill-defined vascular space just beneath the skin. C, These lobules focally assumed a pseudopapillomatous architecture without true
fibrous or fibrous cores. B, Note the thinning of epidermis and loss of dermal appendages in the skin immediately overlying the vascular proliferation (left from
center).
Intravascular examples of pyogenic granuloma are described as solitary intravenous polyps composed of lobules of capillaries within a fibromyxoid stroma, attached to the wall of a vein by a fibrovascular stalk. In a study of 18 of such intravascular pyogenic granulomas, Cooper et al found only 5 lesions that contained thrombi, all of which were small and localized, and only 3 of which showed small deposits of iron. By contrast, thrombosis and hemorrhage were prominent in congenital nonprogressive hemangiomas, evident both radiologically and histologically and in the absence of complicating ulceration.

The consistent presence of thrombosis and hemosiderin deposition in congenital nonprogressive hemangiomas invites comparison with Masson lesion, currently termed intravascular papillary endothelial hyperplasia. This peculiar histologic pattern, originally called vegetant intravascular hemangioendothelioma by Masson in 1923, is seen within many different types of vascular lesions. It is thought to be an exuberant form of endothelial hyperplasia accompanying organization of intravascular thrombi and consists of complex, spongiform ramifications of fibrinous or fibrous papillae lined by endothelial cells. These are often seen in association with recognizable thrombus material and hemosiderin deposits, consistent with the proposed origin from organizing thrombus.

Intravascular papillary endothelial hyperplasia can occur rarely as an isolated mass without a known underlying pathologic entity, but foci of this process are extremely common in venous malformations, reflecting the high frequency of thrombosis in these slow-flow lesions. Foci are also occasionally seen in pyogenic granulomas (including several in this study), hematomas,
GLUT1, LeY, FCYRRII, and merosin, that is shared by the vessels of the malformation. Unusually high density of thin-walled channels, some large and gaping, others small and numerous, throughout their substance. The rapid involution reported by others for some congenital hemangiomas might reflect extensive postthrombotic sclerosis of lesional capillary beds, and subsequent connective tissue contraction in the absence of autonomous capillary proliferation. Noninvoluting examples of congenital hemangioma may be intrinsically different or may simply maintain a more even balance between reactive neovascularization and sclerosis, perhaps affected by size and type (e.g., lymphatic vs venous) of the "parent" vessels of the malformation. Unfortunately, resections and biopsies of these unusual lesions are very rare, making systematic comparison of noninvoluting and rapidly involuting examples at different stages of development difficult. Again, studies based on multi-institutional collections of archival materials may be helpful.

Although the above discussion concerning the potential link between congenital nonprogressive hemangiomas and malformations remains speculative, our results strongly suggest that congenital nonprogressive hemangiomas are not related in any meaningful biological sense to true infantile hemangiomas. The latter are invariably postnatally developing lesions, although they may be evident as nascent lesions at birth. True infantile hemangiomas are not only histologically distinct from congenital nonprogressive hemangiomas, but are universally positive for an unusual set of vascular antigens: GLUT1, LeY, FCYRRII, and merosin, that is shared by the microvasculature of placenta. These striking and apparently unique similarities in microvascular immunophenotype displayed by infantile hemangiomas and placental vessels suggest a fundamental pathogenic link between the vasculature of infantile hemangiomas and the microvasculature of placenta, possibly involving either embolization of placental cells to fetal tissues during gestation or birth, or aberrant differentiation of vascular precursor cells within fetal tissues (skin and subcutis) toward the placental microvascular phenotype. The absence of GLUT1 and LeY expression in the congenital nonprogressive lesions described here obviates these pathogenic considerations for these congenital lesions, and suggests that their etiology is intrinsically different from that of infantile hemangioma.

We have not excluded the possibility that rare nonprogressive hemangiomas, similar in clinical and histologic appearance to the congenital lesions reported in this study, may present in older children and adults or may show GLUT1 and/or LeY immunopositivity. We have examined only 6 of these unusual cases, restricted by study design to neonatal samples. Similarly, we cannot exclude the possibility that rare GLUT1-positive infantile hemangiomas may present fully formed at birth, without subsequent postnatal growth. However, we have not identified any such lesions in the past 20 years at Arkansas Children's Hospital, suggesting that these lesions, if they exist, must be exceedingly rare.

As a final note, our study has uncovered another point of diagnostic classification in need of clarification: the concept of hemangiomatosis. We have demonstrated that while some patients clinically diagnosed as having diffuse hemangiomatosis have lesions that exhibit the histologic appearance and immunophenotypic features of true infantile hemangiomas (i.e., the patient with multiple cutaneous and hepatic hemangiomas described herein), other patients given this same clinical diagnosis may have lesions of a different nature, similar to infantile hemangiomas on casual clinical inspection but distinct from hemangiomas histologically and immunophenotypically (i.e., the unusual patient with hundreds of atypical pyogenic granuloma-type lesions and a large cutaneous stain described herein). Focused clinicopathologic study of a larger series of these rare cases of hemangiomatosis, with and without visceral involvement, seems warranted.

In summary, we describe a distinct clinicopathologic entity, the congenital nonprogressive hemangioma, that differs from classic infantile hemangioma in clinical development, histologic and radiologic appearance, and immunophenotype. Lesions of this type have been considered clinical and morphological variants of infantile hemangioma. However, our findings show that these lesions are pathogenically distinct from infantile hemangioma. The histologic features of these lesions suggest that thrombosis, possibly within lymphatic or vascular malformations, may be important in their etiology. In the past, the word hemangioma has been used to lump together a diverse group of vascular tumors and malformations. By including so many different entities with differing clinical presentations, natural histories, and histologic features, hemangioma has ceased to have any real diagnostic meaning. As this article demonstrates, several clinically and histologically distinct vascular tumors can be recog-
nized. Hemangioma cannot function as a stand-alone diagnosis for these tumors. Instead it must be modified with adjectives to indicate the specific clinicopathological entity being described (ie, infantile hemangioma, congenital nonprogressive hemangioma, tufted angioma, etc). Adoption of this more specific terminology should help decrease diagnostic confusion and assist in patient management.

Following submission of this article, an important article was published by Enjolras et al.," describing the clinical and histologic features of noninvoluting congenital hemangiomas. These tumors, as beautifully described in that article, are histologically distinct from the congenital nonprogressive hemangiomas described in the present article. Thus, these 2 tumor types probably represent different entities despite certain clinical similarities. However, the etiologic relationship between these tumors remains to be determined.

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Corresponding author and reprints: Paula E. North, MD, PhD, Department of Pediatric Pathology, Arkansas Children's Hospital, 800 Marshall St, Little Rock, AR 72202 (e-mail: northpaulac@uams.edu).

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