Early White Discoloration of Infantile Hemangioma

A Sign of Impending Ulceration

Sheilagh M. Maguiness, MD; William Y. Hoffman, MD; Tim H. McCalmont, MD; Ilona J. Frieden, MD

Objective: To evaluate the relationship between early white discoloration of infantile hemangioma (IH) and ulceration.

Design: Retrospective cohort study.

Setting: Tertiary referral center.

Patients: A case series of 11 infants with early white discoloration of IH are described. An additional 55 infants with IH, aged 3 months, were evaluated retrospectively from a photograph archive to further explore the relationship between early white discoloration and presence or development of ulceration.

Main Outcome Measures: Patient demographics and hemangioma size, location, and subtype are documented. Sensitivity and specificity of white discoloration in relationship to ulceration are estimated.

Results: Ten of the 11 infants in the case series were girls (90%); all IHs were of segmental or indeterminate subtype. Average age at first ulceration was 2.6 months, with average age at healing 5.2 months. No intervention halted progression of ulceration. Of the 55 additional 3-month-old infants, 14 had white discoloration and 12 of these 14 had or developed ulceration (86%). When the hemangioma was either white or slightly white, sensitivity for predicting ulceration was 1.00 (95% confidence interval [CI], 0.78-1.00), with a specificity of 0.68 (95% CI, 0.51-0.81). In contrast, in infants with either slightly white or no white discoloration, the sensitivity for not developing ulceration was 0.80 (95% CI, 0.52-0.96), with a specificity of 0.95 (95% CI, 0.83-0.99), suggesting that a lack of substantial white discoloration early in infancy indicates low risk of ulceration.

Conclusion: Early white discoloration of infantile hemangioma is highly suggestive of impending ulceration.

Arch Dermatol. 2010;146(11):1235-1239

Infantile hemangiomas (IHs) are the most common benign vascular tumors of infancy. Ulceration is the most common IH complication, occurring in approximately 15.8% of cases in a referral population. Most hemangiomas have a predictable and characteristic growth pattern. They are either absent or present as precursor lesions at birth and go on to proliferate rapidly over the first few months of life, with proliferation typically completed by age 4 to 6 months.

For editorial comment see page 1295

During the proliferative phase of hemangioma growth, the clinical appearance is usually a brightly erythematous plaque with slight follicular accentuation resembling a strawberry, or if the hemangioma is mixed (ie, has both superficial and deep components), it may appear as a bluish soft-tissue nodule with a brightly erythematous plaque at the surface. These clinical appearances usually predominate throughout the first 4 months of life.

The clinical characteristics heralding involution include simultaneous softening of the tumor and a milky white or gray discoloration of the superficial surface typically beginning in the center and progressing centrifugally. Involution can begin when the child is as young as a few months, but more commonly it begins after IH growth has been completed, between ages 5 and 10 months.

We describe herein 11 infants in whom early white discoloration of the IH surface (Figure 1) heralded extensive, relentless ulceration, a finding we refer to as the “early white hemangioma” sign (Figure 2 and Figure 3). To confirm the significance of this finding, we evaluated 55 more infants selected from a photograph archive of patients with IH to determine the degree to which early whitening of IH predicted ulceration.
In the retrospective cohort of 11 patients with early white discoloration of IH, we recorded information regarding clinical characteristics, location, size, morphologic traits, and treatment methods (Table). As a second component of the study, to determine the specificity of early whitening, we analyzed a consecutive, cross-sectional sample of clinical photographs of 55 three-month-old infants with IH. Patients were excluded from evaluation in this cross-sectional study if they did not have follow-up visits for at least 2 more months. The patients' sex and history of ulceration were recorded as were the location, distribution, and extent of white IH discoloration. We recorded whether the IHs were white, slightly white, or not white at 3 months, as judged by unblinded investigators (S.M.M. and I.J.F.). If a substantial amount of the hemangioma exhibited white discoloration, it was considered white. Slightly white hemangiomas were those with less than 20% white discoloration. Both studies were approved by the University of California, San Francisco committee on human research.

Patient 1 was born at 36 weeks’ gestation of an uncomplicated pregnancy. She was seen at our pediatric dermatology clinic at age 3.5 months with a giant (>500 cm²), mixed, segmental hemangioma covering her entire mid thoracic spine (Figure 1). On initial examination, we found a reticulate white and gray

![Figure 1](image1.png)

Figure 1. Segmental infantile hemangioma of the left forearm. A, A age 2.5 months with characteristic white surface discoloration. B, Extensive ulceration at age 5.5 months.

![Figure 2](image2.png)

Figure 2. Large hemangioma of the right cheek. A, White-gray discoloration at age 1.5 months. B, Complete ulceration at age 3 months. C, Healing after pulsed-dye laser therapy.

![Figure 3](image3.png)

Figure 3. Segmental hemangioma of the right shoulder. A, White-gray dusky surface discoloration at age 1.5 months. B, Complete ulceration at age 4 months. C, Healing of ulceration and increased volume due to growth of deep component at age 1 year.
appearance to the entire tumor and maceration within skin folds. Suspecting a high risk of ulceration, we treated the patient with low-dose oral corticosteroids (prednisolone, 1 mg/kg/d divided twice daily) and low-dose aspirin.

At age 4 months, on return to clinic, the infant had multiple sites of ulceration, and treatment at this time included conservative local wound care with metronidazole gel, petrolatum (Aquaphor; Beiersdorf Inc, Hamburg, Germany), topical platelet-derived growth factor (PDGF) (becaplermin gel), and nonadherent dressings. At age 5 months, the patient was seen again for dramatic, extensive ulceration of the entire tumor with substantial pain (Figure 4). Bacterial infection with methicillin-sensitive Staphylococcus aureus was also present. Owing to the extensive ulceration and pain, the patient underwent surgical debridement and primary closure of the largest involved areas. All systemic therapy was discontinued.

Histopathologic findings of the lesion included substantial necrosis of the hemangioma down to fascia. Scattered areas of fibrosis were found in the superficial dermis, which appeared to correspond to clinically whitened areas (Figure 5). Magnetic resonance imaging of the spine and brain showed extensive soft-tissue hemangioma of the thoracic spine as well as intraspinal involvement and involvement of the aorta. Ongoing ulceration, chronic pain, and frequent staphylococcal superinfection necessitated treatment with interferon alfa-2b at age 14 months.

**RESULTS**

The Table summarizes the clinical characteristics, treatments, and time to healing in all 11 patients. The average age at the time of ulceration in our cohort was 2.6 months, and the average age at healing was 5.2 months. All patients received some form of wound care, principally petrolatum, metronidazole gel, and nonadherent dressings. Most (9 of 11) received topical PDGF (becaplermin gel). Oral corticosteroids were given in 6 of 11 cases, low-dose-aspirin in 3 cases, and oral propranolol in 1 case. None of these treatments seemed effective at halting the progression of ulceration; however, topical becaplermin appeared to accelerate wound-healing in 2 patients. Pulsed-dye laser treatment resulted in fast and complete healing in 2 patients, and early surgical excision in 2 patients also helped to control pain, and the surgical wounds healed promptly.

<table>
<thead>
<tr>
<th>Patient No./Sex/Gestational Age, wk</th>
<th>Hemangioma Location</th>
<th>Size, cm²</th>
<th>Subtype</th>
<th>Age at First Ulceration, mo</th>
<th>Treatment</th>
<th>Age at Healing, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/36</td>
<td>Back</td>
<td>500</td>
<td>Segmental</td>
<td>4</td>
<td>Bevacaplermin, prednisolone, aspirin, surgical resection</td>
<td>&gt;14</td>
</tr>
<tr>
<td>2/F/37</td>
<td>Shoulder</td>
<td>35</td>
<td>Segmental</td>
<td>2</td>
<td>Bevacaplermin, aspirin</td>
<td>6</td>
</tr>
<tr>
<td>3/F/36</td>
<td>Face</td>
<td>110</td>
<td>Segmental</td>
<td>0.5</td>
<td>Bevacaplermin, prednisolone ×3 mo</td>
<td>4</td>
</tr>
<tr>
<td>4/F/40</td>
<td>Perineal</td>
<td>100</td>
<td>Segmental</td>
<td>0.75</td>
<td>Bevacaplermin, prednisolone, interferonα</td>
<td>Still not healed at 5α</td>
</tr>
<tr>
<td>5/M/40</td>
<td>Shoulder</td>
<td>32.5</td>
<td>Indeterminate</td>
<td>2</td>
<td>Prednisolone ×2 wk, PDL</td>
<td>3.5</td>
</tr>
<tr>
<td>6/F/38</td>
<td>Torso</td>
<td>14</td>
<td>Indeterminate</td>
<td>6</td>
<td>Bevacaplermin, PDL</td>
<td>6.75b</td>
</tr>
<tr>
<td>7/F/39</td>
<td>Thigh</td>
<td>42</td>
<td>Indeterminate</td>
<td>2.5</td>
<td>Bevacaplermin, prednisolone, aspirin ×2 wk</td>
<td>8</td>
</tr>
<tr>
<td>8/F/32</td>
<td>Face</td>
<td>10.5</td>
<td>Indeterminate</td>
<td>2.5</td>
<td>Bevacaplermin, PDL</td>
<td>4.5</td>
</tr>
<tr>
<td>9/F/40</td>
<td>Trunk</td>
<td>43</td>
<td>Segmental</td>
<td>3.5</td>
<td>Surgical excision</td>
<td>5</td>
</tr>
<tr>
<td>10/F/37</td>
<td>Perineal</td>
<td>60</td>
<td>Segmental</td>
<td>3</td>
<td>Bevacaplermin</td>
<td>Unknown</td>
</tr>
<tr>
<td>11/F/33</td>
<td>Forearm</td>
<td>75</td>
<td>Segmental</td>
<td>2</td>
<td>Bevacaplermin, PDL, propranolol</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviation: PDL, pulsed-dye laser.

α One patient with an extensive perineal hemangioma causing urinary obstruction received interferon at another institution and was not seen in follow-up at our institution.

b Pulsed-dye laser in this patient accelerated healing within 3 weeks.

**Figure 4.** Giant segmental infantile hemangioma of the back. A, At age 4.5 months with dusky gray-white surface change and areas of ulceration. B, Extensive ulceration down to fascia at age 7 months.
Histopathologic sections from 2 surgical specimens of excised white hemangiomas (patients 8 and 9) were analyzed in an attempt to correlate clinically white areas with underlying microscopic alterations. In both specimens, the hemangiomas showed areas of extensive necrosis (with ulceration down to fascia in patient 1) adjacent to areas of superficial dermal fibrosis, a finding not well characterized or reported in typical proliferating IHs (Figure 5). Specimens were found to be GLUT-1 positive, and in both cases, p53 staining was judged to be minimal or negative.

In the cross-sectional sample of 55 three-month-old infants with IH, 14 of 55 had white discoloration. Of these, 12 of 14 had or developed ulceration (86%). All were of segmental or indeterminate subtype. Fourteen of the 55 patients were designated as having slight white discoloration, and of these patients 3 of 14 developed ulceration (21%). In the 27 patients where no white discoloration was observed, none developed ulceration.

When the hemangioma was either white or slightly white, the sensitivity for associated ulceration was 1.00 (95% confidence interval [CI], 0.78-1.00), with a specificity of 0.68 (95% CI, 0.51-0.81). Patients with documented ulceration were 80% more likely to have early white discoloration of their hemangioma than those with either slight or not white lesions, and the corresponding specificity was 0.95 (95% CI, 0.83-0.99). Therefore, in 95% of patients without substantial white discoloration, ulceration did not develop during the duration of follow-up.

**COMMENT**

Ulceration is the most common complication of IH. The incidence in a referral population is generally reported to be between 15% and 25%. In a prospective study of 1096 patients reported by Chamlin et al, the median age at ulceration was 4.0 months, which correlates with the end of the proliferative phase. Risk factors for ulceration include segmental morphologic characteristics, large size, and mixed superficial and deep subtype. Anatomic location is also a risk factor for ulceration, and IHs on the lower lip, neck, and anogenital area are more likely to ulcerate than those on other sites. Interestingly, in our subset of patients, only 4 of 11 lesions were located on the head and neck or genital area, and most of the hemangiomas with early white discoloration were on the trunk and extremities, areas that in typical IH are not at high risk for ulceration.

The cause of ulceration in IH is not well understood. There has been speculation that ulceration may arise due to rapid hemangioma growth, with the lesion thus outstripping its oxygenated blood supply. Some believe that ulceration may herald involution; however, prospective studies have documented that most ulceration occurs in the late proliferative phase of hemangioma growth (patient age 4-6 months). In our study, patients had even earlier ulceration (age 2.6 months) than is typically seen. Early gray-white discoloration in the columellar area, a sign of impending cartilage destruction, has been reported in 3 infants with segmental facial hemangiomas involving the upper lip and perinasal skin, a finding strikingly similar to our patients with early white-gray discoloration. As in our patients, no treatment was effective in halting progressive ulceration.

The histopathologic analysis in 2 of our patients showed fibrosis in the upper dermis. A similar exuberant fibrocytic reaction was recently reported in small, localized, early-regressing IH. These findings may imply a different mechanism of action leading to early regression or ulceration. In both specimens, negative p53 staining suggests that accelerated apoptosis cannot explain the early ulceration. Recently, the role of hypoxia in hemangioma proliferation has been studied. Hypoxia-inducible factor (HIF) and related cytokines are elevated in proliferating hemangiomas, indicating a possible role for hypoxia in the development of IHs. It is possible that the fibrosis seen in patients with early white discoloration of IHs may form as a result of tissue hypoxia, as in certain types of scarring processes such as keloids in which HIF is also upregulated. A study examining ultrasonograms of cutaneous hemangiomas did not show correlation between blood vessel flow characteristics and likelihood of ulceration. This raises the possibility that hypoxia may be related to tissue oxygenation, occurring within smaller vessels, and lead-
ing to fibrosis and then to ulceration. Although not definitively proven, the white color change perceived at the surface of this interesting group of hemangiomas may correspond to the scarlike areas of superficial dermal fibrosis.

In conclusion, early white discoloration of IH appears to be highly sensitive and relatively specific for predicting hemangioma ulceration. This finding in infants younger than 3 months, rather than heralding early involution, appears to be a sign of early ulceration. Clinicians should be aware of this phenomenon and anticipate complications in these patients. Anecdotally, early excision (when feasible) and administration of topical becaplermin, pulsed-dye laser, and oral propranolol were useful in expediting healing and controlling pain.

Accepted for Publication: April 8, 2010.
Correspondence: Sheilagh M. Maguiness, MD, Department of Pediatric Dermatology, Children’s Hospital Boston, 300 Longwood Ave, Fegan 6, Boston, MA 02115 (Sheilagh.Maguiness@childrens.harvard.edu).

Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Maguiness and Frieden. Acquisition of data: Maguiness, Hoffman, and Frieden. Analysis and interpretation of data: Maguiness, McCalmont, and Frieden. Drafting of the manuscript: Maguiness. Critical revision of the manuscript for important intellectual content: Maguiness, Hoffman, McCalmont, and Frieden. Administrative, technical, and material support: Maguiness and Frieden. Study supervision: Maguiness, Hoffman, and McCalmont.

Financial Disclosure: Dr McCalmon has served as a consultant for Cutera Lasers and as a medicolegal consultant for dermatopathology cases. Dr Frieden has served as consultant for Pierre Fabre Dermatology.

Additional Contributions: Alan Bostrom, MD, assisted with the statistical analysis in this study.

REFERENCES