Congenital Disseminated Pyogenic Granuloma: Characterization of an Aggressive Multisystemic Disorder

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Objective To describe the clinical, radiologic, and histopathologic features of "congenital disseminated pyogenic granuloma" involving various organs with high morbidity related to cerebral hemorrhagic involvement.

Study design We searched the database of the Vascular Anomalies Center at Boston Children's Hospital from 1999 to 2019 for patients diagnosed as having multiple vascular lesions, visceral vascular tumors, congenital hemangiomatosis, multiple pyogenic granulomas, or multiple vascular lesions without a definite diagnosis. A retrospective review of the medical records, photographs, histopathologic, and imaging studies was performed. Only patients with imaging studies and histopathologic diagnosis of pyogenic granuloma were included.

Results Eight children (5 male, 3 female) had congenital multifocal cutaneous vascular tumors. Lesions also were found in the brain (n = 7), liver (n = 4), spleen (n = 3), muscles (n = 4), bone (n = 3), retroperitoneum (n = 3), and intestine/mesentery (n = 2). Less commonly affected were the spinal cord, lungs, kidneys, pancreas, and adrenal gland (n = 1 each). The mean follow-up period was 21.8 months. The cerebral and visceral lesions were hemorrhagic with severe neurologic sequelae. The histopathologic diagnosis was pyogenic granuloma with prominent areas of hemorrhage and necrosis. The endothelial cells had enlarged nuclei, pale cytoplasm and were immunopositive for CD31 and negative for D2-40 and glucose transporter 1.

Conclusions Congenital disseminated pyogenic granuloma is a distinct multisystemic aggressive disorder that primarily affects the skin, brain, visceral organs, and musculoskeletal system. Differentiation of this entity from other multiple cutaneous vascular lesions is critical because of possible cerebral hemorrhagic involvement. *(J Pediatr 2020;226:157-66)*.

Pyogenic granuloma is a mucocutaneous vascular lesion that typically affects children. A small erythematous papule enlarges rapidly to a friable, pedunculated lesion; the cervicofacial region, trunk, and upper extremities are the most common locations.[1-3] The etiology of pyogenic granuloma recently has been linked to somatic mutations in GNAQ, KRAS, and BRAF.[4]

Pyogenic granuloma usually is considered an acquired, solitary lesion, but the uncommon variants, including multiple, visceral, intravenous, and congenital disseminated forms have been reported.[2,3,5-8]

This study analyzes the clinical, imaging and histopathologic characteristics of a congenital form of pyogenic granuloma presenting with multiple lesions in the skin, central nervous system, visceral organs, and musculoskeletal system with an aggressive clinical course. We also differentiated congenital disseminated pyogenic granuloma (CDPG) from other congenital multifocal vascular lesions, particularly the more common infantile hemangiomas.

Methods

This retrospective study was reviewed and approved by the Boston Children's Hospital Committee on Clinical Investigation. We identified a cohort of children by culling the database of the Vascular Anomalies Center at Boston Children's Hospital from 1999 to 2019 for patients with multiple vascular lesions, visceral vascular tumors, congenital "hemangiomatosis," multiple pyogenic granulomas, or multiple vascular lesions. The collected clinical data included demographics, age at onset, locations, size of lesions, initial diagnosis, and natural history. A retrospective review of the medical records, photographs, and imaging studies was performed. Histopathologic slides were

CDPG	Congenital disseminated pyogenic granuloma
CNS	Central nervous system
GLUT-1	Glucose transporter 1

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reviewed from all patients with the exception of one in which only electronic images were available. In total, there were 26 lesions from the skin, 4 from the subcutaneous region of the thigh, and 1 each from the nostril, tongue, liver, and temporal lobe of brain. At least 1 cutaneous specimen was available for review in all patients and, notably, histopathology from 11 such lesions was available in 1 other patient. At least 1 specimen from all patients had immunohistochemical staining performed for Glut-1, and 6 specimens had additional immunohistochemical staining performed for 1 or more of the following: CD31, CD34, and D2-40. Only patients with imaging studies and histopathologic diagnosis of pyogenic granuloma were included.

Results

Patients

Eight children (5 male, 3 female; 6 white, 1 black, and 1 Hispanic) had histologically confirmed extensive cutaneous and multivisceral pyogenic granulomas of congenital onset. Four infants were born full-term (patients 1, 2, 4, 6); 3 via normal vaginal delivery and 1 via cesarean delivery because of placenta previa (patient 4). Two infants were born prematurely at 35 weeks of gestation (patients 7, 8). Patient 8 had a late prenatal sonographic diagnosis of an intracranial vascular lesion at 35 weeks of gestation. Family history was unremarkable other than consanguineous marriage of the parents in one instance (first cousins, patient 2). The mean follow-up period was 21.8 months (range 2-54 months). The referring diagnoses included multiple congenital hemangiomas, diffuse neonatal hemangiomatosis, cutaneovisceral angiomatosis with thrombocytopenia, and nonspecific vascular lesions.

Clinical Features

The demographic data, clinical, and imaging findings are summarized in Table I. Multifocal pyogenic granulomas were noted in the skin (n = 8), brain (n = 7), liver (n = 4), spleen (n = 3), muscles (n = 4), bone (n = 3), retroperitoneum (n = 3), and intestine/mesentery (n = 2). Less frequently involved organs included the spinal cord, lung, kidney, pancreas, and adrenal gland (n = 1 for each).

Transient coagulopathy developed after birth in 4 patients (patients 1, 6, 7, 8) who had extensive involvement of the liver, spleen or muscles. Patient 6, who had a large thigh muscular lesion, developed severe thrombocytopenia (lowest level 20 000/μL), hypofibrinogenemia (<60 mg/dL), anemia, and elevated D-dimer. He was transfused with platelets and fresh frozen plasma. The platelet count gradually improved reaching 322 000/μL at 2 weeks of age. Fibrinogen also rose to 110 and 277 mg/dL at 2 and 6 weeks of age, respectively. The D-dimer remained elevated (>20.0 μg/mL) beyond the neonatal period but dropped to 0.7 μg/mL at 6.5 months of age. Chronic normocytic anemia persisted with hemoglobin level of 10.0 g/dL at 2 weeks of age, and the level fluctuated between 7.6 and 10.6 g/dL during

Table I. Clinical and imaging findings of CDPG

Patient no., sex	Skin	Brain	Visceral	MSK	Bone	Others	Follow-up, mo	Medications
1, male	+	–	Liver, spleen	–	–	Intestine/mesentery	48	C, P
2, male	+	+	Liver, pancreas, adrenal	+	Ribs	Lung, spinal cord, retroperitoneum	18	C, P
3, male	+	+	–	–	–	–	14	C, P, S
4, male	+	+	–	–	–	–	28	C, P
5, female	+	+	Spleen	–	–	–	8	C, P, T
6, male	+	+	–	+	–	–	54	C, M, VC, VB
7, female	+	+	Liver	+	Femur	Kidneys, intracranial, retroperitoneum	3	P, S
8, female	+	+	Liver, spleen	+	Iliac	Intracranial, intestine/mesentery, retroperitoneum	2	C, P, VC

C, corticosteroid; *M*, methotrexate; *MSK*, musculoskeletal; *P*, propranolol; *S*, sirolimus; *T*, timolol; *VB*, vinblastine; *VC*, vincristine.
+denotes present; – denotes absent.

the next 7.5 months. Patient 7 with numerous hepatic, cerebral, splenic, muscular, and hemorrhagic intra-abdominal pyogenic granulomas developed gastrointestinal bleeding in the first week of life requiring repeated transfusions. Two weeks following initiation of treatment with sirolimus and propranolol at 4 weeks of age, thrombocytopenia and gastrointestinal bleeding resolved. Patient 8, who was born with multiple hemorrhagic lesions in the skin, brain, liver, and spleen, developed thrombocytopenia (platelet count 69 000-80 000/μL), hypofibrinogenemia (<60 mg/d), and anemia requiring frequent transfusions. Patient 1 had mild hypofibrinogenemia (117 mg/dL), which was treated with transfusion with platelets and fresh frozen plasma. Coagulopathy largely resolved in several weeks in the 3 patients (patients 1, 6, 7) with follow-up. Echocardiography in 3 patients (patients 1, 6, 8) demonstrated mild cardiac overload in patient 8 and normal heart function in patients 1 and 6.

Cutaneous Pyogenic Granulomas

All children were born with cutaneous pyogenic granulomas, either multifocal (n = 6) or solitary (n = 2). Two newborns (patients 2, 4) with solitary lesions at birth developed numerous lesions early in the neonatal period. The cutaneous lesions were red to pink or bluish gray and were located in the head and neck, trunk, and extremities (**Figure 1**, A). Larger lesions had subcutaneous extension or were primarily located in the subcutis (**Figure 1**, B). Most pyogenic granulomas were papular, some were grouped (**Figure 1**, C) or pedunculated (**Figure 1**, D) and ranged in size between 2 and 33 mm. Ulceration and bleeding were frequent (**Figure 1**, E).

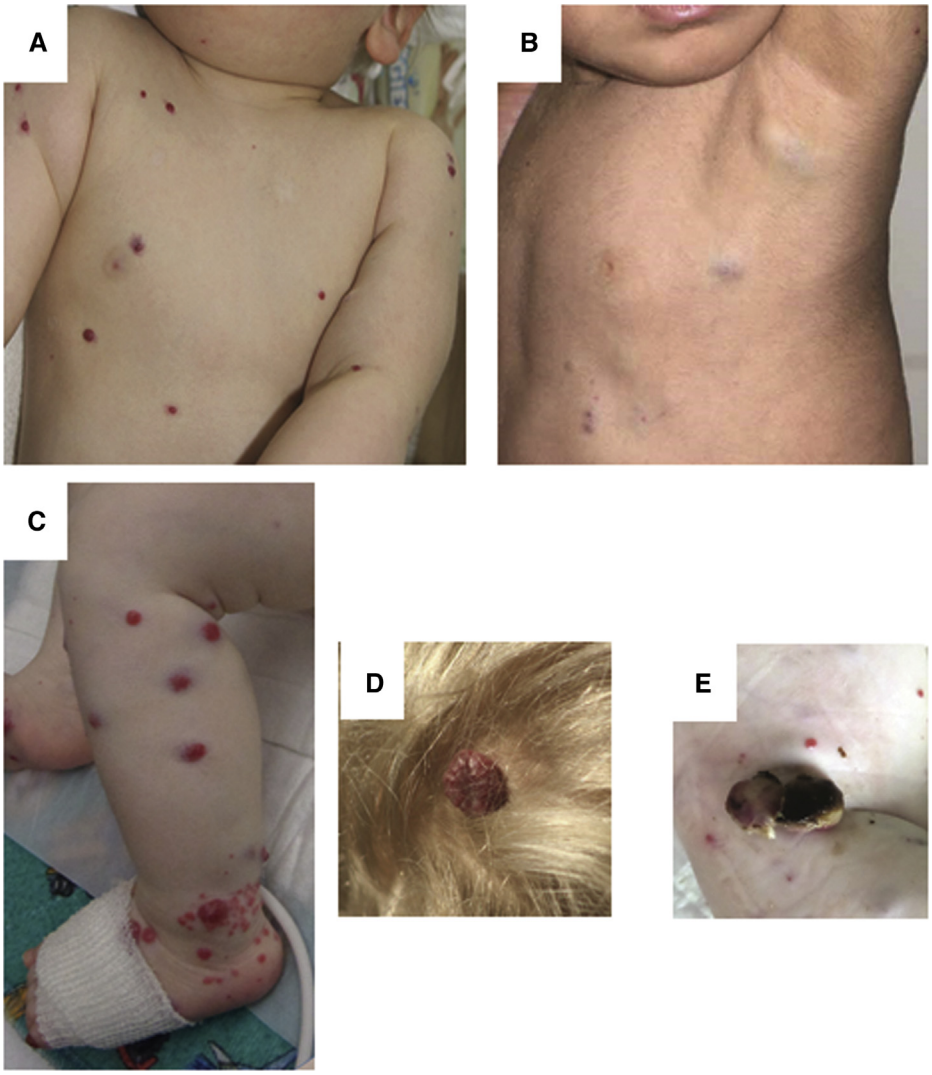

Figure 1. Cutaneous pyogenic granulomas. **A,** Multiple small red lesions involving head, trunk, and upper extremities. **B,** Subcutaneous nodules with faint bluish discoloration of the overlying skin. Note **C,** grouped, **D,** pedunculated, **E,** and ulcerated pyogenic granulomas.

The clinical course of cutaneous pyogenic granulomas was characterized by early progression followed by concomitant slow regression. The number and size of lesions significantly increased during the neonatal period in 7 patients (patients 1, 2, 3, 4, 6, 7, 8) and in the infantile period in 5 (patients 1, 2, 3, 6, 8) with 6-18 months' follow-up. The pyogenic granulomas did not grow significantly after birth in patient 5 until the age of 8 months.

Regression of pyogenic granulomas (Figure 2) was associated with development and growth of other lesions between 11 weeks and 14 months. Cutaneous pyogenic granulomas gradually disappeared by the age of 12 months (patient 6), 22 months (patient 6), 28 months (patient 4), and 4 years (patient 1).

Cerebral and Spinal Pyogenic Granulomas

Seven patients had intracranial pyogenic granulomas. Five of them developed multiple hemorrhagic parenchymal masses at birth with major neurologic sequelae, including seizures and motor impairment (Figure 3, A). Two patients (patients 7, 8) had intracranial, extra-axial hemorrhagic lesions with cystic degeneration; the latter was diagnosed prenatally at 35 weeks of gestation. Patient 6 had a small asymptomatic cerebral lesion and a hemorrhagic extra-axial, dural-based lesion. Patient 1, who was imaged at 2 months, had no intracranial involvement. Resolution of cerebral lesions was noted at the age of 1 year in patient 4. A solitary pyogenic granuloma was found in the spinal cord in patient 2 at the age of 7 months.

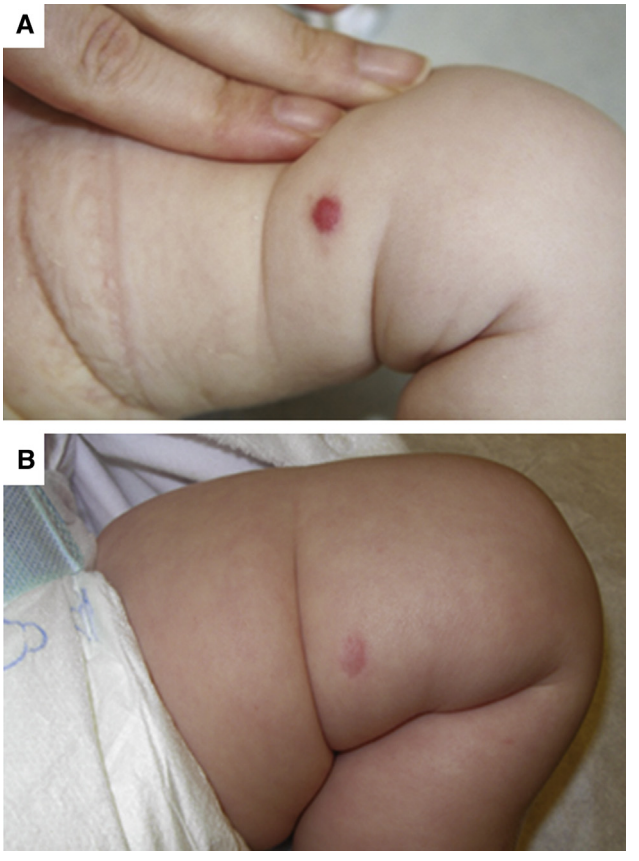

Figure 2. Interval regression of a cutaneous lesion in patient 1 between **A,** 2 and **B,** 5.5 months of age.

Hepatic Pyogenic Granulomas

Four children (patients 1, 2, 7, 8) were found to have hepatic vascular masses as early as at birth. There were 2 main types: the multifocal (n = 2, patients 1, 2) and the diffuse, confluent types with near-total involvement including innumerable solid and massive cystic lesions (n = 2, patients 7, 8) (Figure 3, B and C).

Splenic Pyogenic Granulomas

Diffuse splenic involvement with splenomegaly was detected in 3 patients (patients 1, 5, 8). Two of them (patients 1, 8) had concomitant hepatic and intestinal–mesenteric lesions. Intestinal–mesenteric pyogenic granulomas mesenteric involvement, intestinal thickening and enlarged mesenteric vessels were noted in 2 children (patients 1, 8); both had concomitant hepatic, splenic, and intestinal–mesenteric lesions.

Musculoskeletal Pyogenic Granulomas

In 4 patients (patients 2, 6, 7, 8), multiple hypervascular solid masses were documented in the skeletal muscles of the head, neck, trunk, and extremities between birth and 4 months of age. Of these, 3 (patients 2, 6, 8) had concomitant osseous lesions. Patient 6 was born with a large hypervascular intramuscular mass in the left thigh (Figure 3, D) with overgrowth of the entire limb. The well-defined, lobulated, hemorrhagic lesion substantially grew during infancy with a femoral fracture at the age of 7 months. The cutaneous and muscular lesions increased in size and a new lesion in the temporal bone was noted. At 1-year follow-up, the cutaneous lesions had resolved and the thigh lesion markedly regressed without treatment (Figure 3, E), although the limb remained overgrown at 54-month follow-up.

Other Locations

A large well-defined solid pulmonary mass was discovered at the age of 4 months in patient 2 with interval growth on a follow-up scan at 18 months of age. Three patients (patients 2, 7, 8) had lesions in retroperitoneal fat; 1 patient (patient 2) had a large hemorrhagic cystic lesion in the pancreatic head with smaller lesions in the adrenal gland. Multiple renal masses were noted at birth in patient 7.

Histopathologic Findings

The cutaneous and mucosal biopsies typically showed anastomosing rounded and elongated vascular lobules involving the dermis and mucosa respectively (Figure 4, A). On occasion, the subcutaneous fat was also or only involved. There was a range of histopathology, with variation within individual lesions and among lesions in an individual

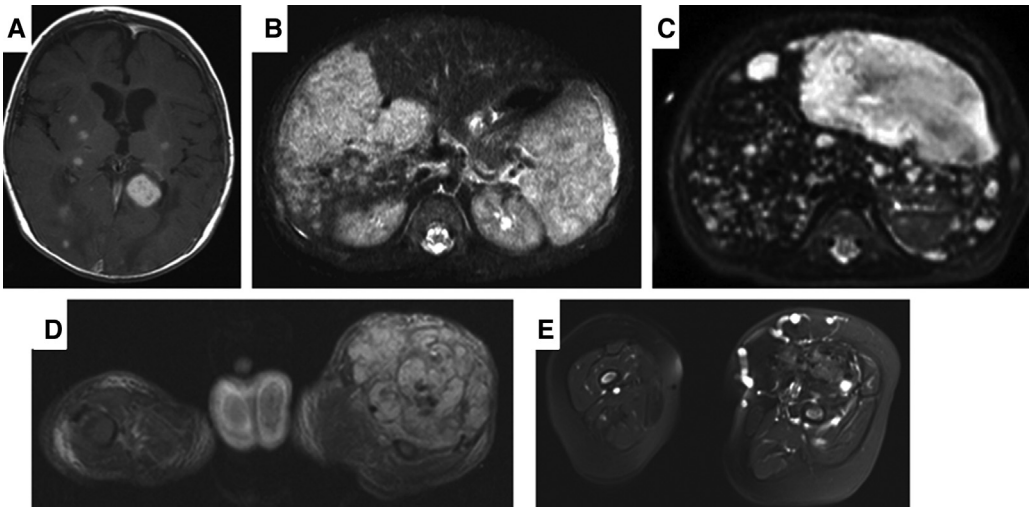

Figure 3. **A,** Cerebral pyogenic granulomas. Axial contrast-enhanced T1-weighted images at 3 months of age demonstrating multiple solid enhancing cerebral lesions. **B,** Liver and spleen pyogenic granulomas. Contrast-enhanced fat-saturated axial T1-weighted image at 1 month of age demonstrating extensive involvement of right hepatic lobe and spleen. **C,** Axial fat-saturated T2-weighted image at the age of 2.5 months demonstrating a large cystic lesion in the left liver lobe with numerous smaller lesions throughout the liver and spleen. **D,** Musculoskeletal pyogenic granulomas. Axial fat-saturated T2-weighted images at birth showing a large, well-defined, lobulated, hypervascular intramuscular mass in the left thigh. **E,** Marked shrinkage of the pyogenic granuloma with residual dilated veins at 1 year of age.

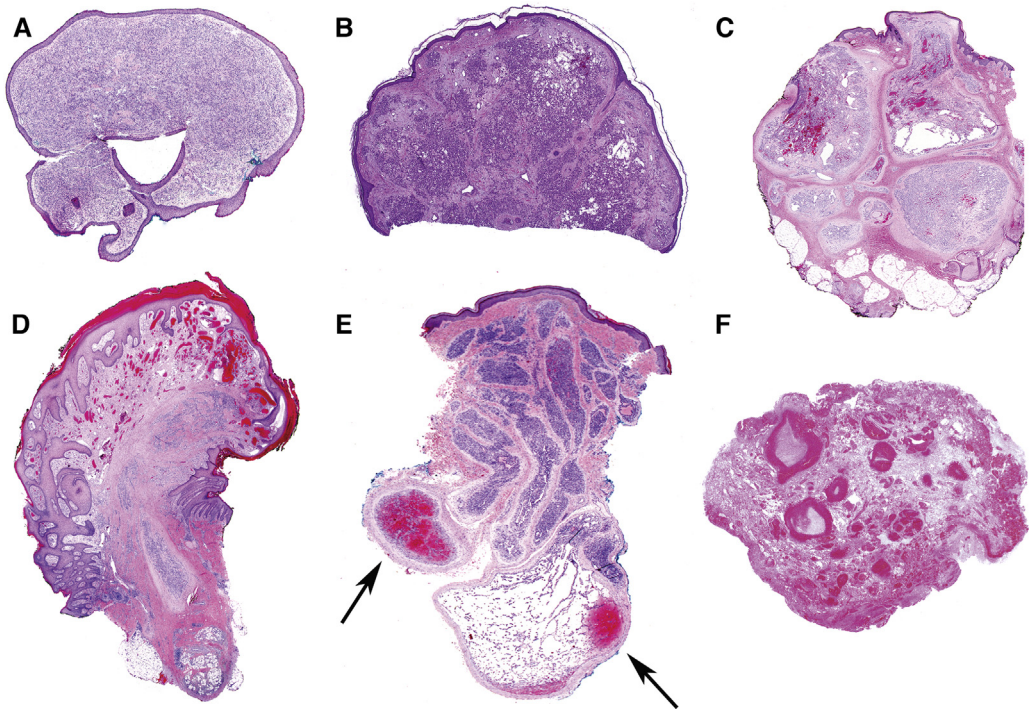

Figure 4. **A-F,** Variation in cutaneous lesions at scanning magnification (H&E stain × 20). **A,** Dermal tiny lobules with inconspicuous canalization. **B,** Characteristic rounded and vertically elongated interconnected dermal lobules elevating the epidermis. **C,** Marked variation in lobular size, some lobules with fibrous collars. **D,** Broad expanse of dilated capillary channels in upper dermis. **E,** Hemorrhage within one nodule (*arrows*) and a prominent anastomotic pattern in another. **F,** Whole mount of a 2.5-cm mass in the temporal lobe with numerous foci of hemorrhage and necrosis of varying size (H&E stain). *H&E*, Hematoxylin and eosin.

patient. In some specimens, particularly if they were small, the lobules were tiny, the endothelial cells were enlarged, nuclear size was greater than usual, the cytoplasm was pink and canalization was barely discernible (Figure 4, A). In most specimens, the epidermis was elevated, often had a peripheral collar and was occasionally ulcerated with accompanying inflammation. Some lesions had lobules of fairly uniform size (Figure 4, B) and others had lobules of varying sizes (Figure 4, C), sometimes reaching massive proportions and obscuring lobularity. In many specimens, the capillary channels were enlarged several times over, involving part of or the entire lobule, sometimes resulting in a large expanse of dilated vessels either from expansion of a single lobule or confluence of multiple lobules (Figure 4, D). The vessels were round or elongated but an anastomotic motif was common (Figure 4, E) and was the only pattern in the cerebral lesion (Figure 4, F). Intralobular hemorrhage was sometimes observed (Figure 4, E and F) and at times accompanied by necrosis (Figure 4, F) The endothelial cells had slightly or moderately enlarged round-to-oval nuclei with fine chromatin and occasional mitosis. The nuclei imparted a degree of endothelial disarray because of variation in distances between nuclei and lack of consistent orientation of the ovoid nuclei in relation to the basement membrane (Figure 5, A). The cytoplasm was pale and minimally increased. Lesional endothelial cells were immunopositive for CD31, variably for CD34, and immunonegative for D2-40 and Glut-1. Pericytes were less conspicuous than the endothelial cells. Foci of papillary endothelial hyperplasia were sometimes present, particularly in larger lesions. Individual channels were separated by delicate fibrous stroma containing occasional lymphocytes and mast cells and sometimes extramedullary hematopoiesis. Some lobules displayed fibrosis, either within their substance, as a collar or both. Arteries and veins were inconspicuous. In the hepatic core needle biopsy, the lesional capillaries were similar to cutaneous ones and exhibited infiltration along the sinusoids (Figure 5, B). In the cerebral lesion, lobularity was not evident and areas of hemorrhage and necrosis were prominent (Figure 5, C) and an anastomotic pattern was dominant (Figure 5, D).

Treatment

The patients were treated with various combinations of medications (Table I) at different referring centers with limited longitudinal data regarding the outcome. Growth and/or development of cutaneous and visceral lesions were noted

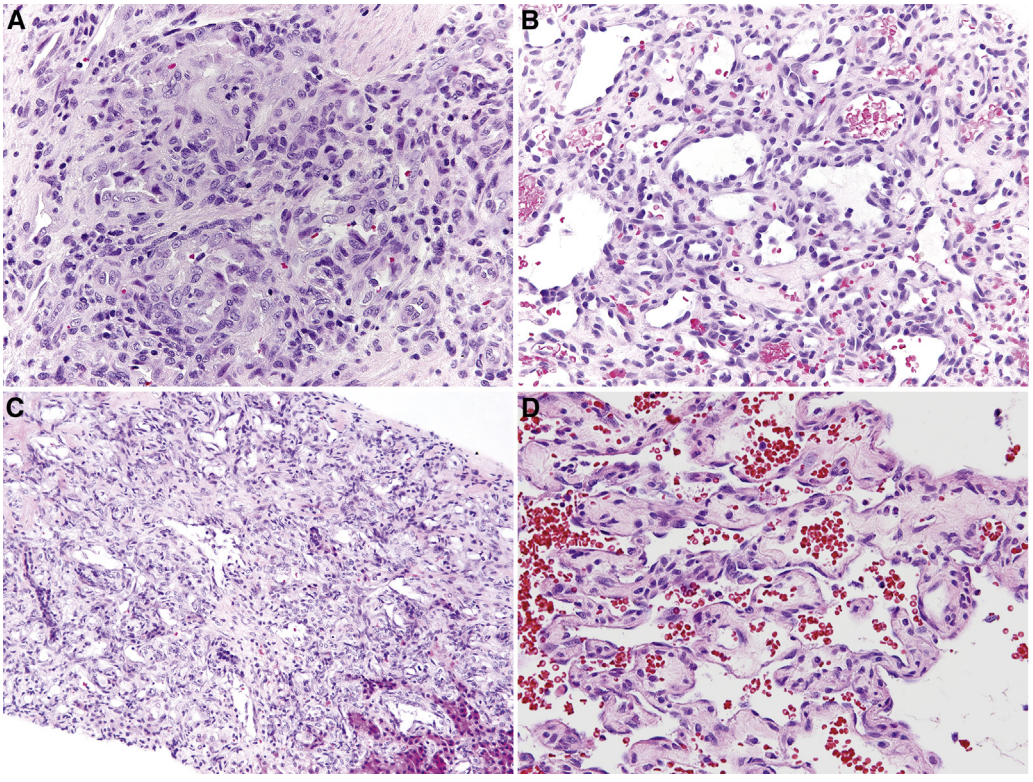

Figure 5. **A,** Cutaneous lesion depicted in Figure 4, A showing capillary channels lined by unusually plump endothelial cells with redundancy and possible dyscohesion (H&E, × 400). **B,** Cutaneous lesion with typical round and elongated capillary channels and minimally enlarged endothelial cells with non-uniformity in spacing and nuclear orientation (H&E, × 400). **C,** Hepatic core needle biopsy revealing a confluence of capillary channels surrounding bile ducts and separating hepatic cords (H&E, × 200). **D,** Temporal lobe lesion depicted in Figure 4 F with dominant anastomotic canalicular pattern (H&E, × 200). *H&E*, Hematoxylin and eosin.

despite treatment with corticosteroid and propranolol (n = 4), propranolol and sirolimus (n = 1), sirolimus (n = 1), corticosteroid, methotrexate and vinblastine (n = 1), and corticosteroid and propranolol and vincristine (n = 1). In other patients, shrinkage of the lesions was noted with prednisolone (n = 1), sirolimus (n = 1), and topical timolol (n = 1). Four patients had excision of pyogenic granulomas from the skin (patients 3, 6, 8) or the brain (patient 2).

Discussion

We highlight an aggressive clinical course of multisystem congenital pyogenic granuloma in neonates and young children. Multiple histopathologically proven pyogenic granulomas arose in the skin, central nervous system (CNS), liver, spleen, muscles, bone, bowel, mesentery, retroperitoneum, lung, kidney, and adrenal glands. The clinical presentation was related to location, number, and size of these lesions as well as associated bleeding with the most serious morbidity primarily caused by hemorrhagic cerebral lesions. The evolution of pyogenic granulomas was characterized by an early proliferation with frequent ulceration and bleeding followed by slow involution. Although lesions were evident at birth or even prenatally, new pyogenic granulomas appeared in metachronous and synchronous fashions in the neonatal and infantile periods in the majority of patients. Involution of some pyogenic granulomas may commence early during infancy and other lesions develop and proliferate. Cutaneous pyogenic granulomas involuted as early 12 months. Both intralesional and perilesional hemorrhagic complications occurred with pyogenic granulomas causing marked cystic expansion of the hepatic, retroperitoneal, and intracranial extra-axial lesions. Transient coagulopathy, characterized by thrombocytopenia and/or hypofibrinogenemia, and anemia were noted in 4 neonates with extensive or very large lesions. Transient thrombocytopenia and anemia, particularly in the neonatal period, have been reported with other congenital vascular lesions including hepatic rapidly involuting congenital hemangioma.[9] vascular anomalies are known to cause different types of coagulopathy. Kasabach–Merritt phenomenon is a persistent profound coagulopathy including thrombocytopenia, hypofibrinogenemia, and elevated D-dimer that typically occurs in kaposiform hemangioendothelioma and tufted angioma.[10] Venous malformations are frequently associated with chronic consumptive "localized intravascular coagulopathy" characterized by elevated level of D-dimer and hypofibrinogenemia.[11] Mild sustained thrombocytopenia is a core manifestation of cutaneovisceral angiomatosis with thrombocytopenia.[12] Unlike Kasabach–Merritt phenomenon, localized intravascular coagulopathy, and cutaneovisceral angiomatosis with thrombocytopenia, coagulopathy in our patients with CDPG was transient with spontaneous improvement within weeks.

The cutaneous manifestations of "congenital disseminated pyogenic granuloma" were initially reported by Browning et al in 2 infants.[5] A 3-month-old Hispanic girl who was born with 2 pyogenic granulomas then developed numerous lesions on the trunk and extremities shortly after birth; however, no abdominal or cerebral lesions were noted. The second child with congenital numerous pyogenic granulomas in the trunk, face, and extremities developed more lesions after birth, hepatomegaly and a questionable hepatic nodule. The congenital presentation of cutaneous and noncutaneous pyogenic granulomas or "pyogenic granuloma-like vascular lesions" has been reported in 2 patients.[13-15] North et al described a neonate with numerous congenital cutaneous, pulmonary, and muscular vascular lesions which were glut-1 negative and some feature suggestive of pyogenic granuloma.[13] Uyama et al reported a female newborn with congenital "disseminated hemangiomas" with cystic changes in the skin, liver, spleen, pancreas, kidneys, pleura, and cerebellum and thrombocytopenia with inconsistent response to corticosteroids.[14] Mallet et al reported a newborn with multiple congenital cutaneous vascular lesions with postnatal development of cerebral and hepatic lesions.[15] Despite initial improvement with corticosteroid, vincristine and propranolol, acute intracranial hypertension developed at the age of 2 months due cystic changes in the cerebral lesion. Pathologic features were strongly suggestive of pyogenic granuloma with negative glucose transporter 1 (GLUT-1) and D2-40 immunostains. Rothe et al described a premature male neonate with numerous congenital cutaneous lesions with poor response to corticosteroids.[16] During 20-months follow-up, skin lesions continued to proliferate, ulcerate, and bleed with failure to thrive. The authors considered the diagnosis of "disseminated pyogenic granuloma" but favored the diagnosis of "neonatal hemangiomatosis." The authors also reviewed 9 reports of multiple congenital "hemangiomas" with gastrointestinal bleeding, hepatosplenomegaly, coagulopathy, jaundice, and heart failure without histopathologic confirmation. Some of the features reported, such as the congenital onset, resolution starting early in infancy, and the presence of calcified CNS lesion, are not typical for infantile hemangioma and may represent CDPGs.

Differentiation of CDPG from Other Vascular Anomalies

The clinical and radiologic features of CDPG may overlap with other multifocal congenital vascular lesions, most commonly with multiple infantile hemangiomas, "diffuse neonatal hemangiomatosis," cutaneovisceral angiomatosis with thrombocytopenia, capillary malformation-arteriovenous malformation, and multiple venous malformations (**Table II**).[17-22]

Multifocal infantile hemangiomas typically appear and proliferate in early infancy then involute, have positive GLUT-1 immunostaining, and do not typically affect the brain parenchyma,[23] spinal cord, muscles, and bones. Although both infantile hemangiomas and CDPG have proliferative and involutive phases, CDPG manifests at birth with both metachronous and synchronous development and concomitant proliferation and involution of different lesions. CDPG exhibits negative GLUT-1 immunostaining and cerebral and

Table II. Comparison of CDPG with other multifocal vascular anomalies in early infancy[17-22]

Disorder/OMIM #	Sex/genetics	Common involvement	Onset	Differentiating features
CDPG	Unknown	Skin, brain, liver	Congenital	Hemorrhagic cerebral and visceral lesions, transient coagulopathy
Multiple IHs #602089	F > M	Skin, subcutis	Neonatal-early infancy	Phasic evolution
DNH #106070	F > M	Skin, liver, brain, lungs	Neonatal > congenital	
CAT	M = F	Skin, GI, lungs	Congenital	Red–brown or blue macules, GI bleeding, persistent mild thrombocytopenia
CM-AVM #608354	M = F RASA1 mutation. AD	Multiple CMs with pale halo, AVM in brain, face or limbs	Congenital	Parkes–Weber syndrome
BRBNS/multiple VMs #112200	M = F Somatic TEK (TIE2)	Skin, subcutis, GI, muscles	Congenital	LIC, anemia
GVM #138000	M = F Glomulin mutation AD	Multiple bluish small cutaneous and subcutaneous lesions	Congenital	Pain, cobblestone appearance

AD, autosomal dominant; *BRBNS*, blue rubber bleb nevus syndrome; *CAT*, cutaneovisceral angiomatosis with thrombocytopenia; *CM-AVM*, capillary malformation–arteriovenous malformation; *DNH*, diffuse neonatal hemangiomatosis; *GI*, gastrointestinal; *GVM*, glomuvenous malformation; *IH*, infantile hemangioma; *LIC*, localized intravascular coagulopathy; *OMIM*, Online Mendelian Inheritance in Man; *VM*, venous malformation.

musculoskeletal involvement is common. Multifocal and diffuse types of hepatic involvement in CDPG resemble patterns in infantile hemangiomas.[24] Dickie et al described 5 patients with GLUT-1–negative or indeterminate cutaneous and hepatic vascular lesions which involuted rapidly within months.[25] These lesions may have been CDPGs.

The term "diffuse neonatal hemangiomatosis" has been loosely used for a life-threatening spectrum of cutaneous, visceral and cerebral vascular lesions. In a meta-analysis of published literature, diffuse neonatal hemangiomatosis was evident at birth (72%) and thrombocytopenia was frequent (40%).[21] Multiple vascular lesions were noted in the skin (100%), liver (72%), lungs (43%), brain (35%), and intestine (29%), with less frequent involvement of the head and neck, bone, spleen, pancreas, and adrenal glands. In addition, extra-axial leptomeningeal and muscular lesions have been reported.[26-28] Nevertheless, in an evidence-based review of 73 published cases reported to have diffuse neonatal hemangiomatosis, 43 had infantile hemangiomas, 17 had cutaneovisceral angiomatosis with thrombocytopenia, and 13 had multifocal vascular lesions, not otherwise specified.[19] Of particular interest are reports of diffuse neonatal hemangiomatosis with multiple congenital vascular lesions involving the skin, brain, liver, spinal cord, muscles, lungs, pleura, intestine, and mesentery, described to have had poor response to corticosteroids.[26-33] In retrospect, several published reports of multifocal infantile hemangioma or diffuse neonatal hemangiomatosis may have been examples of CDPG.

Unlike the nodular or exophytic cutaneous pyogenic granulomas, cutaneovisceral angiomatosis with thrombocytopenia, also known as multifocal lymphangioendothe liomatosis with thrombocytopenia, presents at birth with multiple discrete, red–brown or blue vascular macules and maculopapular lesions in the skin, gastrointestinal tract, lungs, liver, spleen, bone, and muscle in association with mild thrombocytopenia.[12] Lesional endothelial cells in cutaneovisceral angiomatosis with thrombocytopenia are immunopositive for lymphatic vessel endothelial hyaluronan receptor 1 and negative for GLUT-1 and D2-40.[34] Gastrointestinal hemorrhagic lesions are common in cutaneovisceral angiomatosis with thrombocytopenia and cerebral involvement is infrequent. cutaneovisceral angiomatosis with thrombocytopenia was also reported without skin involvement.[35,36]

Venous malformations are congenital lesions that can present with multiple cutaneous and deep lesions. Multiple venous malformations can be sporadic or associated with blue rubber bleb nevus syndrome, cutaneomucosal venous malformation, or glomuvenous malformation.[37] Blue rubber bleb nevus syndrome is a rare disorder characterized by multiple cutaneous, deep and gastrointestinal venous malformations. Unlike the firm hypervascular pyogenic granulomas, venous malformations are typically bluish, soft, and compressible. The development of new lesions, rapid progression, spontaneous involution, and hemorrhagic cerebral and visceral involvement are not typical features of venous malformations.

Our study highlights the importance of including CDPG in the differential diagnosis for any newborn with multiple cutaneous and visceral vascular lesions. Given its rarity, severity, and multiorgan involvement, children with CDPG should preferably be assessed and managed by an experienced interdisciplinary team. When CDPG is suspected, proper clinical and imaging workup for critical organ involvement should be performed at birth or at the time of initial presentation. Testing for potential hematologic abnormalities, primarily anemia and coagulopathy, and fecal occult blood testing is recommended. Evaluation of cardiac function is also recommended because of possible cardiac overload. Liver infantile hemangiomas express type 3 iodothyronine deiodinase that converts thyroid hormone to its inactive form, causing severe hypothyroidism.[37] Although the status of the thyroid function in CDPG with hepatic involvement is not known, assessment of the thyroid function is recommended. Close follow-up,

especially in the infantile period, is mandatory to characterize progression of the disease and development of new lesions. Whole-body magnetic resonance imaging at birth may reveal cerebrospinal, visceral, or deep musculoskeletal lesions. Organs with clinically significant involvement can be further investigated with dedicated imaging. Abdominal visceral involvement can be followed closely with serial abdominal ultrasonography (eg, every 6-8 weeks) in the first year of life or until involution of the lesions. Although the diagnosis of CDPG can be suggested on the basis of clinical and imaging findings, it is imperative that the definitive diagnosis is established with tissue biopsy. Excisional biopsy of cutaneous pyogenic granulomas or image-guided biopsy of large lesions, preferably with molecular profiling, should not be delayed.

Our retrospective study has several limitations. Foremost, several patients in this small cohort were primarily managed at outside institutions and then referred to our center for consultation; resulting in gaps in the available data and variable follow-up. This restricted the ability to elucidate the natural history of the disease over a long period of time or to monitor response to treatment. Many of the imaging studies were performed at the referring institutions using various modalities and protocols. In addition, the findings in this cohort may overrepresent children with severe manifestations because of potential referral and ascertainment biases. Lastly, we were unable to perform genomic evaluation on the available tissue samples for putative causative mutations, which may offer a potential specific targeted therapy for this disorder, Congenital disseminated pyogenic granuloma is a clinically and histopathologically distinct disorder with multisystemic involvement of the skin, central nervous system, viscera, muscles and bone. Serious morbidity is related to hemorrhagic CNS lesions. It should be considered when evaluating multiple congenital vascular lesions in neonates or during prenatal imaging. Differentiating congenital disseminated pyogenic granuloma from other disorders has crucial clinical and therapeutic implications. Imaging of the brain and viscera should be considered if this disorder is suspected. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Changes in Miller Fisher Landscape

Qaqundah BY, Taylor WF. Miller Fisher Syndrome in a 22-Month-Old Child. J Pediatr 1970;77:868-70.

Miller Fisher syndrome was first characterized in 1956 by its classical triad of ataxia, ophthalmoplegia, and areflexia. We now describe Miller Fisher syndrome as a spectrum of symptoms manifesting as isolated ophthalmoplegia or ataxia, or combined ascending limb weakness, ptosis, mydriasis, or altered mentation (owing to overlap with Bickerstaff brainstem encephalitis). Miller Fisher syndrome can mimic a myriad of pediatric conditions, including acute cerebellar ataxia, infectious or postviral encephalitis, heavy metal poisoning, botulism, and myasthenia gravis. This 22-month-old girl presented with ataxia, nystagmus, and subsequent change in mentation. Cerebrospinal fluid was initially normal, and Miller Fisher syndrome was only recognized after a subsequent spinal tap revealed elevated protein with persistently normal cell count (cytoalbuminologic dissociation) in association with development of areflexia and ophthalmoplegia.

Anti-GQ1b antibodies were subsequently shown to be a more sensitive indicator of Miller Fisher syndrome than cytoalbuminologic dissociation. Cerebrospinal fluid protein slowly increases over 3 weeks, but anti-GQ1b is found in 81% of patients within the first week of symptoms.[1] This antibody targets ganglioside epitopes concentrated in cranial nerves III, IV, and VI, and the dorsal root ganglia, corresponding with Miller Fisher syndrome symptoms.[2] Anti-GQ1b is particular toward Miller Fisher syndrome and Miller Fisher syndrome-like variants, less in classic Guillain-Barre syndrome.

The patient fully recovered at 6 months after a course of prednisone in 1970, but Miller Fisher syndrome is now considered a self-limited condition. The majority of patients show full recovery at 5 months without treatment, and steroids do not shorten the course.[3] Intravenous immunoglobulin or plasmapheresis can be considered in severe Miller Fisher syndrome, but demonstrate limited benefit in outcome, with full recovery at 6 months in 89% and 66%-96% of patients, respectively.

Over the past 50 years, a clearer picture of the Miller Fisher syndrome spectrum has evolved, with a better serologic marker for diagnosis and improved treatment options.

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