FEATURE ARTICLE

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Clinical Presentation, Complications, and Management of Infantile Hemangiomas

A Case Report and Review of the Literature

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ABSTRACT: Infantile hemangiomas are the most common benign, vascular tumor of childhood; approximately 2%–5% of infants will develop one. Infantile hemangiomas go through a period of rapid growth followed by involution; however, serious complications may develop in a subset of affected patients. For these patients, medical treatment may be necessary. Currently, oral propranolol has shown much promise in the management of these patients with high-risk hemangiomas.

Key words: Hemangioma, Infantile Hemangioma, Propanolol, Pediatric Dermatology, Pediatric Vascular Dermatoses

CASE REPORT

The pediatric dermatology service was consulted to evaluate an enlarging, red vascular nodule on the lower lip of a hospitalized, 80 day-old female, Caucasian infant who was born prematurely at 25 weeks with a birth weight of 0.65 kg. Initially, the lesion was noticed on the patient's left lower lip at approximately 50 days of age, and it was thought to be a bruise because of a previously placed endotracheal tube. Over the course of a month, the lesion continued to grow and deepen in color. The patient's history was notable for respiratory distress syndrome, pulmonary hemorrhage, retinopathy of prematurity, apnea of prematurity, and a patent ductus arteriosus, which was repaired.

Examination revealed a 1.5 x 1.2 cm soft, fleshy deep-red-to-purple nonblanching vascular lesion, which distorted the inferior vermillion border and spanned the entire left half of the lower lip. The lesion extended to the left inferior gingival sulcus and onto the lower left gumline. No areas of ulceration were appreciated; however, a grayish hue at the central aspect of the hemangioma was noted (Figure 1).

A diagnosis of mixed focal infantile hemangioma (IH) of the lower lip was made. Because of distortion of the lip and risk for ulceration, the patient was initiated on oral propranolol, which was titrated to 2 mg/kg per day divided three times daily during her hospital admission. This regimen was continued at discharge.

During follow-up appointments, the color and size of the IH were markedly improved with continued propranolol treatment. The patient's mother noted that the infant was tolerating the medication well without cardiovascular or pulmonary symptoms, although patient was noted to have cold hands and feet since starting the medication. The progression of the patient's IH was documented with photographs in Figures 1–3. The patient, now 1 year of age, has continued oral propranolol treatment without ulceration or other complications from the IH or medical therapy.

DISCUSSION

Epidemiology

IHs are the most common benign, vascular tumor of childhood. It is estimated that approximately 2%–5% of infants born in the United States will develop an IH before 3 months of age (Kanada, Merin, Munden, & Friedlander, 2012; Kilcline & Frieden, 2008). A large prospective study found that infants with IH were more likely to be

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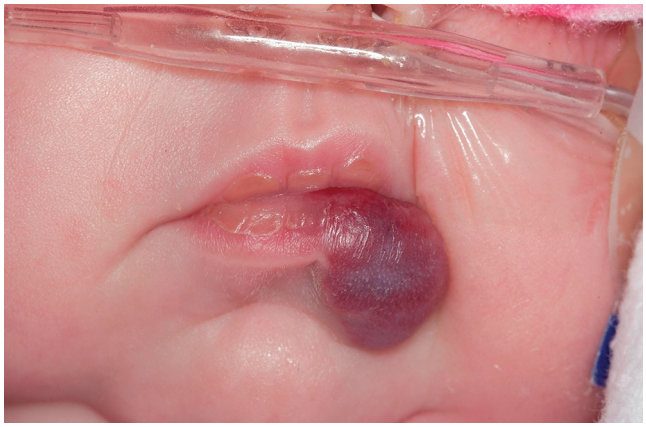

FIGURE 1. Clinical photograph of an infantile hemangioma involving the left lower lip of a 3-month-old infant before the initiation of oral propranolol therapy.

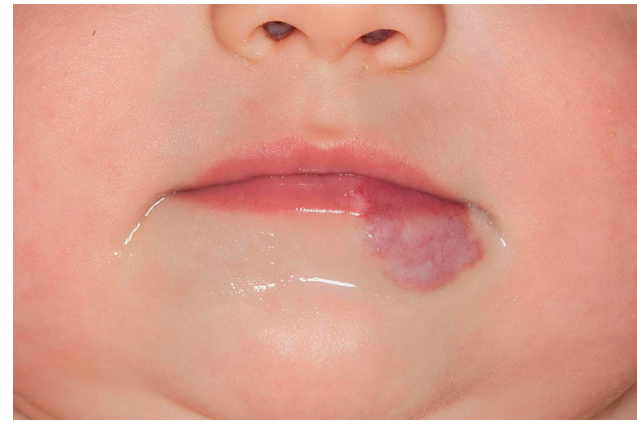

FIGURE 3. Clinical photograph of an infantile hemangioma involving the left lower lip of a 12-month-old after 9 months of oral propranolol therapy. The lesion shows progressive, marked regression in size and color over time.

female, white, premature with a history of low birth weight, products of multiple gestation, and born to mothers of advanced maternal age (Haggstrom et al., 2007).

Clinical Presentation

Clinically, IHs present at birth as a precursor lesion or within several weeks after birth and occur as superficial, deep, or mixed lesions. Superficial lesions are bright red vascular papules, plaques, and nodules, which may blanch with pressure. Conversely, deep IHs are subcutaneous nodules and tumors that are light to deep blue and may present with overlying telangiectasias. Often, there are both superficial and deep components. IHs are further classified as segmental, focal, or indeterminate lesions.

In contrast to congenital hemangiomas, which are present at birth, IHs typically become evident at 2–3 weeks of life. IHs progress through three phases of development: the proliferative, plateau, and involutional stages. Recently, it was found that the most rapid period of growth in the proliferative phase occurs between ages 5.5 and 7.5 weeks (Pride, Tollefson, & Silverman, 2013; Tollefson & Frieden, 2012). Approximately 80% of volumetric growth will be completed by 5 months of age (Chang et al., 2008). IHs will subsequently enter a period of quiescence, known as the plateau phase. Finally, the onset of the involutional phase may be marked by a change in coloration to a whitish gray that usually occurs at least 6 months into life (Pride et al., 2013). Complete involution of IHs occur at 10% per year, meaning that greater than 90% of lesions will have involuted by 9–10 years (Paller & Mancini, 2011).

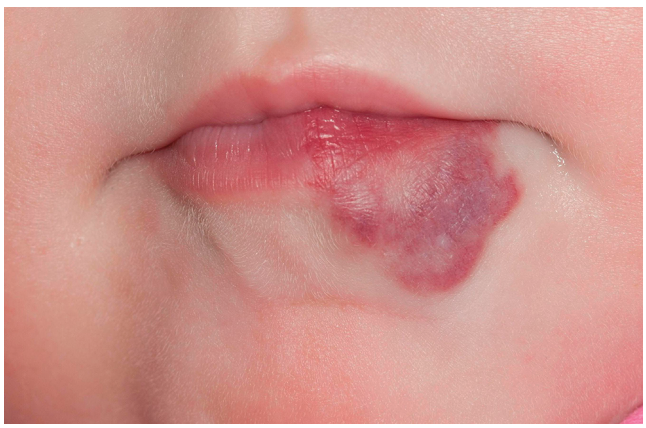

FIGURE 2. Clinical photograph of an infantile hemangioma involving the left lower lip of a 6-month-old infant after 3 months of oral propranolol therapy.

Pathogenesis

The pathogenesis of IH is not completely understood; however, several theories implicate a response to hypoxia, angiogenic peptides, placental embolization and seeding, and somatic mutation (Jinnin et al., 2008; Mihm & Nelson, 2010; Walter et al., 2002). Perhaps, the most widely accepted theory involves the proliferation of stem cells, more specifically termed endothelial progenitor cells, which migrate to areas of relative hypoxia in the newborn, such as embryonic fusion plates (Chen, Eichenfield, & Friedlander, 2013). Microscopically, IHs are noted to stain positive for glucose transporter-1 (GLUT-1), which has been described as a type of hypoxia censor (North, Waner, Mizeracki, & Mihm, 2000). Although IHs are not routinely biopsied, GLUT-1 positivity may differentiate IHs from other pediatric vascular lesions such as congenital hemangiomas (Enjolras et al., 2001).

Complications

Potential complications of IHs include permanent disfigurement, ulceration and scarring, bleeding, visual compromise, airway obstruction, congestive heart failure, and death (Drolet et al., 2013). As compared with focal lesions, segmental IHs are associated with higher risk of ulceration, functional and anatomic compromise, and therefore, greater need for therapy (Haggstrom, Lammer, Schneider, Marcucio,

& Frieden, 2006). Of concern, IHs that arise near the eyes, nose, mouth, central face, and lumbosacral and genital regions are at greater risk for complications such as ulceration and functional compromise (Chen et al., 2013).

IHs may be associated with other medical and anatomical concerns. PHACE syndrome is the association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities (Frieden, Reese, & Cohen, 1996). A 9:1 female predominance has been reported in the literature and usually arises in association with large facial hemangiomas (Haggstrom et al., 2010). Of the associations, neurological and cerebrovascular anomalies are the most common extracutaneous features of patients with PHACE syndrome (Metry, Dowd, Barkovich, & Frieden, 2001). Recently, some of these patients were found to also have a higher incidence of gastrointestinal bleeding because of ulcerated segmental gastrointestinal IHs (Drolet et al., 2012; Pride et al., 2013). In patients with facial hemangiomas greater than or equal to 5 cm, a thorough evaluation for PHACE syndrome should be performed. The evaluation should include magnetic resonance imaging and magnetic resonance arteriogram of the brain, cardiovascular imaging, visualization of the vessels of the upper chest and neck, and an ophthalmological evaluation (Chen et al., 2013).

Another worrisome constellation of medical problems associated with IHs is the LUMBAR syndrome. It is defined as the association of lower body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies (Iacobas et al., 2010). This association of pathology may arise in patients with large segmental hemangiomas on the lower half of the body.

Multifocal IH, with or without extracutaneous disease, was previously known as diffuse neonatal hemangiomatosis. This is a term that describes infants with multiple IHs and acknowledges possible visceral involvement (Glick, Frieden, Garzon, Mully, & Drolet, 2012). In patients with visceral hemangiomas, hepatic involvement is most common. Hepatic ultrasound is therefore indicated for patients with five or more cutaneous IHs (Horii et al., 2011). Of importance, consumptive hypothyroidism has been observed in these patients, and therefore, basic thyroid function laboratories should be drawn at evaluation (Huang et al., 2000).

Management

Most IHs will regress without complication and may be monitored by the physician, physician assistant, or nurse practitioner with active nonintervention. However, a retrospective study found that 12% of IHs are complex and will require early referral to a specialist for management (Haggstrom et al., 2006). Although there are no FDA-approved treatments for IHs, there are multiple medications that have been used off-label for the treatment of IHs (Leonardi-Bee, Batta, O'Brien, & Bath-Hextall, 2011). Some IHs may be amenable to topical treatments, but often, high-risk and complicated IHs may require systemic treatment.

Historically, systemic glucocorticoids have been the mainstay of treatment for patients with complex IHs requiring systemic intervention. They are thought to decrease expression of vascular endothelial growth factor A, an angiogenic peptide implicated in the development of new blood vessels (Greenberger, Boscolo, Adini, Mulliken, & Bischoff, 2010). Interferon alpha and vincristine have also been used; however, each may present significant adverse effects (Ezekowitz, Mulliken, & Folkman, 1992; Perez-Valle et al., 2010).

More recently, the cautious use of oral propranolol, a nonselective beta blocker, has become the standard of care in patients who require systemic medical management. Originally described in 2008, Léauté-Labrèze fortuitously observed the resolution of an IH in a patient who was receiving propranolol during the treatment of a corticosteroid induced cardiomyopathy (Leaute-Labreze et al., 2008). Since this was described, there have been many promising case reports and case series on its use.

In a further study, propranolol was proven to be effective when compared with placebo, and propranolol was superior to glucocorticoids by efficacy and cost (Hogeling, Adams, & Wargon, 2011). Price et al. (2011) found that patients who underwent propranolol treatment had less surgical interventions and fewer adverse effects as compared with patients who received corticosteroids. Recently, a meta-analysis of 56 studies showed a 97% response rate for propranolol in the treatment of IHs versus just 69% for corticosteroids (Izadpanah, Kanevsky, Belzile, & Schwarz, 2013). Of interest, topical timolol, originally an ophthalmic solution for the treatment of glaucoma, has shown efficacy for superficial IHs (Chan, McKay, Adams, & Wargon, 2013).

Systemic propranolol therapy has been revolutionary to the treatment of IHs. However, children must be monitored closely for adverse effects linked to pharmacological beta blockade. Theoretical and observed adverse effects include symptomatic hypoglycemia, hypotension, bronchial hyperreactivity, seizure, restless sleep, cold extremities, and constipation (Lawley, Siegfried, & Todd, 2009).

Recently, a report of a consensus conference was published on the indication and use of propranolol among patients with IHs. This report contained the recommendations from nearly 30 experts in the field. Notably, reported indications for treatment with oral propranolol include presence of ulceration, impairment of a vital function, or risk of permanent disfigurement (Drolet et al., 2013). Relative contraindications to treatment include cardiogenic shock, sinus bradycardia, hypotension, heart block, heart failure, bronchial asthma, and hypersensitivity to propranolol (Drolet et al., 2013). Before prescribing oral propranolol, the prescribing subspecialist with experience in treating IHs should obtain a detailed cardiac and pulmonary history and physical examination data, paying particular attention

to the patient's heart rate and blood pressure. Electrocardiogram may be indicated. In patients with PHACE syndrome, the benefits of propranolol must be carefully weighed against the risks of theoretical hypoperfusion and be preceded by appropriate imaging.

Propranolol is titrated to a mean dose of 2 mg/kg per day divided to three times daily dosing with at least 6 hours between doses (Drolet et al., 2013). Oral propranolol should be taken with food to prevent hypoglycemia. There is currently some debate on observation requirements for patients who started on oral propranolol. However, Drolet et al. provided age-dependent recommendations for propranolol initiation. Infants less than 8 weeks of gestationally corrected age; infants of inadequate social support; and any infant with cardiovascular, pulmonary, or glycemic comorbidities should be monitored in the inpatient setting for observation. Otherwise, patients may be observed closely in the outpatient setting. Specific monitoring parameters and dose initiation are reported by Drolet et al.

It is certainly an exciting time to study and care for patients with IHs. IHs, although common, may present with substantial complications requiring treatment. In such patients, cautious therapy with oral and topical beta blockers may be warranted in their management. Further research and clinical trials will be required to further study the appropriate use and indications of propranolol for patients with complicated IHs. ■

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