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ORIGINAL ARTICLE

Giant Chorioangioma Treated *In Utero* via Laser of Feeding Vessels with Subsequent Development of Multifocal Infantile Hemangiomas

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We report a case of a giant placental chorioangioma (15.6 cm diameter) complicated by polyhydramnios and severe fetal heart failure. Fetoscopic laser occlusion of a dominant feeding vessel was performed at 29 weeks' gestation and partial devascularization was achieved. In the 33rd week of the pregnancy, the decision was made to preemptively deliver the fetus due to persistent signs of fetal cardiac failure. After birth, the infant developed multifocal infantile hemangiomas with extracutaneous involvement. We posit that the development of infantile hemangiomas may be linked to the presence of the large chorioangioma. Further study is required to ascertain if fetal treatment of the chorioangioma may have been an exacerbating factor.

Keywords: placental tumor, chorioangioma, fetoscopy, fetal treatment, hemangioma

INTRODUCTION

Chorioangiomas are the most common nontrophoblastic placental tumors, occurring in 1% of placentas. Placental chorioangiomas are typically small and have no clinical significance [1]. Chorioangiomas greater than 4—5 cm in diameter, arbitrarily called giant or large chorioangiomas, are rare with a prevalence varying from one in 9000–50 000 pregnancies [2]. They are associated with severe perinatal complications, including polyhydramnios, hydrops, fetal anemia, heart failure and fetal growth restriction [3]. Ominous rates of perinatal mortality as high as 30–40% have been reported, thus several therapeutic interventions have been proposed in order to avoid fetal death [4].

Likewise infantile hemangiomas are the most common tumor of childhood, affecting 5–10% of infants [5]. They are benign tumors that develop within the first few weeks

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of life. Infantile hemangiomas typically grow and develop in size during the first several months of life. The lesions then slowly involute with time, usually spanning years. The presence of 5 or more cutaneous infantile hemangiomas has a higher likelihood of being associated with multiple organ involvement [6]. In contrast to benign multiple infantile hemangiomas that are limited to the skin, multifocal infantile hemangiomas with extracutaneous disease may be associated with more life-threatening complications and outcomes [7]. If left untreated, morbidity and mortality can be as high as 60% due to high-output cardiac failure, gastrointestinal hemorrhage, disseminated consumptive coagulopathy and consumptive hypothyroidism [8, 9].

The present article describes a case of a giant placental chorioangioma with secondary severe fetal heart failure treated *in utero* via fetoscopic-guided laser occlusion of the feeding vessels, with subsequent development of multifocal infantile hemangiomas with extracutaneous disease. Clinical considerations and literature review are addressed.

CASE REPORT

The mother was a 30-year-old, gravida 2, para 0, female. Her pregnancy was uneventful until 28–5/7 weeks of gestational age (GA), at which time an ultrasound identified a large placental mass. She was referred to Los Angeles Fetal Therapy (University of Southern California) at 29–0/7 weeks of GA for evaluation and possible fetal treatment. Ultrasound findings confirmed a large placental chorioangioma ($15.6 \times 11.2 \times 10.6$ cm) (Figure 1) with two large feeding vessels, polyhydramnios (maximum vertical pocket of amniotic fluid = 12.0 cm), severe fetal cardiomegaly (cardiac-to-thoracic ratio 0.73) (Figure 2), pulsatile flow in the umbilical vein, elevated middle cerebral artery peak systolic velocity (MCA-PSV = 60.3 cm/s, 1.56 MoM) [10] and a cervical length of 2.4 cm. No other abnormalities were observed. Fetal echocardiogram confirmed cardiac findings consistent with severe heart failure.

After consultations with pediatric cardiology and neonatology, management options were reviewed and the patient elected to proceed with fetoscopic laser photocoagulation of the chorioangioma feeding vessels. Corticosteroids for fetal lung/organ maturation were provided. The surgery was performed at 29–1/7 weeks of GA. Fetoscopic laser occlusion of a dominant surface feeding vessel was performed with difficulty, due to the large caliber of the vessel, using techniques described previously [11]. At the conclusion of the surgery, color Doppler interrogation revealed no detectable flow through the targeted feeding vessel. A gentle amnioreduction of 645 ml of amniotic fluid was performed.

Follow up ultrasounds revealed significantly less but persistent flow through the targeted feeding vessel. The cardiac findings and the umbilical vein pulsatility persisted but did not worsen after surgery. At 33 weeks' GA, the patient was counseled regarding the prematurity risks of a nonhydropic fetus versus continuation of the pregnancy closer to term and the possible development of fetal deterioration and hydrops. The decision was made to preemptively deliver the breech fetus via cesarean section at 33–4/7 weeks of GA. The mother delivered an 1890 g male infant with Apgar scores of 3, 6, and 7 at 1, 5, and 10 minutes, respectively. The neonate was resuscitated via nasal cannula positive pressure ventilation in the delivery room and then transferred to the neonatal intensive care unit (NICU) for prematurity and respiratory distress (RDS). Physical examination of the infant revealed an appropriate for gestational age neonate with no dysmorphic features. Admission exam was remarkable for hepatomegaly and a poorly defined echymotic appearance to the distal feet bilaterally, right proximal arm, suprasternal chest, and left shoulder, which were attributed to bruising from delivery. Gross and histological placental findings included the following:

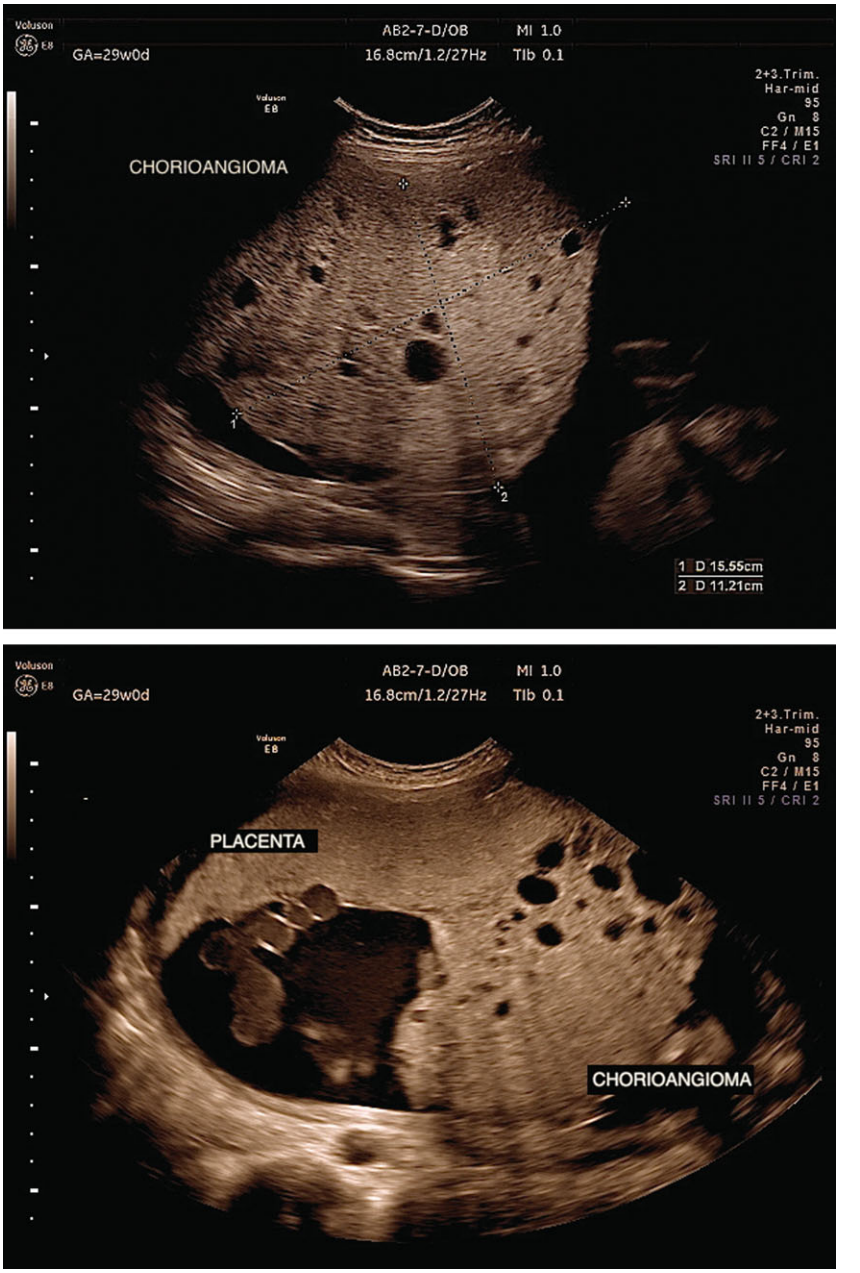

Figure 1. Fetal ultrasound performed at 29 0/7 weeks' gestation demonstrating the giant chorioangioma. The lesion measured 15.6 cm by 11.2 cm by 10.6 cm, arose from the placenta, and occupied approximately half of the amniotic cavity.

(1) multiple chorioangiomas, including a large 15 × 15 × 3 cm diffuse chorioangioma; (2) estimated involvement of the placenta by chorioangiomas is 80%; (3) placenta villi showing chronic villitis; and (4) fetal thrombotic vasculopathy.

Initial interventions in the NICU included surfactant administration via INSURE technique for RDS. The newborn was stabilized on nasal cannula. Admission complete blood count showed a hemoglobin level of 10.5 g/dl and hematocrit of 32.2%, for which the patient was transfused with 15 ml/kg of packed red blood cells.

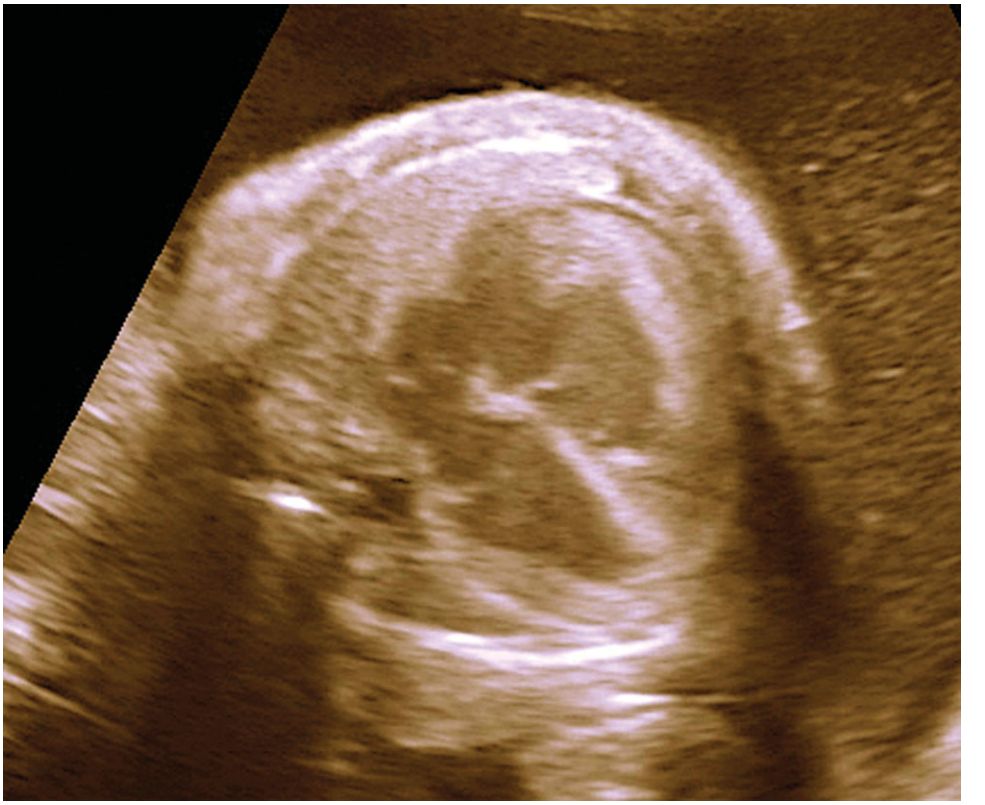

Figure 2. Fetal ultrasound at 29 0/7 weeks' gestation demonstrating severe cardiomegaly. The cardiac to thoracic ratio measured 0.73.

Initial echocardiogram showed proportional enlargement of all cardiac chambers and evidence of pulmonary hypertension. Despite these echocardiographic findings, the patient remained hemodynamically stable with adequate tissue perfusion.

Over the next three to six days of hospitalization, the patient developed multifocal infantile hemangiomas seen throughout the body (Figure 3, Figure 4). Aside from a hemangioma that developed in the suprasternal region, the location of the hemangiomas did not appear to be in the same place as the echymotic areas noted on initial admission. Multiple hepatic hemangiomas were also identified by liver ultrasound and by computed tomography (CT). Additionally, a 1-cm hemangioma at the medial left lung base was found by CT. Treatment with propranolol was initiated on day of life 4. Vascular endothelial growth factor (VEGF) levels were drawn on day of life 4 and found to be in normal range. On postnatal day 5, the patient developed increased work of breathing requiring escalation in respiratory support to nasal continuous positive airway pressure (CPAP). Otolaryngology was consulted and a bedside flexible laryngoscopy revealed a supraglottic hemangioma on the right arytenoid. Additional therapy with systemic steroids was then initiated. The baby was weaned to room air on postnatal day 18.

Repeat bedside flexible laryngoscopy done just prior to discharge showed decreasing supraglottic hemangiomas. He was discharged home on day of life 53 on propranolol at 2.5 mg/kg/day orally divided twice daily. The patient received systemic steroids for a total of 35 days. Repeat echocardiography at the time of discharge showed mild right ventricular enlargement, normal biventricular contractility, and

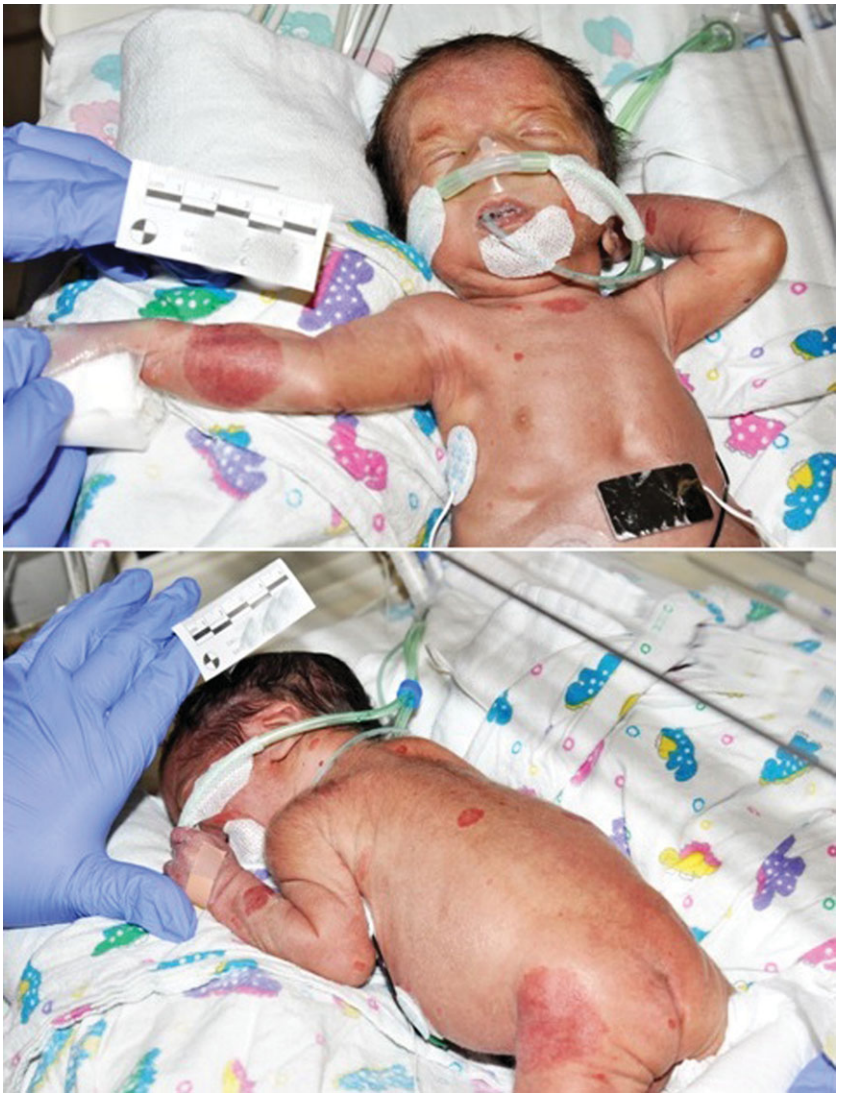

Figure 3. Multiple hemangiomas on the skin of the newborn on postnatal day 6.

resolution of the pulmonary hypertension. The patient remained hemodynamically stable throughout his hospital course. He never required intubation or mechanical ventilation. Ophthalmologic examination was normal. Cranial ultrasounds did not reveal any intracranial hemangiomas or other intracranial abnormalities. The patient never developed thrombocytopenia or abnormalities in thyroid function testing.

DISCUSSION

Chorioangiomas with fetal repercussion can be treated by several different methods. Conservative management with delivery can be the preferential treatment if the gestational age permits. Amnioreduction, intrauterine transfusion, alcohol ablation of the tumor, ultrasound-guided transcutaneous embolization with microcoil or glue, interstitial laser destruction and fetoscopic laser photocoagulation of feeding vessels have been reported in obstetrical literature with various degrees of success [11, 12].

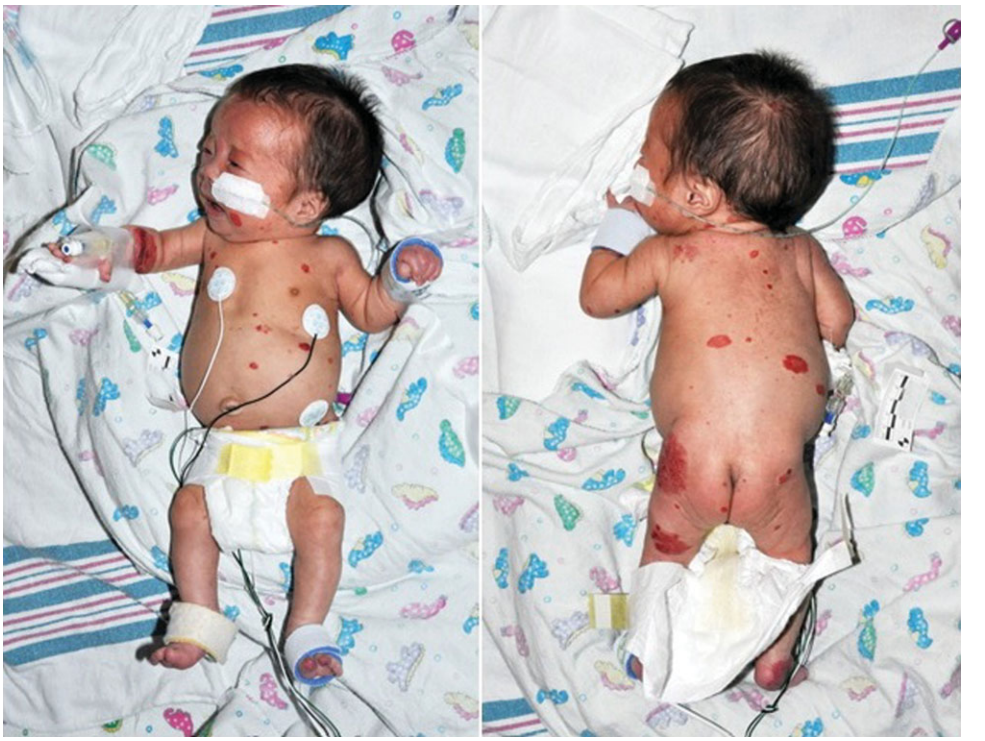

Figure 4. Multiple hemangiomas on the skin of the neonate on postnatal day 49.

We report a case of fetoscopic-guided laser photocoagulation of the feeding vessels that resulted in partial devascularization of the placental tumor. This allowed for continuation of the pregnancy to a gestational age that was deemed appropriate for delivery. The newborn was delivered without complications but developed multifocal infantile hemangiomas with extracutaneous involvement within the first week of life. The hemangiomas were characterized by numerous cutaneous lesions on the body with no specific distribution, diffuse hepatic hemangiomas, a lung hemangioma and supraglottic hemangiomas. To the best of our knowledge, there are approximately a dozen reported cases in the literature exploring the association between placental chorioangiomas and infantile hemangiomas [13–20].

There has been recent histopathological research investigating the possibility that chorioangiomas and infantile hemangiomas share the same pathophysiological origins. Histochemical markers such as GLUT-1, Lewis Y antigen, FcyRII and merosin present in infantile hemangiomas are also present in normal placental tissue. One speculation is that placental cells are "embolized" to the fetal cutaneous vessels, proliferating in areas with relative hypoxia [21]. Another speculation is that infantile hemangiomas result from somatic mutations in a gene that mediates endothelial cell proliferation [22]. And finally, since infantile hemangiomas often exhibit an "ischemic" or blanched progenitor appearance before the onset of vascular proliferation, it has been hypothesized that local ischemia, brought about by some unknown event, may create hypoxic conditions that drive growth factor expression from the large number of myeloid cells present within the proliferating lesion [23]. Giant chorioangiomas place the fetus at risk for hypoxia secondary to significant uteroplacental insufficiency [24]. Hypoxia as a driving factor for vascular proliferation is supported by the association of hypoxia-related conditions, such as low birth weight and retinopathy of

prematurity, being over-represented in infantile hemangiomas [25, 26]. Additionally, prenatal conditions such as placenta previa and preeclampsia were more common in children with infantile hemangiomas [27]. On the other hand, given that the independent prevalence of both chorioangiomas and infantile hemangiomas are relatively common, there remains the possibility that these are two independent lesions that can coincidentally occur in the same patient.

A theoretical role of obstetric interventions in the pathogenesis of neonatal hemangiomas should also be considered. It is already known that infants born following chorionic villus sampling have an increased incidence of this benign vascular tumor [28, 29]. However, it is not completely clear if other fetal interventions may play a role in the development of infantile hemangiomas. Of concern is the possibility that laser occlusion of the chorioangioma feeding vessels *in utero* may have facilitated subsequent embolization of placental cells to a susceptible fetus. It should be noted that this explanation remains purely conjecture at this time, and that the risks associated with infantile hemangiomas seem relatively mild relative to an *in utero* intervention that may prove to be life saving to a critically ill preterm fetus.

CONCLUSION

Mothers with large placental chorioangiomas should be followed closely by obstetricians and maternal-fetal medicine specialists to monitor for life threatening complications to the developing fetus. In our case, we believe that intrauterine fetoscopic laser photocoagulation of a feeding vessel with partial devascularization of the chorioangioma resulted in stabilization of the fetal status to allow for delivery closer to term. Although we cannot prove causality between chorioangiomas and infantile hemangiomas, our case does suggest an association between the two given the parallel pathophysiological factors. Further study is necessary to determine if fetal treatment of a large chorioangioma may contribute to the development of multifocal infantile hemangiomas. It seems prudent that all neonates born to mothers with chorioangiomas should be evaluated closely for the development of infantile hemangiomas and its more rare, yet severe form, multifocal infantile hemagiomas, with or without extracutaneous disease.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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