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Multifocal Vascular Tumors and Fetal Hydrops

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A female infant weighing 3085 g was born at 33 and 4/7 weeks to an 18-year-old, gravida 1 para 0 mother after induction of labor for severe, nonimmune fetal hydrops. This singleton pregnancy was uncomplicated, including a normal 20-week ultrasound, until 32 weeks' gestation, when discordant maternal size and dates were noted. Findings of ultrasonography demonstrated polyhydramnios; edema of the fetal scalp, thorax, and abdomen; and an increased middle cerebral artery peak systolic velocity (102 cm/s). Fetal cordocentesis revealed hemoglobin of 7 g/dL, mean corpuscular volume of 125.8 fL, mean red cell distribution width of 99.7 fL, nucleated red blood cell percent of 140.1%, and platelet count of 42 000 per mm^3. Percutaneous in utero transfusion increased the hemoglobin levels from 7 to 12.8 g/dL. Cells in amniotic fluid had a 46XX karyotype and negative tests on polymerase chain reaction for parvovirus, herpes simplex virus 1 and 2, and toxoplasmosis. Subsequently, the mother developed pulmonary edema, lower-extremity edema, and increased liver enzymes (aspartate aminotransferase 70 U/L, alanine transaminase 57 U/L) consistent with mirror syndrome (a manifestation of severe fetal hydrops in which the mother displays the same pathologic manifestations as the fetus, also known as Ballantyne syndrome).[1] Delivery was induced and ultimately resulted in cesarean delivery for failure to progress.

After delivery, the infant was intubated for respiratory failure. Apgar scores were 2 and 7 at 1 and 5 minutes, respectively. Findings of the physical examination were remarkable for an infant with no spontaneous movement. She had a grade III/VI systolic ejection murmur, hepatosplenomegaly, and a distended abdomen. The skin was diffusely edematous and was covered with multiple 0.5- to 2-cm erythematous, blanchable, soft papules and plaques covering the entire body (**Figure 1**). Chest radiograph revealed massive cardiomegaly, diffuse pulmonary infiltrates, and small bilateral pleural effusions. Echocardiogram showed a dilated and hypertrophied right ventricle with septal flattening, bidirectional shunting through a large patent ductus arteriosus, left-to-right shunting through a patent foramen ovale, and a small pericardial effusion. Abdominal ultrasound demonstrated massive hepatomegaly with multiple, highly vascularized hepatic hemangiomas. Ultrasonography of the head demonstrated bilateral intraventricular hemorrhages, moderate hydrocephalus, and a right parietal hemangioma.

The infant was ventilated with high-frequency oscillatory ventilation due to hypoxemic respiratory failure. Inhaled nitric oxide was initiated for a persistent differential in the pre- and postductal oxygen saturations in conjunction with findings of suprasystemic pulmonary hypertension on echocardiogram. The infant was anemic with an initial hemoglobin of 8.8 g/dL and a reticulocyte percentage of 8.1% and found to have disseminated intravascular coagulation (partial thromboplastin time 103.4 seconds, prothrombin time 41.4 seconds, international normalized ratio 4.3, D-dimer 11340, fibrinogen <20 mg/dL, platelets 26 000 per mm^3). She was treated with numerous blood products, including fresh-frozen plasma, cryoprecipitate, platelets, and packed red blood cells.

Clinical Discussion

Fetal hydrops is defined as the accumulation of fluid in at least 2 fetal compartments, including the subcutaneous, pleural, peritoneal, and/or pericardial space. Nonimmune hydrops fetalis accounts for the majority of cases of fetal hydrops. It affects 1:1500 to 1:3750 deliveries and has a perinatal mortality rate of 55%-98%, depending upon the etiology.[2] The etiologies for nonimmune fetal hydrops are numerous, although some of the more common causes include aneuploidy, congenital infection (TORCH—ie, toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes infections—infections, congenital viral infections, congenital bacterial infections), congenital cardiac anomalies, genetic syndromes, hematologic abnormalities (fetal anemia, consumptive coagulopathies, hemoglobinopathies, thalassemias, or twin-twin transfusion syndrome), and tumors. The innumerable and widespread distribution of highly vascularized tumors in this patient, effectively functioning as arteriovenous shunts, caused cardiac overload and high-output cardiac failure.[3] Fetal anemia from a consumptive coagulopathy with microangiopathic hemolysis was evident by immature red blood cell production, schistocytes on peripheral blood smear, and thrombocytopenia. The anemia also contributed to high output cardiac failure and vascular leak, cumulatively producing

CH	Congenital hemangioma
DNH	Diffuse neonatal hemangiomatosis
GLUT-1	Glucose transporter protein-1
IH	Infantile hemangioma
KHE	Kaposiform hemangioendothelioma
MLT	Multifocal lymphangioendotheliomatosis
RICH	Rapidly involuting congenital hemangioma

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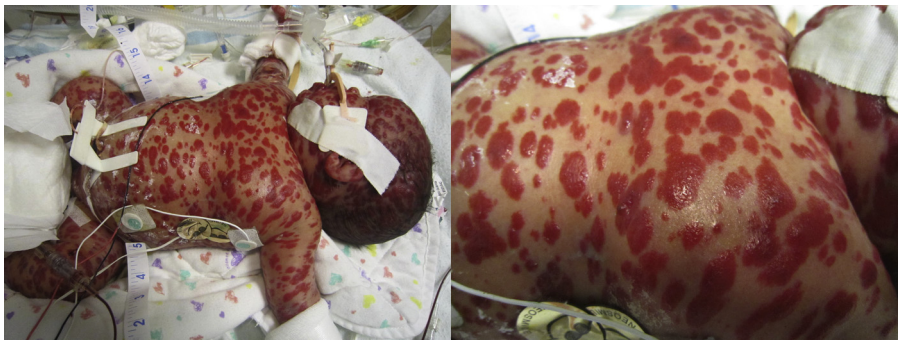

Figure 1. Red vascular tumors involving the majority of the skin surface are seen. Photos taken on the second day after birth.

fetal hydrops. Hydrops fetalis has been reported from hepatic vascular tumors, though it is a rare finding and has a high mortality rate.[4,5]

A variety of vascular tumors and malformations may present with a multifocal distribution in a neonate. The differential diagnosis includes infantile hemangiomas (IHs), congenital hemangiomas (CHs), kaposiform hemangioendotheliomas (KHEs), tufted angiomas, pyogenic granulomas, and multifocal lymphangioendotheliomatosis (MLT). Vascular tumors are characterized by their proliferative potential, whereas vascular malformations are considered developmental anomalies. Multifocal malformations include venous malformations (the so-called blue rubber bleb nevus syndrome), glomuvenous malformations, and capillary malformation-arteriovenous malformation syndrome.

The most common vascular tumor, IH, is a benign proliferation of endothelial cells that occurs in approximately 4%-5% of infants.[6,7] IHs typically arise in the neonatal period and follow a unique pattern of growth and regression characterized by rapid enlargement in the first few months of life, followed by slower growth and subsequent slow involution over several years. IHs often are absent or minimal at birth and come to attention within the first few weeks of life when rapid growth begins. Tollefson and Frieden[7] used parental photographs of patients with IH to better elucidate their growth pattern and found that IHs undergo rapid growth earlier than once thought, with an accelerated growth phase between 5.5 and 7.5 weeks of life.[7] Subtle precursor lesions are seen in up to 65% of neonates and include telangiectasias, pallor, or bruise-like lesion.[7] Unlike other vascular tumors, IH express glucose transporter protein-1 (GLUT-1), which can be stained for on histopathologic specimens.[6,8] IH typically present as solitary skin lesions, although multiple lesions can be seen. The presence of multiple lesions is associated with IH in other organs, primarily the liver. The uncommon pattern of numerous small IH in a generalized distribution has been termed hemangiomatosis (diffuse or disseminated) and is also associated with risk for involvement of other organs.

CHs are less common vascular tumors that present at birth fully formed, presumably as the result of intrauterine growth. Two subtypes are described: rapidly involuting CH (RICH) and noninvoluting CH. RICHs undergo rapid involution within the first year of life. The noninvoluting type tends to grow proportionately with a child over time and does not spontaneously involute. CHs lack GLUT-1 expression.[6] Although most CHs, including hepatic CH, are isolated tumors, multifocal presentation has been reported.[9]

KHEs are vascular tumors that most commonly present within the first 2 years of life but can more rarely be present at birth. They appear as vascular macules, plaques, or nodules, or as deep masses. KHE often are complicated by Kasabach-Merritt phenomenon, which involves platelet trapping within the tumor and subsequent severe thrombocytopenia. KHE may be infiltrative and can cause death from direct tumor infiltration. Distant metastasis does not occur.

Tufted angiomas also can be associated with Kasabach-Merritt syndrome. These rare tumors typically occur in children and young adults and can be present at birth. They present as red macules or plaques that may develop vascular papules or nodules. They tend to be slow growing over months to years and have variable regression.

Pyogenic granulomas are common benign vascular tumors that often present in childhood. They typically develop as small erythematous papules that enlarge to 5-10 mm over several weeks. They can be pedunculated and often bleed easily. There are rare reports of congenital pyogenic granulomas in the literature. Browning et al[10] reviewed these cases, and presented 2 cases of congenital disseminated pyogenic granulomas in 2009. Unlike IH, pyogenic granulomas lack GLUT-1 expression.

MLT typically presents at birth or in the neonatal period as hundreds of cutaneous red-brown papules and plaques with central pallor. Lesions may be confused clinically with the "blueberry muffin" lesions that characterize some forms of intrauterine infection or other causes of extramedullary hematopoiesis. MLT lesions tend to grow slowly and new lesions continue to appear. The vascular tumors are GLUT-1 negative and often are associated with profound thrombocytopenia and widespread extracutaneous disease.[11] Tumors in the gastrointestinal tract typically cause intestinal bleeding, and tumors in the lungs may lead to hemoptysis. Other organ involvement has been documented as well, including