Early Growth of Infantile Hemangiomas: What Parents' Photographs Tell Us

WHAT'S KNOWN ON THIS SUBJECT: Infantile hemangiomas have a period of rapid growth in early infancy. Most hemangioma growth is completed by 5 months of age, but the majority of patients are not seen by a specialist until after the growth phase is complete.

WHAT THIS STUDY ADDS: The most rapid hemangioma growth is between 1 and 2 months of life, much earlier than previously believed. Patients with high-risk hemangiomas should be followed closely, and treatment initiation should be considered before or during the most rapid growth phase.

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abstract

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BACKGROUND AND OBJECTIVES: Infantile hemangiomas (IH) are recognized as growing rapidly during the first months of life, but details of early growth before 3 months of age have not been well-characterized. Our goal was to study early IH growth by using parental photographs of infant children with facial IHs to better understand early hemangioma growth, with the aim of improving guidance for physicians and parents of infants with high-risk IH.

METHODS: Serial images of 30 infants showing IH at intervals of 1 to 2 weeks up to 6 months were analyzed for characteristics of color, thickness, and distortion of anatomic landmarks. The presence or absence of an IH precursor at birth was noted. Mean scores per age interval were compiled. Results were analyzed by using signed rank test. An assessment of "optimal time for referral" was made.

RESULTS: IH growth was nonlinear; most rapid growth occurred between 5.5 and 7.5 weeks of age. The mean "optimal age for referral" was 4 weeks of age. Hemangioma precursors were present at birth in 65% of patients.

CONCLUSIONS: The most rapid hemangioma growth occurs before 8 weeks of age, much earlier than previously appreciated. Specialty evaluation and initiation of treatment, however, typically occur after the age of most rapid growth. Our findings suggest a need for a paradigm shift in the timing of referral and initiation of treatment of high-risk IH so that therapy can be initiated before or early in the course of most rapid growth, rather than after it is already completed. *Pediatrics* 2012;130:e314–e320

Infantile hemangiomas (IH) are the most common tumor of infancy, estimated to occur in ~4% of white infants.[1] The natural history of IH is typically of rapid proliferation followed by slower involution. Although most IH do not cause serious morbidities, a significant minority can cause permanent disfigurement or functional compromise, particularly if located on the face or involving vital organs.[2] In addition, quality of life may be significantly affected for both parents and affected individuals, including feelings of loss of control, anxiety, guilt, grief, and concern for parents and low self-esteem and bullying by peers for children with visible disfigurement.[1] For those hemangiomas needing treatment, the ideal time to treat is before or as soon as evidence of permanent anatomic distortion or medical sequelae develop.

The general outlines of hemangioma growth have long been appreciated. IH generally proliferate during the first year of life, with most growth being completed by age 6 to 9 months.[3] A recent prospective cohort study of more than 1000 infants found growth occurring even earlier: 80% of hemangioma growth is completed by age 3 months, and 80% of hemangiomas have completed growth by age 5 months.[4] The mean age of presentation to a pediatric dermatologist, however, was 5 months of age, a time that most growth and many complications of hemangiomas may have already occurred. These findings led to our desire to study hemangioma growth before 3 months of age, both to better delineate growth characteristics and to determine whether growth appeared to be linear or nonlinear. Understanding early hemangioma growth could help to determine optimal timing of reevaluation in neonates and young infants with hemangiomas, as well as when referral or initiation of treatment in infants with high-risk hemangiomas (those deemed

to be at higher risk for scarring or other complications) should be considered. To study early hemangioma growth, we used parents' photographs from birth through the first few months of life.

METHODS

Institutional review board approval was obtained for this study. Patients were recruited through the University of California at San Francisco pediatric dermatology clinics and the National Organization of Vascular Anomalies, a patient advocacy group, between January 2009 and March 2011. Parents were asked to fill out a short parental questionnaire and submit photographs of their children that demonstrated their infantile hemangiomas over time. Photographs taken approximately every 2 weeks apart during the first 2.5 to 6 months of life were requested. Seventy-two families expressed interest in the study. Of these, 36 parents returned materials including a consent form, a short parental questionnaire, and photographs via compact disc, secure E-mail, or hard copy. Six of these were excluded because of incomplete materials, inadequate photograph spacing, or photographs of poor quality.

The remaining 30 patients met inclusion criteria. Hemangiomas, if not seen personally, were confirmed by the authors to be infantile hemangiomas and classified as either segmental or localized and as superficial, mixed, or deep. Demographic data as supplied by the parents on questionnaire were noted. Medical records were not reviewed. Photographs were arranged sequentially in ~2-week intervals (Figs 1 and 2), with some intervals being slightly longer or shorter depending on the images available. Dates and ages were removed from the arranged photographs. At least 2 months lapsed in each of the cases from the time of arrangement of the photographs to

review by MMT and IJF. Both MMT and IJF reviewed photographs of patients not included in the study before reviewing study cases. From this joint review, consistency in review methodology and interreviewer reliability was established.

Each photograph was given a score for each of 3 characteristics: color, thickness, and presence of local anatomic distortion. Intensity of color was rated from 1 through 4 (1 = imperceptible, 2 = barely perceptible, 3 = red, 4 = bright red), thickness of tumor was rated from 1 through 4 (1 = flat/none, 2 = slight elevation, 3 = moderate elevation, 4 = marked thickness), and distortion of local anatomic landmarks was rated from 1 through 3 (1 = no, 2 = yes, minimal, and 3 = yes, marked). For each patient, the 2 consecutive photographs that demonstrated the greatest difference in hemangioma volumetric growth were determined independently by each reviewer (MMT and IJF). A composite score consisting of a tally of each of the 3 measured characteristics was calculated for each patient.

RESULTS

Demographic Data

Thirty patients met criteria for inclusion in this study. Twenty-two (73%) were female and 8 (27%) were male. Nineteen (63%) had localized hemangiomas, and 11 (37%) had segmental IH. The majority of patients had primarily superficial hemangiomas (24 patients, 80%), 1 (3%) had a primarily deep hemangioma, and 5 (17%) patients had mixed hemangiomas. Five (17%) of the 30 patients were premature (<37 weeks' gestation); the remainder were born at term. All but 1 subject (a twin) were products of a single gestation. Each patient had 1 hemangioma that was studied. Of these, 28 (93%) were located on the face, with 2 located on the scalp and neck.
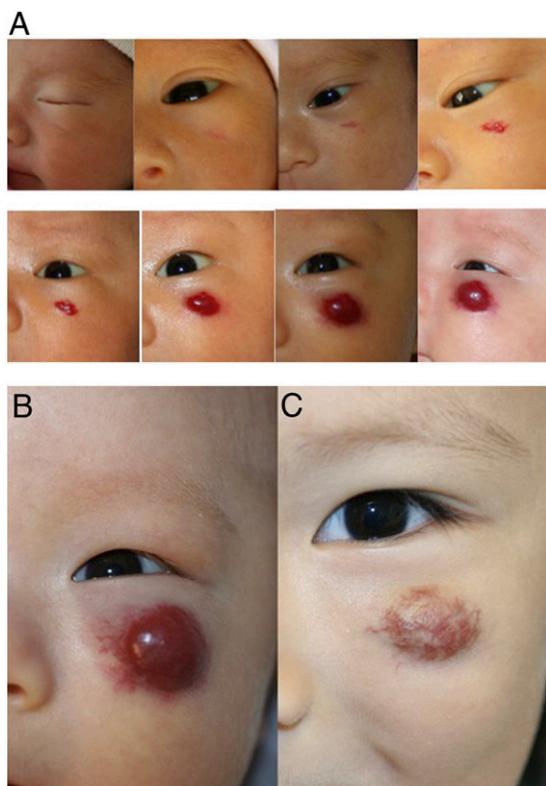
FIGURE 1
A, Evolution of an exophytic localized hemangioma from birth to 3 months. B, Same patient at 2.5 months and C, 3 years . Despite initiation of systemic therapy with steroids at 2.5 months, followed by propranolol, residual telangiectasia and fibrofatty skin changes persisted, emphasizing that early growth, especially of superficial hemangiomas, can lead to irreversible skin changes.

Hemangioma Precursors and Growth Characteristics

Patient photographs were analyzed up to a mean of 19.1 weeks (median 20.8, range 9.4–24.9 weeks, 95% confidence interval [CI] 17.4–21.2). Only 2 patients had their last photograph available at an age of <12 weeks. Twenty-six (17 localized, 9 segmental) of 30 patients had photographs available from the first day of life, and of these, 17 (65%) had evidence of a cutaneous precursor lesion in their initial photograph shortly after birth including 10 of 17 (59%) patients with localized hemangiomas and 7 of 9 (78%) patients with segmental hemangiomas.

Differences in color, thickness, and anatomic distortion were all demonstrated when comparing changes during the first 8 weeks of life versus age 8 weeks and older ($P < .05$) (Fig 3). The rate of change in color was deemed to be faster than rates of change in thickness and anatomic distortion, but this did not reach statistical significance. The most rapid rate of infantile hemangioma growth, as assessed by composite score, was determined to be from day 1 of life to 8 weeks of age ($P < .001$) versus 8 weeks and beyond (Figs 4 and 5).

To determine whether growth was linear or nonlinear, that is, if the rate of change in growth was the same throughout the growth period or if there was a critical period of nonlinear accelerated growth, we compared changes in interval photographs. The average interval length was 2.2 weeks (median 2.1 weeks, 95% CI 2.0–2.7). The intervals when greatest change (ie, fastest rate of growth) appeared to be taking place were determined. Twenty-nine of 30

patients (97%) were judged to have nonlinear growth, with the time period of greatest growth being between 5.5 weeks (95% CI 4.6–6.3) and 7.5 weeks (95% CI 6.7–8.4, median 4.3–6.8). Only 1 patient (3%) was judged to have an even rate of growth throughout. We also determined, via subjective assessment, the point in time when we would have preferred to first see the patient in consultation before the time of greatest proliferation such that if treatment was needed, it would have the greatest potential impact. The average age at which referral was desired using this "retrospectoscope" was at a mean of 4.0 weeks (median 3.6, 95% CI 2.7–4.9).

Treatment

Twenty (67%) of the 30 patients received some form of treatment. Eight (40%) of these received 2 modalities of treatment, and 12 (60%) received 1 type of treatment. Treatment modalities used included topical and/or intralesional steroids (9 patients), oral propranolol (6), oral steroids (5), surgery or pulsed dye laser (5), and topical timolol (3). Treatment was initiated at a mean of 11.4 weeks (median 10.7, 95% CI 8.8–13.6), and only 6 patients received treatment before 9 weeks of life. Of these 6 patients, 2 were treated with topical steroids, 2 with pulsed dye laser, 1 with oral steroids, and 1 with oral propranolol. Four of these 6 patients went on to receive a different modality of treatment at a later age: 2 oral propranolol, 1 topical timolol, and 1 surgical debulking. Removing the 6 patients who received early treatment (before 9 weeks of life) resulted in the same results of rate of infantile hemangioma growth as assessed by composite score, again determined to be from day 1 of life to 8 weeks of age ($P < .005$) versus 8 weeks and beyond (Fig 6). The time of greatest growth for these 24 patients was between 5.6 weeks (95% CI 3.2–8.0) and 8.1 weeks (95% CI 4.6–11.5). Subgroup analysis of the 10 patients who

FIGURE 2
A, Evolution of a localized hemangioma from birth to 4 months of age. B, Same patient at 3 months and C, 1 year. Despite initiation of systemic therapy with propranolol at 3 months, residual telangiectasia and fibrofatty skin changes ultimately requiring surgical intervention had already occurred.
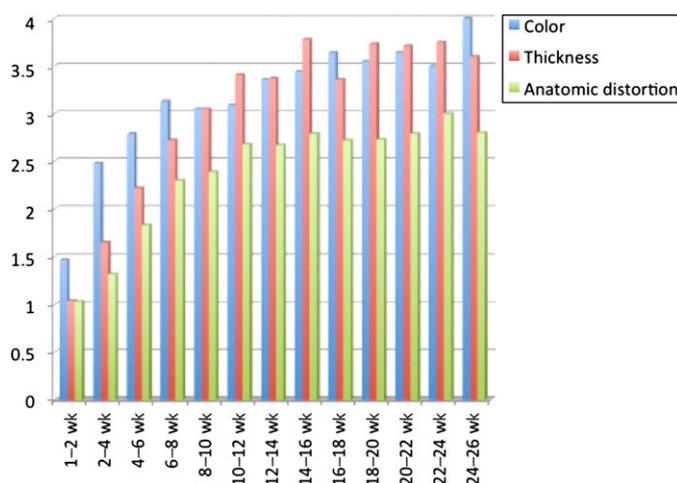
FIGURE 3
Rate of growth for individual characteristics of color, thickness, and anatomic distortion.

were not treated confirmed that the fastest rate of growth as measured by composite score was during the first 8 weeks of life ($P < .05$). The time of greatest growth for untreated patients was between 6.4 (95% CI 4.7–8.0) and 8.5 weeks (95% CI 6.4–10.7).

DISCUSSION

Growth is an essential, defining feature of infantile hemangiomas. Although the general outlines of the natural history of IH are understood, details of early growth have not been well characterized.

The primary goal of this study was to characterize the period of early growth as determined by color, thickness, and anatomic distortion. In this study, we used the unique method of examining parents' photographs of their children to characterize hemangioma growth in early infancy and to define a period of maximum growth velocity.

Our patients had photographs available up to the mean age of 19.1 weeks, by which time, as recently discovered, IH growth is largely completed.[4] We found that, at least in the case of superficial hemangiomas, the majority of this growth occurs before 8 weeks of age. There also appears to be a period of accelerated growth velocity between 5.5 to 7.5 weeks, suggesting that hemangioma growth is nonlinear during that time period. When patients who were treated before age 9 weeks were excluded, findings were found to be nearly identical, likely reflecting the relatively small number of patients who were treated that early and the variety of treatment modalities used, which may have resulted in variable responses. Additionally, when untreated patients were analyzed separately the findings were quite similar.

A detailed description of early hemangioma growth has not been previously studied. Our findings suggest the need for a paradigm shift in management: early hemangiomas need to be recognized more promptly, and infants with high-risk hemangiomas (Table 1) should be watched closely (eg, seen weekly or biweekly), have treatment initiated, or be referred to specialists promptly, ideally by 4 weeks of age, because a period of accelerated growth occurs between 5.5 and 7.5 weeks of life. The age of 4 weeks was also suggested in our determination of the ideal age at which an infant might initially be seen for consultative care using a retrospectospcope. On the receiving end, specialists must have mechanisms in
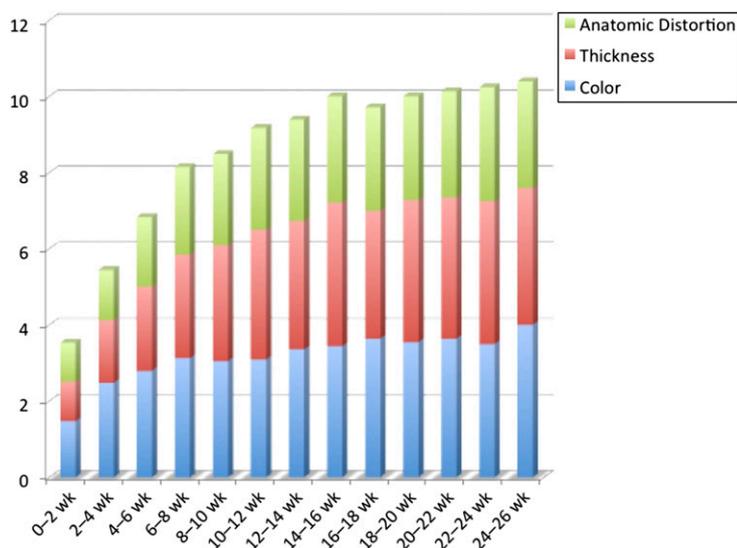
FIGURE 4
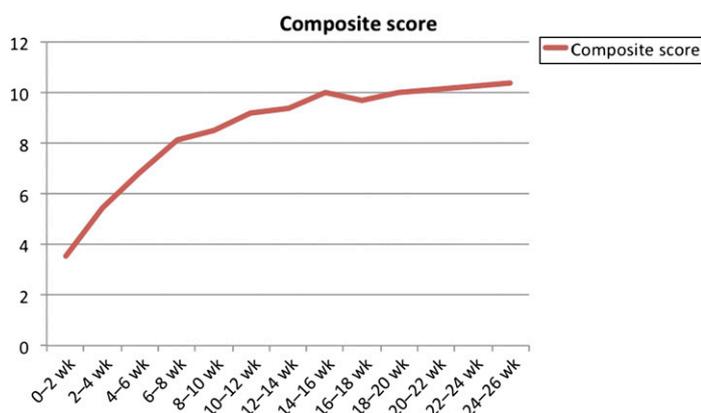Rapid rate of growth through week 8 for all 3 parameters.

FIGURE 5
Composite score showing highest rate of growth until week 8.

place for urgent evaluation of infants with high-risk IH, or at least a triage system for reviewing clinical photographs to determine optimal timing of consultation and management.

Several studies have shown that patients with IH are generally not seen by a subspecialist until 3 to 5 months of age.[4–6] In our cohort, treatment was first initiated at an average of 11.4 weeks, with only 20% of patients receiving treatment before 9 weeks. Thus, nearly all patients had initiation of treatment after the period of maximal growth was over. Although there have not been studies to date proving that treatment initiated earlier is better than later, both the study by Chang et al[4] and our findings strongly support the idea that significant growth of hemangiomas and resultant skin changes occur early in the course of disease. Effective treatments to prevent the skin changes that occur during this rapid growth phase are thus likely to help prevent irrevocable skin changes.

Which patients require active treatment is still a matter of controversy. Infantile hemangiomas do involute spontaneously, but in addition to uncommon but well-defined medical morbidities, many leave residual skin changes. Bauland et al[7] have recently reported on the long-term follow-up of nearly 100 children with untreated infantile hemangiomas seen in a multidisciplinary referral center in the Netherlands. They found residual skin changes in 69% of cases, with superficial nodular hemangiomas being much more likely to leave residual skin changes (74%) than deep hemangiomas (25%). Although residual skin changes in this cohort are undoubtedly higher than in patients seen only by primary care physicians because of an ascertainment bias, such outcomes are not rare. A large cohort study found that 24% of patients with hemangiomas experienced ≥1 complications, and 38% received some form of treatment.[8] In our much smaller study, we had an even higher rate of treatment with two-thirds of these infants receiving ≥1 forms of treatment. This difference is at least in part due to the fact that nearly all hemangiomas were located on the face, a site far more likely to be treated than hemangiomas located elsewhere on the body.[8] In addition, the use of β-blockers (both topical and systemic) as a new modality of treatment also likely contributed to a higher rate of treatment.

As newer, more effective treatments become available,[9,10] earlier referral and treatment of high-risk hemangiomas may have an even greater potential for preventing hemangioma-related complications and permanent irreversible skin changes or complications. Similarly, when designing clinical trials studying the efficacy of such medications, it is vital that infants be enrolled before the phase of greatest nonlinear growth so that the efficacy and potential impact of the medications can be appropriately evaluated. Although oral propranolol can be efficacious beyond the proliferative phase,[11] irreversible skin changes may have already occurred (Figs 1C and 2C), again emphasizing the importance of early treatment whenever
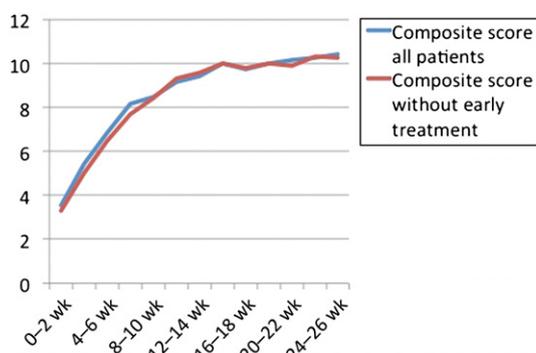
FIGURE 6
Composite score showing highest rate of growth until week 8 for all patients and for all patients not treated before 9 weeks of life.

TABLE 1 High-risk Hemangiomas

Clinical Scenario	Potential Sequelae
Potentially disfiguring sites	Permanent distortion of anatomic landmarks, including fibrofatty residua, anetoderma, textural changes, and hyperpigmentation
Nasal tip	Residual telangiectasias
Perioral	High risk of ulceration, especially perioral and neck fold hemangiomas
Glabella	
Ear	
Eyebrow	
Central facial location, particularly those medial to the outer canthi and >0.5 cm in size	
Superficial thick or exophytic hemangiomas, in areas not easily covered by clothing	
Periocular hemangiomas	Astigmatism or visual axis obstruction potentially resulting in permanent amblyopia
	Strabismus
Facial hemangiomas >5 cm in diameter or segmental facial hemangiomas	PHACE syndrome (cerebrovascular, cardiac, coarctation of aorta, ocular, and other anomalies)
	Ulceration, scarring, residual skin changes
Lumbosacral or perineal hemangiomas	High risk of ulceration
	Tethered spinal cord
	Lipomyelomeningocele
	Genitourinary abnormalities
Airway hemangioma ± "beard area" skin hemangiomas	Life-threatening airway obstruction, usually between 4–6 wk of life
Multifocal (≥5) infantile hemangiomas	Hepatic hemangiomas: can be asymptomatic or result in abdominal compartment syndrome, heart failure, and hypothyroidism

PHACE, Posterior fossa anomalies, Hemangioma, Arterial lesions, Cardiac abnormalities/coarctation of the aorta, Eye abnormalities.

possible.[12,13] It is also important to note that many hemangiomas will display rebound growth after discontinuation of medications such as propranolol. Thus, although early treatment before the period of greatest proliferation is vital, treatments may need to be continued well beyond the period of most rapid growth to prevent rebound growth.

Our cohort was relatively small, but its demographic findings, including female gender and rates of prematurity, were similar to those of previously described large cohorts of patients with infantile hemangiomas.[14–16] More had segmental hemangiomas (37%) than are typically seen,[8,14] a difference that most likely reflects an ascertainment bias,

because parents willing to participate in the study were more likely to have children at the more severe end of clinical spectrum. This disproportionate number of segmental hemangiomas may actually have led to an underestimation of early growth because segmental hemangiomas grow for a mean of 1 month longer than their localized counterparts.[4] Although our sample size was not large enough to separate these 2 groups for this analysis, the finding of accelerated early growth is likely to be generalizable to both localized and segmental hemangiomas.

A secondary goal of this study was to determine the prevalence of hemangioma precursors evident at birth. A classic teaching is that most hemangiomas are absent at birth and appear rapidly thereafter.[3] Previous retrospective reviews found hemangioma precursors to be present at or near the time of birth in 36% to 48% of patients.[14,17] Our study, the first to examine parents' pictures from the first day of life rather than relying on parental memory, found that 65% of patients had a visible hemangioma precursor noted on the first day of life, a rate far higher than previous reports but likely to be more accurate because of the objective photographic confirmation. Some precursors, although clearly visible in retrospect, might not have been easily distinguished from other marks in the immediate newborn period, but nearly all became obvious within 1 or 2 weeks as other postpartum changes subsided. An increased awareness of hemangioma precursors would be helpful in identifying infants to be seen promptly, particularly in high-risk locations and for larger precursor lesions suggesting segmental distribution (Table 1).

Our study has certain limitations. First, it is a fairly small study sample because participation did require some amount of effort on the part of busy parents.

Because of the limited of number of participants, we were unable to analyze subsets of patients per type and location of hemangioma or by treatment modality. Additionally, although hemangiomas at all sites were encouraged, our patients had only head and neck hemangiomas because frequent photos of infants' faces are far more likely to be taken than of other body sites. Thus, using parental photographs also limited our ability to study early growth characteristics of hemangiomas at other body sites, particularly those involving the lower half of the body, where less vigorous growth is often found.[18] In addition we were unable to collect precise volumetric measurements of hemangiomas, which might have given more quantitative results regarding hemangioma growth. Perhaps the most important limitation is that the majority of our patients had primarily superficial hemangiomas, and the growth characteristics found may be less generalizable to deeper hemangiomas, which can arise later in life and often grow for longer.[5] Twenty percent of our cohort, however, did have mixed type or primarily deep hemangiomas, which could potentially have delayed the period of maximum growth calculated in our study. Our sample size was not large enough to separate the growth characteristics of superficial versus deep hemangiomas, although clearly the findings apply best to those with superficial skin involvement.

CONCLUSIONS

We have demonstrated via parental photographs that rapid, accelerated growth of infantile hemangiomas most often occurs before 8 weeks of age, often peaking between 5.5 and 7.5 weeks. This finding suggests that, at a minimum, frequent evaluation either in person or via photographs, should be undertaken for hemangiomas at high-risk sites and that early initiation of treatment or specialty referral should be strongly considered in such cases with the goal of preventing permanent skin changes and growth-related complications.

ACKNOWLEDGMENT

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