Case Report

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Medical treatment of infected, ulcerative infantile hemangioma covered with pseudomembrane

Shadi A. Alsmadi^{1*}, Rebecca A. Megchelsen¹, Similolu M. Akintorin², Allison L. Byrd³, Manhal H. Khilfeh¹

¹Division of Neonatology, ³Department of Pediatrics, John H. Stroger, Jr. Hospital of Cook County, Chicago, USA ²Keck School of Medicine of USC, Los Angeles, USA

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*Correspondence: Dr. Shadi A. Alsmadi,

E-mail: shadi.alsmadi@cookcountyhhs.org

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ABSTRACT

Infantile hemangiomas (IH) are benign vascular tumors in children which usually spontaneously resolve. Although these tumors are common, very few require treatment. If treatment is required, the hemangioma can be treated medically or surgically. The case described in this article is unique as it depicts a neonate with a large ulcerative IH which presented with a pseudomembrane covering the entire surface of the lesion and was subsequently found to be infected with *Pseudomonas aeruginosa*. The hemangioma was treated medically rather than surgically, and the medical management of this tumor resulted in the involution of the lesion and the healing of the ulcer.

Keywords: Infantile hemangiomas, Pseudomembrane, Pseudomonas aeruginosa

INTRODUCTION

Infantile hemangioma (IH) is a type of benign tumor in infants which is present under the skin as an abnormal growth of vascular endothelium. The incidence of IH is estimated to be 4-5%. While the exact etiology of IH is unknown, they are hypothesized to be derived from placental tissue. Prematurity and very low birth weights are significant risk factors for IH.²

IH occurs in three phases, the proliferation phase, the stable phase, and the apoptotic involution phase.² These tumors develop during the first few weeks of life. During the proliferative phase, 80% of these lesions grow to their maximum size by 3 months of age.¹

Regression occurs roughly in roughly 25% by age of 2 years, 40-50% by age 4 years, 60-70% by age 6 years, and 95% by adolescence.³ Most lesions resolve spontaneously without complications and can be managed by observation alone.¹ However, a minority of hemangiomas can be

complicated by ulceration, infection, functional obstruction, or cause significant disfiguration, all of which may indicate a need for treatment.⁴

Here we present a case of an extremely premature infant with a large IH complicated by ulceration and infection with *Pseudomonas aeruginosa*.

CASE REPORT

A female infant was born at 25 weeks and 5 days gestation with a birth weight of 835 grams to a 30-year-old G3P0200 mother. The pregnancy was complicated by incompetent cervix for which cervical cerclage was placed at 15 weeks. The prenatal labs and fetal survey were normal. The patient was born by cesarean section due to preterm labor and fetal tachycardia. The mother received two doses of betamethasone, latency antibiotics, and magnesium for neuroprotection prior to delivery. The patient was intubated immediately after delivery, given a dose of surfactant, and transferred to the neonatal intensive care unit (NICU).

Initial physical examination of the skin was unremarkable. On day of life 2, a red discoloration of the skin on the right buttock was noted on physical exam. On follow up exams, there was an irregularly shaped, beefy red-colored skin lesion first observed at 2 weeks of life, slowly growing on the patient's right buttock. The lesion did not cross the midline and did not cover genitalia or the anus. The hemangioma was initially measured to be 2×2 cm when the patient was 20 days of age (Figure 1).



Figure 1: Red hyperpigmented slightly raised macule that was the initial presentation of the hemangioma in the NICU.

Dermatology was consulted on day of life 35 as the hemangioma enlarged and raised above the skin surface. At that time, the hemangioma measured 3×2.25 cm. Dermatology concluded the lesion was more likely to be an IH rather than congenital hemangioma since the color was beefy red rather than blue or purple. The patient's platelet level had been stable, so the hemangioma was not concerning for Kasabach-Merritt phenomenon. As the location was right-sided and not midline, the suspicion for lower body hemangioma, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies and renal anomalies (LUMBAR syndrome) was low.

Abdominal and sacral ultrasounds were done as well as an ultrasound of the hemangioma itself. The sacral ultrasound showed a normal spinal cord that had no connections with skin (Figure 2 and 3). The abdominal ultrasound to rule out any connections to hemangioma was unremarkable.

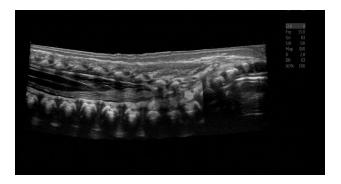


Figure 2: Spinal ultrasound with no notable abnormalities in the spinal cord.

Cardiology was consulted and cleared the patient for propranolol treatment. However, given the patient's extreme prematurity, there was increased risk for adverse effects of hypotension, hypoglycemia and bradycardia with propranolol treatment. In addition, dermatology did not recommend treatment during the NICU stay, as the growth of the hemangioma was consistent with the rate of growth of the patient. Dermatology suggested waiting on the progression of the growth of the lesion to determine if treatment would be needed.

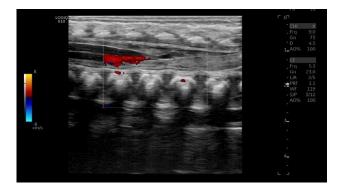


Figure 3: Doppler spinal ultrasound. No connections between spine with the skin or the hemangioma.

During the course of the NICU stay, the hemangioma grew in size gradually. At the time of NICU discharge at 98 days of life and weight of 3220 grams, the hemangioma measured 6×5 cm. The patient was discharged with dermatology follow up. Other medical conditions of the patient at the time of discharge included gastroesophageal reflux disease (GERD) and retinopathy of prematurity (ROP).

At the follow up appointment one week after discharge, when the patient was 106 days old and weighed 3500 grams, the hemangioma measured 7.5×6 cm without ulceration. At a pediatric dermatology appointment at age 116 days, the patient was found to have a 0.7 cm ulcer in the center of the hemangioma without bleeding. She was topicaly treated with vasline, zinc oxide and metronidazole. At age 4.5 months, physical exam showed the hemangioma measured 7×5 cm with a 1 cm healed area. As the ulcerated area was healing, oral propranolol was deferred.

Three months after NICU discharge, the patient presented with a second ulceration with light bleeding. The hemangioma measured 7×5 cm and the ulcer measured 1.5×3 cm (Figure 4). After discussing all treatment options, including non-intervention and topical timolol, the parents opted for oral propranolol therapy. The patient was cleared by pediatric cardiology with normal vital signs and electrocardiogram (EKG). The risks were discussed, including hypotension, bradycardia, hypoglycemia, bronchospasm, sleep disturbances, cold extremities, diarrhea, and somnolence (especially in the first few days of therapy).³ The parents were also counseled to hold propranolol if the patient had any upper respiratory

infection (URI) symptoms or if the patient was vomiting or not feeding well. The patient was started on oral propranolol 1 mg/kg/day divided bis in die (BID) or twice daily at least 10 hours apart. After the initial dose was given, the patient's vital signs were monitored in the clinic for 4 hours. The ulcer was noted to be healing at subsequent exams.



Figure 4: Large raised hemangioma with 2 ulcerations. No signs of acute infection.

Four months after NICU discharge, at a dermatology follow up, the entire hemangioma was ulcerated and covered with a pseudomembrane (Figure 5). It still measured 7×5 cm. Per mother's history, the hemangioma had been ulcerating for the last 3 weeks. The patient had been taking propranolol 1 mg/kg/day divided BID for four weeks at that time. Wound cultures were done and the patient was admitted to the pediatric floor. The patient had a fever on the first day of admission. Upon admission, intravenous piperacillin/tazobactam was initiated, the propranolol dose was increased to 1.5 mg/kg/day, and a two-week course of prednisone was started at 1.5 mg/kg/day. Plastic surgery was consulted, but no surgical intervention was required at the time. Surgery recommended weekly follow up as an outpatient. The wound culture grew Pseudomonas aeruginosa +3, which was found to be sensitive to piperacillin/tazobactam. Intravenous piperacillin/tazobactam was given for seven days. The wound was washed with hydrogen peroxide, and topical metronidazole, mupirocin, and Vaseline gauze were applied. The interventions resulted in improvement in purulence, and the patient was discharged after seven days with close follow up.



Figure 5: Large raised hemangioma. There is ulceration of the entire surface, bleeding and covered in a psudomembrane.

The patient was readmitted to the hospital eight days after discharge because the hemangioma was again infected. A wound culture and blood culture were sent, and the patient was started on piperacillin/tazobactam. The wound culture regrew *Pseudomonas aeruginosa*, and the blood culture was negative. After three days of hospitalization, she was discharged home on oral ciprofloxacin for 7 days. The follow up appointment after one week showed a flat discolored hemangioma with a healed ulcer and a clear wound (Figure 6).



Figure 6: Healing hemangioma that is smaller in size. There is hyperpigmentation and mild scarring of the skin.

DISCUSSION

IH is the most common vascular tumor of infants, appearing in up to 4-5% of children. It is associated with female sex and low birth weight; in fact, over 30% of patients with birth weight under 1 kg are affected.³ IH are characterized by their clinical course: a rapid growth phase followed by an involution phase. Recent studies and clinical trials have shown that most hemangiomas have a rapid growth phase between the ages of 1 and 3 months, often growing to 80% of their final size by 3 months of age and completing their growth by the age of 5 months.⁵ The same trials show that the period of involution is much longer, usually starting around the age of 1 year and continuing for a period of months to years; most hemangiomas do not improve in appearance after the age of 3 to 4 years.^{4,5} Though many hemangiomas involute completely without a trace, others leave behind permanent skin changes and scarring, and hemangiomas in certain locations can lead to disfigurement.4

Structural anomalies associated with IH, such as posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/cortication of the aorta, eye anomalies (PHACE syndrome) is characterized by large IH of the face, neck and/or scalp that are associated with developmental defects. IH of the lower body can be associated with LUMBER syndrome. Large hemangiomas can cause thrombocytopenia and low fibrinogen secondary to intralesional trapping with platelet activation and fibrinogen consumption, also known as Kasabach-Merritt phenomenon.

Recent guidelines published by the American Academy of Pediatrics (AAP) have identified five criteria that classify a hemangioma as high-risk, and therefore should be considered for early treatment. Those categories include life-threatening hemangiomas, such as airway hemangiomas, liver hemangiomas or profusely bleeding hemangiomas; hemangiomas that could cause functional impairment, such as periocular and oral cavity hemangiomas; ulcerating hemangiomas; those that are associated with structural anomalies as detailed by PHACE and LUMBAR syndromes; and those that can cause permanent disfigurement or scarring.⁴

The patient described in this article had a hemangioma which qualified as high risk due to the repeated episodes of ulceration, which was the criterion that prompted medical management.⁴ Ulceration is a relatively common complication of IH, but infection is rare. 9 A multicenter prospective study of 1096 patients with IH found that 15.8% of those hemangiomas were complicated by ulceration, largely during the proliferative phase. ⁹ Among those patients who had ulceration, only 16% of those patients had infection as a complication. While there were no patient or maternal characteristics associated with ulceration as a complication, the location and size of the hemangioma were significant risk factors. 50% of IH in the anogenital area ulcerated, more than any other area of the body. Ulcerated hemangiomas were on average 27.6 cm^2 larger than non-ulcerated hemangiomas. Pseudomonas aeruginosa, Staphylococcus aureus, group A Streptococcus and gram negative bacteria were the most common organisms found to infect IH.⁹ To the best of our knowledge, following a search of the literature, a hemangioma whose entire surface is covered with a pseudomembrane of Pseudomonas aeruginosa infection has heretofore not been described in the literature.

The AAP guidelines recommends oral propranolol dosed at 2-3 mg/kg/day as the mainstay of treatment for IH.⁴ Propranolol is a nonselective beta-1 and beta-2 adrenergic receptor antagonist. While propranolol's specific mechanism of action on hemangiomas is not known, its effects are thought to be due to the drug causing peripheral vasoconstriction, inducing apoptosis in the lesion, and inhibiting angiogenesis and nitric oxide production.4 Propranolol has replaced oral corticosteroids as the preferred treatment modality due to a more favorable safety profile and greater efficacy. However, propranolol is associated with certain adverse effects, including sleep disturbance, hypoglycemia, and bronchial irritation.⁴ These risks were particularly concerning for our patient who was extremely premature and therefore already susceptible to pulmonary underdevelopment and hypoglycemia. This is the reason the propranolol was deferred as the hemangioma continued to grow along with the patient without complications. However, when the patient presented with her second ulceration, it was decided that the benefits of treating the hemangioma outweighed the risks at that point in time.

When oral propranolol therapy failed as a monotreatment, prednisone was added to the treatment regimen. This was in accordance with the AAP guidelines, which recommend oral prednisone as an adjunct treatment if oral propranolol is ineffective or as an alternative treatment if oral propranolol cannot be tolerated.⁴ There are several adverse effects with systemic steroid treatment, including growth retardation, increased risk of infection, hypertension, and Cushing syndrome.⁴ Other options for medical management include intralesional injections triamcinolone or betamethasone, topical timolol, or recombinant interferon alpha 2a if steroids are contraindicated or ineffective. 4,10 Recent studies have described good response to treatment with topical timolol as well as with brimonidine-timolol cream. 11,12

Surgical treatment of IH is infrequently indicated but is an option according to the AAP recommendations. Indications for surgical management include hemangiomas which are ulcerating or obstructing an eye or airway and have not responded to medical management. Even when necessary, surgery is not generally performed in infancy. Surgical management is usually delayed until age 3-5 years, due in part to the risks of anesthesia and hemorrhage which are higher in infancy, and also because many lesions will resolve by that age.

Evidence for using pulse dye laser (PDL) to treat IH is controversial. While some trials found that PDL reduced the size of hemangiomas compared with controls which received no treatment, there may be increased risk of ulceration and scarring when PDL is used during the infancy period.⁴ However, a multicenter study by Chamlin et al found that ulcerated hemangiomas were more likely to be treated with PDL than non-ulcerated hemangiomas.⁹

CONCLUSION

In this patient with an IH complicated by ulceration, pseudomembrane and infection, the medical management with oral propranolol, prednisone, antibiotic treatment with intravenous piperacillin/tazobactam and oral ciprofloxacin resulted in the complete involution of the lesion. The area remaining is still discolored, but it is no longer raised and the ulcer is healed. The monotherapy with propranolol was not effective in healing the ulcer, but increasing the dose of the propranolol and adding a course of oral prednisone, as well as treating the infection with antibiotics, was sufficient in treating the wound. No surgical management was needed to resolve this hemangioma with multiple complications.

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