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Management of Cutaneous Hemangiomas in Pediatric Patients

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Cutaneous hemangiomas (CHs) are common benign vascular tumors of childhood. Clinically, they are characterized by a typical evolution profile, consisting of a rapid proliferation during the first year of life and slow involution that usually is completed by 5 to 10 years of age. In most cases, no treatment is necessary. However, when CHs are located in areas at risk for functional complications; are of considerable size; or repeatedly undergo bleeding, ulceration, or superinfection, a prompt and adequate treatment approach is required. First-line approaches include topical, intralesional, and systemic corticosteroids. Second-line options include interferon alfa-2a and -2b, laser therapy, and surgical therapy. Third-line approaches include cytotoxins, embolization, and angiogenesis inhibitors. Other therapies and procedural approaches including intermittent pneumatic and continuous compression; cryosurgery; radiotherapy; implantation of copper needles; sclerotherapy; electrocautery; electroacupuncture; imiquimod cream 5%; and prospective agents, such as OXi4503 (diphosphate prodrug of combretastatin A1) and cidofovir, are discussed. Treatment options for ulcerated CHs also are described.

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Cutaneous hemangiomas (CHs) are common benign vascular tumors of childhood. Clinically, they are characterized by a typical evolution profile, consisting of a rapid proliferation during the first year of life and slow involution that usually is completed by 5 to 10 years of age.[1] For this reason, no treatment is necessary in most cases. However, when CHs are located in areas at risk for functional complications; are of considerable size; or repeatedly undergo bleeding, ulceration, or superinfection, a prompt and adequate treatment approach is required.[2]

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Epidemiology

CHs are present in 1.0% to 2.6% of neonates and in 10% to 12% of infants by 12 months of age.[3] Thirty percent of CHs are first evident at birth; the remainder appear during the second month of life. The frequency of these benign tumors increases in preterm infants, and the female to male ratio is variable from 2:5 to 4:1.[4,5] In a study of 578 infants exposed to chorionic villus biopsy, the incidence of CHs was approximately 21%.[6]

Clinical Assessment

In general, CHs are solitary (80% of cases), measuring approximately a few millimeters to 5 cm in size; less frequently, multiple tumors are present or larger in size.[7] Although every part of the body may be affected, the head and neck are involved in 60% of cases.[8,9]

The appearance of CHs depends on their location within the cutis (superficial, deep, or mixed [superficial and deep]). CHs are classified into localized and segmental forms. Localized forms generally are small, whereas segmental CHs display a linear distribution and/or well-demarcated shapes resembling islands on a map covering larger anatomic regions.[10]

Medical history and physical examination are sufficient to diagnose CHs in 95% of cases.[11] Normally, CHs are asymptomatic but can lead to serious or even life-threatening complications in rare instances.

Sites associated with complications include airways, eyes, and the lumbosacral region.[12] Infants with mandibular and neck CHs in a beard distribution and patients presenting with crouplike cough should be closely observed for respiratory distress and evaluated with direct laryngoscopy if needed.[13] Periocular CHs may have an adverse impact on the visual axis. Obstruction of the visual axis results in stimulus deprivation–induced amblyopia.[14] Pressure on the cornea can lead to astigmatism, which can cause permanent amblyopia. Other ophthalmic complications associated with periocular CHs include tear duct obstruction, proptosis, ptosis, strabismus, and myopia.[14] Infants with periocular lesions should undergo immediate ophthalmologic evaluation.

Patients with lumbosacral CHs should be evaluated for spinal dysraphism, tethered cord syndrome, and genitourinary anomalies. Initially, infants may be asymptomatic, but progressive neurologic damage will occur if the tethered spinal cord is not released. Spinal dysraphism includes anomalies such as abnormal genitalia, rectal fistulas, and anorectal and renal abnormalities.[15,16] CHs in association with other anomalies include PHACE syndrome (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities) and hemangiomatosis.[17-19] Benign and disseminated neonatal hemangiomatosis are 2 distinct categories of disease characterized by multiple CHs.

Ulceration is the most frequent complication of CHs and can lead to infection, bleeding, pain, and scarring. Infants with CHs should be followed closely, especially during the proliferative phase when problematic ulceration is most likely to occur.[20]

Management and Treatment

The goals of managing patients with CHs are prevention of life- or function-threatening complications (eg, obstructed airways, impaired vision) or permanent disfigurement because of residual postinvolution skin changes (eg, nasal hemangioma, large facial lesions); prevention or treatment of ulceration to minimize infection, bleeding, pain, or scarring; and avoidance of aggressive or scarring treatments.[21,22]

CHs of infancy can have a great psychological impact on patients and their parents[23,24]; therefore, education plays an important role in the management of this condition. Regular follow-up visits are needed to provide continuous reassurance and monitor the course of the lesion.

First-Line Therapy—First-line therapies for CHs include topical, intralesional, and systemic corticosteroids. Topical corticosteroids can be used for low-risk CHs and are efficacious and relatively safe if used cautiously under medical supervision. The patient should be warned of adverse reactions such as cutaneous atrophy and striae.[25] Betamethasone dipropionate ointment 0.05%, clobetasol propionate 0.05% ointment or cream, and halobetasol propionate 0.05% ointment or cream have been successfully used.[26]

Intralesional corticosteroids, such as triamcinolone acetonide, can be employed for well-defined and low-risk CHs during the proliferative phase to restrict growth and hasten involution. They may be injected for small lesions (1–2 cm in diameter) on the lips, nasal tip, cheeks, or ears (2–5 intralesional injections at 4–8-week intervals with concentration of 10–20 mg/mL, administered in doses of up to 3–5 mg/kg per treatment session).[20,25] One injection on each visit is administered as needed. They should be used with caution for periocular CHs because of rare complications, such as retinal artery occlusion, eyelid necrosis, temporary eyelid dyspigmentation, and subcutaneous fat atrophy.[25,27] The suggested treatment regimen is a 50:50 mix of triamcinolone acetonide (40 mg/mL) and betamethasone acetate (6 mg/mL) per treatment every 4 to 6 weeks,[27-29] and reported side effects include cutaneous atrophy and pain during injection. The response rate for administration of intralesional corticosteroids may be similar to systemic therapy.

Systemic corticosteroids are the mainstay of therapy for larger, deforming and endangering, or life-threatening lesions, and usually are indicated during their proliferative phase (Figure 1).[30,31] Oral prednisone or prednisolone can be considered and should be tailored to the patient's response at dosages from 2 to 4 mg/kg daily for 2 to 3 months and then gradually tapered over several months.[30] This dosage must be maintained until the functional risks determined by the CHs subside. Stopping treatment before adequate therapeutic response may result in rebound growth. If no response is noted within 3 to 6 weeks, the therapy should be discontinued.[30] Considerably large CHs, with fast growth and atypical behavior, may require higher dosages (up to 8 mg/kg daily).[32] In some cases, the simultaneous injection of intralesional corticosteroids may be particularly advantageous. Approximately 35% of patients will develop complications from prolonged use, including irritability, delayed skeletal growth, hypertension, immunosuppression, cushingoid appearance, and adrenal suppression.[33,34] The use of prophylactic oral ranitidine hydrochloride (2–4 mg/kg once daily to a maximum of 150 mg/d) or cimetidine hydrochloride (20 mg/kg per day) to prevent gastritis from systemic corticosteroids is recommended.[25,31,34]

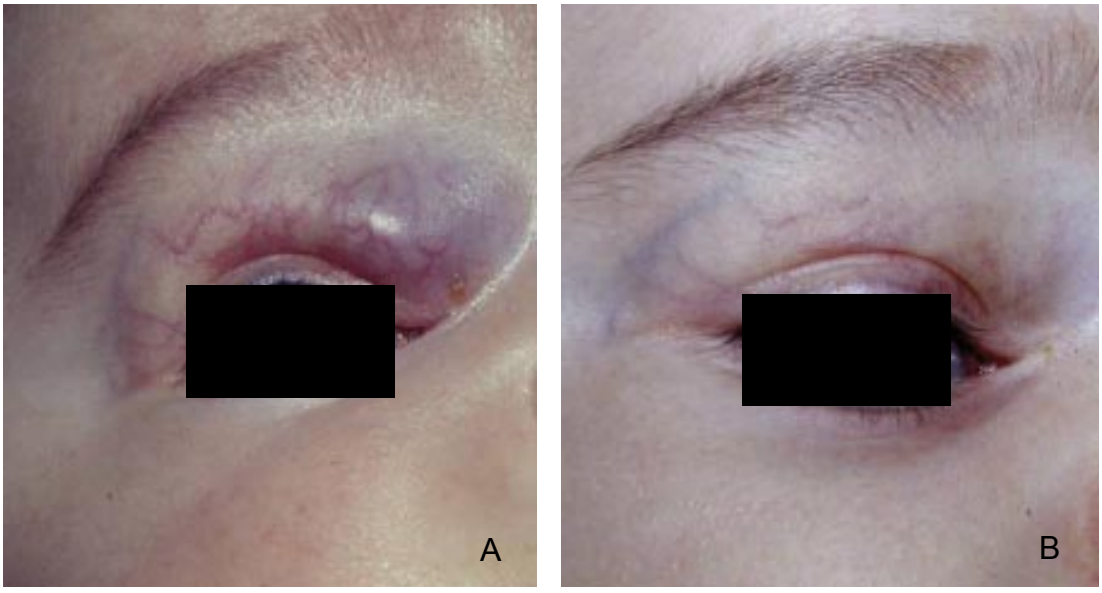

Figure 1. Mixed-type (superficial and deep) cutaneous hemangioma of the upper eyelid before (A) and after 10 weeks of systemic corticosteroid therapy (B). Reprinted with permission from Musumeci et al.[31]

Upon completion of treatment with corticosteroids, patients require stress doses for several months to avoid adrenal crisis. Live viral vaccines should be avoided during the treatment period. Alternatively, prednisone pulse therapy, consisting of cycles of 20 to 30 days at a dosage of 2 to 4 mg/kg daily with 30- to 40-day intervals between cycles, has been proposed to allow for vaccination.[35]

Second-Line Therapy—Second-line therapies include interferon alfa-2a and -2b, laser therapy, and surgical therapy. Interferon alfa-2a and -2b can be used for CHs not responding to corticosteroid therapy or for endangering or life-threatening complications.[36-38] Subcutaneous administration of 1 to 3 million U/m^2 of body surface area daily for 6 to 12 months is recommended.[30] Interferon alfa is not regularly used because of the risk for neurotoxicity and other side effects.[36,37,39,40] Monitoring of the neurologic status, complete blood count, and a liver function test should be performed regularly during treatment.

A variety of lasers with wavelengths between green and yellow (KTP [potassium titanyl phosphate] [wavelength, 532 nm], flashlamp-pumped pulsed dye laser [FPDL][wavelength, 585–600 nm]), near-infrared lasers (Nd:YAG [wavelength, 1064 nm]), and broadband light sources (intense pulsed light [IPL]) have been used for the treatment of vascular lesions. These devices function based on the principle of selective photothermolysis. All devices currently used are proposed in combination with skin cooling, allowing for epidermal protection by increasing fluences.[1] Current recommendations suggest the treatment of an early macular precursor lesion to diminish or even prevent growth. However, lesions rarely are seen early enough. The FPDL has shown to be safe and effective for superficial CHs and residual lesions.[21,41,42] Treatments are spaced at 2- to 3-week intervals for proliferating lesions and 4- to 6-week intervals for nonproliferating lesions.[43] Usual treatment consists of short pulses of light at wavelengths of 585 nm for a duration of 0.45 milliseconds.[21,44,45] Some of the side effects of FPDL include atrophic scarring and ulceration with subsequent pain and scarring.[41,42,46] FPDL is not efficacious for deep CHs because of its limited depth of penetration.[41,45,47,48] It is still unknown, however, if treating uncomplicated CHs with FPDL is more effective than a conservative approach.[44] For deep CHs, the Nd:YAG laser has been used with promising results.[49,50] New approaches include KTP laser therapy and IPL systems. Small CHs are responsive to KTP laser therapy and typically require only one treatment.[51] In one study of 188 patients with facial vascular lesions (45 patients with facial hemangiomas), 174 patients demonstrated 75% to 100% clearance with an IPL source.[52] Because more complications and greater pain levels are associated with IPL use, FPDL is still the preferred method of treatment for initial superficial CHs.[53]

Surgical therapy should be done to produce better results than conservative or medical treatment. The best timing for surgical resection is still under discussion.[5] Indications for surgical intervention include abnormal scarring; excess residual fibrofatty tissue and redundant skin following natural involution;

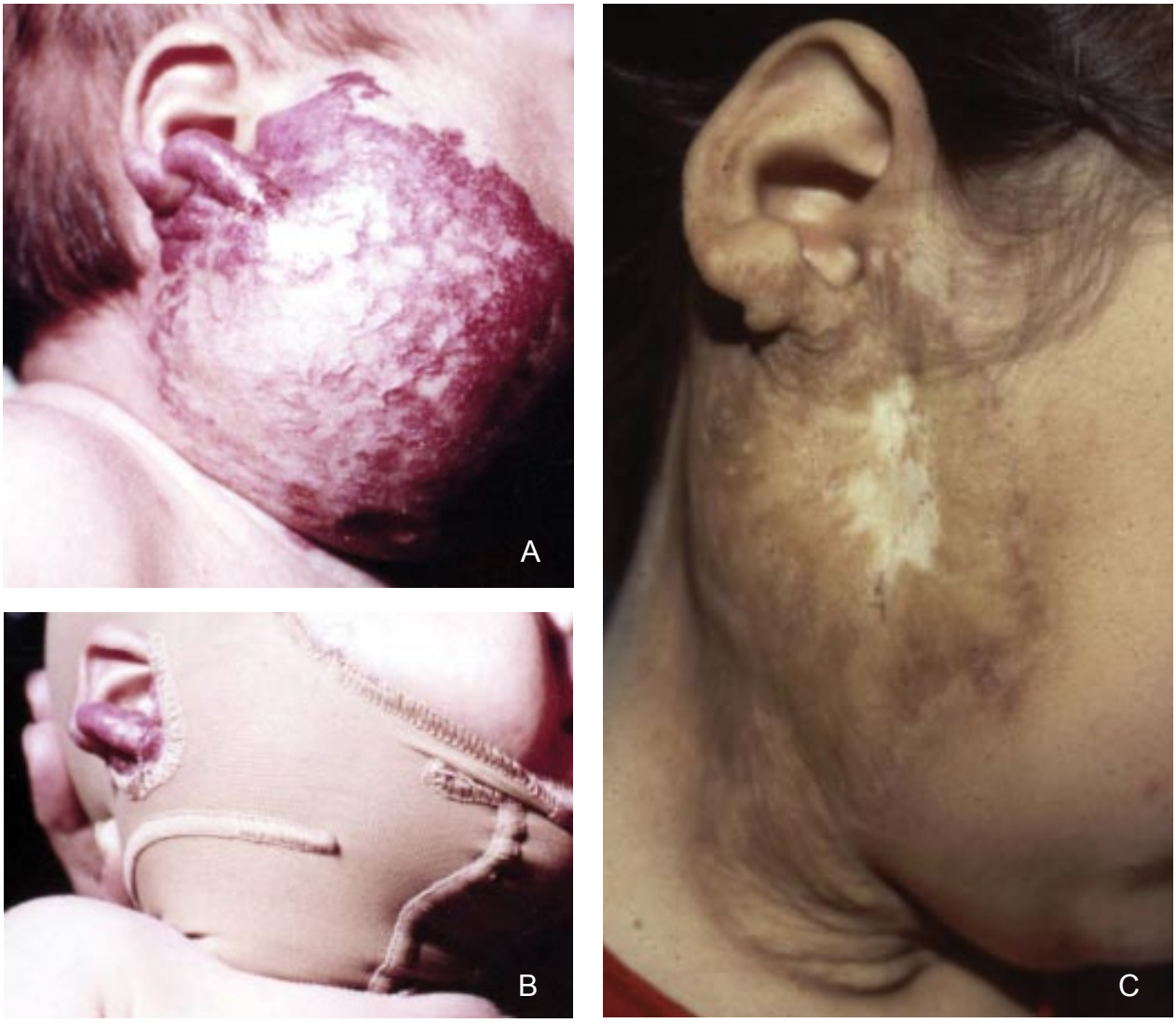

Figure 2. Large segmental cutaneous hemangioma of the neck in a unilateral beard distribution in a 4-month-old infant before (A) and during 12-month compression therapy (B). The patient aged 6 years showing only scar remnants (C).

ulcerated lesions that bleed excessively; or lesions that interfere with development and/or activities, such as tumors of the eye, ear, or larynx.[42,54-58]

Third-Line Therapy—Third-line therapies include cytotoxins, embolization, and angiogenesis inhibitors. Cytotoxins utilized in the treatment of CHs are vincristine sulfate,[25,30] cyclophosphamide,[25,30,59] bleomycin sulfate,[60] and pingyangmycin hydrochloride.[61-63] Use of cytotoxins is limited by their side effects and no data on large series of patients are available. A combination of low-dose cyclophosphamide and interferon alfa-2a for capillary hemangioma of the orbit has been reported.[64] Therapeutic embolization can be used in alarming CHs alone, or more commonly, it can be associated with pharmacologic or surgical therapy.[65]

Based on the concept of hemangioma as an angiogenic disease, another evolving treatment is the use of antiangiogenic therapies. Investigations of angiogenesis inhibitors such as batimastat,[66] thrombospondin,[67] angiostatin,[68] and IL-12[68,69] were conducted using models of vascular tumors in mice. However, further animal studies and safety studies in humans need to be conducted prior to routine use of these agents.[68] The naturally occurring nutrient, omega-3 fatty acid, could become an alternative or an adjuvant treatment for CHs because of its antiangiogenic properties.[70]

Other Therapies and Procedural Approaches—Alternative therapeutic approaches include intermittent pneumatic and continuous compression, cryosurgery, radiotherapy, implantation of copper needles, sclerotherapy, electrocautery, electroacupuncture, imiquimod cream 5%, and prospective agents (eg, OXi4503 [diphosphate prodrug of combretastatin A1], cidofovir).

Intermittent pneumatic[71] and continuous compression[72] may be used to treat CHs in proliferative and involutive phases.[73] Compressive dressings induce early regression and promote wound healing of CHs.[71] Compression is an effective treatment, particularly for CHs located on the extremities (Figure 2). Cryosurgery is popular in some countries in Europe and South America but has not gained much acceptance in the United States.[20] The standard consists of application of a contact probe cooled by liquid nitrogen to treat isolated raised lesions. Because of the low freezing temperature of liquid nitrogen (−70°C to −196°C), complications might include pain, hypertrophic or atrophic scarring, hyperpigmentation and/or hypopigmentation, milia, and retraction of tissue.[74] A new method of cryosurgery, using a device with a constant applicator tip temperature of −32°C, has been developed with good cosmetic results and minor side effects.[75] Radiotherapy was used more widely in the past before complications were recognized.[76] It may be used for lesions with complications that pose a threat to function or life, fail to improve with corticosteroid treatment, and cannot be treated with alternative methods.[77] The implantation of copper needles for the treatment of hemangiomas has been described in a report by Wang,[78] and Ogunsalu et al[79] discussed surgery in combination with implantation of copper wire. In otorhinolaryngology, intralesional magnesium seeds are used for the treatment of hemangiomas of the face with good results.[80] Sclerotherapy consists of a sclerosing substance (eg, ethanolamine oleate, ethyl alcohol, monoethanolamine oleate, polidocanol, sodium tetradecyl sulfate) injected directly through the skin into a lesion.[81,82] Recently, sclerotherapy with monoethanolamine oleate was described as effective in the treatment of CHs with late involution.[81] Sclerotherapy with polidocanol was carried out, mostly on monstrous or rapidly growing CHs mainly localized to the face, with convincing long-term results.[82] Electrocautery consists of lesion destruction with high risk of scarring.[83] A new approach in treating patients with lingual hemangiomas is electroacupuncture, which seems to provide excellent results.[84] Imiquimod cream 5% has been shown to accelerate the regression of proliferating CHs in some cases.[85] OXi4503 is a novel vascular targeting agent tested in animal models with potential use for the treatment of CHs.[76,86] Cidofovir is a potent antiviral agent that has demonstrated antiangiogenic properties in mouse models.[87]

Management of Ulcerated CHs—Treatment of ulcerated CHs falls into 3 categories: halt proliferation, alter the local environment, and manage the associated pain.[5] Local wound care has been the mainstay of treatment for ulcerated CHs.[54,55,88] Compresses used for debridement of the ulcers can be used with topical agents such as bacitracin ointment, mupirocin ointment, or metronidazole gel.[54,55] Becaplermin gel 0.01%, a recombinant human platelet–derived growth factor, also has been reported to be efficacious.[89] Occlusive dressings with zinc oxide paste, hydrocolloid gels, or topical antibiotics may be particularly useful in areas prone to trauma or superinfection, such as the anogenital region.[30]

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