The PHACES syndrome: Multiple episodes of reproliferation of subglottic hemangioma

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ABSTRACT

Subglottic hemangioma is a potentially life-threatening manifestation of the PHACES syndrome. The disease process has been treated with corticosteroids, oral chemotherapeutic agents, endoscopic airway interventions, tracheostomy, and even laryngotracheal reconstruction. Oral propranolol has emerged as an effective therapy and in many cases has led to complete regression of hemangioma during the proliferative phase. There have been several reports of patients showing signs of reproliferation after discontinuing propranolol therapy. This article illustrates a patient who has had multiple episodes of reproliferation of subglottic hemangioma after weaning from propranolol therapy.

KEYWORDS PHACES syndrome; propranolol; subglottic hemangioma

Infantile hemangiomas are the most common benign tumors of infancy. They are characterized by two distinct phases: proliferation and involution.¹ The proliferation phase is characterized by rapid growth for the first 6 to 9 months of life followed by involution over 3 to 7 years.² Most hemangiomas occur in otherwise healthy infants; however, almost one third of patients with hemangiomas >22 cm² also have PHACES syndrome, which stands for posterior fossa, hemangioma, arterial anomalies, cardiac defects, eye abnormalities, and sternal cleft.³ PHACES syndrome is diagnosed by the presence of a facial hemangioma >5 cm in diameter plus one major or two minor criteria involving these systems.⁴ Children with PHACES syndrome can also be afflicted by subglottic hemangiomas, which commonly present with biphasic stridor worsened by crying. Progression of subglottic stenosis can lead to significant airway obstruction necessitating aggressive medical and surgical treatment.⁵ Treatment of airway hemangiomas with propranolol has been well described and shows promising results; however, there are still cases of either failure to respond to propranolol treatment or recurrence after discontinuing therapy.^{6,7} Herein, we describe a particularly challenging-to-treat patient with PHACES syndrome and subglottic hemangioma who had multiple recurrences once propranolol treatment was weaned.

CASE REPORT

A Hispanic female infant who was born full term via vaginal delivery received her 2-week newborn exam and her pediatrician noticed a beard distribution rash described as erythematous and capillary-based without a palpable component. The patient was started on 5 mg/kg/day of prednisolone orally. She then presented to the emergency department at 3 weeks of age with stridor and respiratory distress requiring intubation in the operating room. A diagnostic laryngoscopy and bronchoscopy (DLB) procedure showed hemangiomas associated with the left tongue base and piriform sinus but no obstructing subglottic lesions. She was started on propranolol therapy at 2 mg/kg/day. At 7 weeks of age, she had increased stridor and was found to have hemangiomas involving the entire glottis and subglottic regions necessitating placement of a tracheostomy. At 12 months of age, she had improvement of her facial hemangiomas and was weaned off propranolol and prednisolone.

At 16 months of age, she was restarted on propranolol at 2 mg/kg/day after showing rebound proliferation of the hemangiomas with the development of deep subcutaneous hemangiomas over the parotid, mastoid, and submandibular areas. At 29 months, she underwent another DLB that showed slight improvement of subglottic hemangioma, and a

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propranolol wean was started; however, at 32 months of age, she presented with another reproliferation of her facial hemangiomas with involvement of the left mastoid bone. At 36 months of age, a DLB showed 50% obstruction of the subglottic airway and magnetic resonance imaging showed an increase in size of the left mastoid bone hemangioma. Magnetic resonance angiography of the brain showed hypoplasia of the right anterior cerebral artery confirming the diagnosis of PHACES syndrome. At 45 months of age, she again had progression of her facial hemangiomas after being weaned down to 1.25 mg/kg/day of propranolol; therefore, this was increased to 1.6 mg/kg/day.

At 48 months of age, a DLB showed almost complete regression of subglottic hemangiomas, and her tracheostomy was decannulated successfully at 51 months of age. Propranolol was then weaned off at 61 months of age. Two months later, she was found to have worsening ear disease with hemangioma present in both middle ears with a bilateral 40 dB conductive hearing loss. At 63 months of age, another DLB showed a grade two subglottic stenosis with recurrence of the subglottic hemangiomas requiring balloon dilation, topical mitomycin C application, and injection of Kenalog-40/celestone solution. She required re-intubation after the procedure was concluded and was admitted to the pediatric intensive care unit due to flash pulmonary edema. The decision was made to restart propranolol at 2.0 mg/kg/day. Over the next 3 months, she required two more DLB procedures including balloon dilation with application of mitomycin C topically and injection with Kenalog-40/celestone. At 66 months, she had a mild grade 2 subglottic stenosis but no visible recurrence of the subglottic hemangiomas and propranolol was weaned down to 1.67 mg/kg/day. At 73 month of age, a DLB revealed a grade 2 subglottic stenosis with recurrence of the subglottic hemangiomas.

DISCUSSION

Use of propranolol during the proliferation phase of infantile hemangioma has been well established; however, the literature is not as clear about the role of propranolol therapy in

Figure 2. (a) Direct laryngoscopy revealing grade II subglottic stenosis but no evidence of hemangioma. Taken at age 64 months of age while patient was on 2 mg/kg/day propranolol. (b) Direct laryngoscopy revealing reproliferation of hemangioma along both false vocal folds and along the left lateral subglottic wall. Taken at age 77 months after propranolol was weaned to 1.4 mg/kg/day.

older patients or in those who have reproliferation of disease. Vivas-Colmenares et al reported on a series of 18 patients treated with propranolol in the postproliferative phase, 72.2% of whom demonstrated a complete response and 27.8% of whom demonstrated a partial response.⁸ Bagazgoitia et al described a subset of five patients who had clinically significant reproliferation of hemangioma after withdrawal of propranolol and hypothesized that this was due to withdrawal of systemic therapy during a late proliferation phase.⁹ These studies suggest that propranolol therapy is an effective treatment for episodes of disease reproliferation or reoccurrence. One unique aspect of the current patient is that there were multiple episodes of reproliferation of disease manifested by recurrence of either subglottic or facial hemangiomas. In this patient, these episodes occurred at 16, 32, 45, 63, and 73 months of age, approximately 3 months after weaning propranolol. *Figure 1* and *Figure 2* show examples of reproliferation of disease after weaning propranolol. Our patient required multiple treatment modalities including systemic propranolol, balloon dilation, KTP laser ablation, injection with Kenalog-40/celestone solution, and topical application of mitomycin C to manage recurrent subglottic hemangioma.

Figure 1. (a) Direct laryngoscopy performed at 28 months of age revealing grade II subglottic stenosis with improvement of left lateral subglottic wall hemangioma on 2 mg/kg/day of propranolol. (b) Direct laryngoscopy performed at 36 months after weaning propranolol down to 1.6 mg/kg/day, revealing reproliferation of hemangioma along the left lateral subglottic wall.

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