Infantile Hemangiomas With Unusually Prolonged Growth Phase

A Case Series

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Background: Most infantile hemangiomas (IHs) complete their proliferative growth phase before 9 months of age, but those with unusually prolonged growth create unique clinical challenges. We performed a retrospective case series of IHs with prolonged growth to further characterize these lesions and their treatment.

Observations: We identified 23 patients as having IHs with prolonged growth after 9 months of age, with growth to a mean age of 17 months. All of the IHs had a deep dermal to subcutaneous component, all had either segmental or indeterminate morphologic characteristics, and 39% involved the parotid gland. A total of 20 of 23 received prolonged treatment with systemic corticosteroids (mean duration of treatment, 11 months), and 9 of 20 received additional systemic therapies (vincristine sulfate and/or interferon alfa-2a or alfa-2b).

Conclusions: Prolonged growth was observed primarily in IHs with a deep component and segmental morphologic characteristics. Recognition of this subset of hemangiomas is important for clinicians, and further study of IHs may provide clues to their pathogenesis.

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Methods

Prolonged growth was defined as a proliferative growth phase past 9 months of age with-

For editorial comment see page 1650

Infantile hemangiomas are the most common tumor of infancy and have a well-described natural history of rapid growth during early infancy followed by gradual involution. Although there are other types of vascular tumors sometimes referred to under the umbrella term hemangiomas (eg, lobular capillary hemangioma [pyogenic granuloma]), hereafter in this article the term hemangioma will refer to infantile hemangiomas specifically. The duration of the growth phase can be variable, but it has long been reported that most hemangiomas reach their maximal size within the first 6 to 10 months of life.1-3 The growth characteristics of hemangiomas were more rigorously evaluated in a recent large prospective study,4 which found that the early proliferative growth phase was essentially complete by 5 months of age, and overall growth was nearly always complete before 9 months of age. Although hemangiomas with growth after 9 months of age represent only a small subset, their continued growth can cause therapeutic challenges, functional sequelae, and considerable parental anxiety.

The classification of infantile hemangiomas has been based on their depth of soft-tissue involvement described as superficial, deep, or combined. Deep hemangiomas have been observed to have a longer growth phase compared with superficial hemangiomas.2,5 More recently, hemangiomas have also been characterized by their spatial configurations as segmental, localized, or indeterminate. Segmental hemangiomas have a geographic pattern over a cutaneous territory that frequently corresponds to a developmental segment.6 Previous studies7-9 have found that segmental hemangiomas are more likely to result in complications, such as ulceration, and are more likely to require treatment than localized hemangiomas. Segmental hemangiomas may also have a greater propensity to grow after 6 months of age.1 In addition, anatomic location may be associated with a greater propensity for aggressive growth and recalcitrance to therapy. Hemangiomas involving the parotid gland have been reported to involute more slowly and be less responsive to treatment, although the latter is controversial.9,12 This retrospective case series focusing on hemangiomas with unusually prolonged growth was undertaken to further characterize this small but important subset of hemangiomas.
out treatment, or rebound growth after 1 year of age with treatment. Patients meeting inclusion criteria were identified by clinicians at the following participating institutions: the University of California, San Francisco; Texas Children’s Hospital, Baylor College of Medicine, Houston; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Children’s Hospital Medical Center of Cincinnati, Cincinnati, Ohio; and Hospital de Pediatria, J. P. Garrahan, Buenos Aires, Argentina. Approval for the study was obtained from the University of California, San Francisco, committee on human research and the equivalent review boards at participating institutions as required. Using medical records, including photographs of all patients, a retrospective medical chart review was performed to collect data on the clinical characteristics, treatment, and outcome of patients with infantile hemangiomas identified as having prolonged growth. Hemangiomas were diagnosed based on medical history and clinical appearance, aided by imaging only when clinically indicated. Size was reported as the surface area of involvement in centimeters squared using the longest diameter and the measurement perpendicular to it. Lesions were classified as superficial, deep, or combined and as segmental, localized, or indeterminate by unblinded author agreement using previously defined criteria. Segment numbers for facial lesions were assigned according to the patterns identified by Haggstrom et al with segment 1 (S1) corresponding to the frontonasal region; segment 2 (S2), the maxillary region; segment 3 (S3), the mandibular region; and segment 4 (S4), the frontonasal region. Response to treatment was based on the clinical assessment of the physician(s) caring for these infants.

RESULTS

We identified 23 patients with infantile hemangiomas meeting our criteria for prolonged growth. The characteristics of these patients and their hemangiomas are summarized in the Table. Eighteen (78%) of the patients were female. The hemangiomas were all located on the head and neck region, although 3 (cases 3, 19, and 23) had lesions extending onto the trunk. Absolute size measurements were not available for all lesions because 6 were noted as being too large to accurately measure. Of the 17 cases with measurements available, the mean (SD) size was 126 (103) cm² (range, 5-315 cm²). Eighteen (78%) were segmental lesions, and the other 5 (22%) were indeterminate. Segment 3 was the most commonly represented, involved in 11 cases (48%). Six (26%) were defined as deep lesions and 17 (74%) as combined lesions. The parotid gland was involved in 9 patients (39%). Three (13%) had clinically significant airway involvement, but only 1 (4%) (case 23) required a tracheostomy. Other complications included ulceration in 12 cases (52%) and growth failure in 5 cases (22%). Three patients (13%) (cases 15, 21, and 23) required gastrostomy tube placement. One patient (4%) (case 3) had congestive heart failure, and 1 patient (4%) (case 21) was found to have a cardiomyopathy thought to be related to high cardiac output demand of the hemangioma or possibly secondary to treatment. None of the patients had hypothyroidism.

The age at last documented growth ranged from 10 to 44 months, with a mean (SD) age of 17.3 (8.0) months. Figure 1 demonstrates growth in case 4 at 6, 12, and 16 months of age; Figure 2, growth in case 14 at 9 and 15 months of age; and Figure 3, growth in case 18 at 4, 16, and 24 months of age.

Twenty-one patients (87%) received systemic corticosteroids (CS), and 12 (52%) had additional therapies, including vincristine sulfate, interferon alfa-2a or alfa-2b, pulsed-dye laser, embolization, and debulking surgery. Two patients (9%) (cases 10 and 11) did not receive any treatments, and 1 patient (4%) received only a very brief course of treatment with discontinuation after 1 month because of problems with health insurance. The mean (SD) age at initiation of CS treatment was 3.2 (2.6) months (range, 3 weeks to 1 year). Starting dosages of CS ranged from 2.5 to 3.1 mg/kg/d, and 1 patient’s dosage (case 17) was increased to 4 mg/kg/d shortly after initiation of treatment owing to poor response. The mean total duration of CS treatment was 11.2 (2.9) months, but CS treatment was intermittent rather than continuous in 10 patients. Thirteen of 19 patients (68%) had an initial decrease in size or growth cessation of their lesion, but the others had slowed or continued growth. (Data documenting initial response was lacking in 2 patients.) All patients had rebound growth during or after the CS taper, except 1 patient (case 3) who was given vincristine during the CS taper after no initial response. In several cases in which alternate-day steroids were used as part of a CS taper, parents reported growth on the “off” days when steroids were not administered. Common complications of CS treatment included Cushingoid features, irritability, and difficulty sleeping. Two patients (cases 17 and 23) had elevated blood pressure. Five patients had somatic growth delay that could have been the result of CS therapy, but conceivably may have been the result of the increased metabolic demands of a very large vascular tumor or difficulties in feeding because of a mass effect.

Vincristine was the most common second-line treatment, used in 6 patients. Two patients had central catheter infections, 1 caused by Candida, and 1 resulting in bacterial sepsis. Two patients received interferon therapy, both initiated after 18 months of age, without neurologic sequelae. The mean (SD) age at which all systemic therapy was complete was 19.9 (8.1) months.

COMMENT

This case series highlights the clinical characteristics and treatments of 23 infants with infantile hemangiomas with unusually prolonged growth. To our knowledge, there have been no previous case series focusing on the “outliers” with late, ongoing growth. A recent prospective study of the growth characteristics of 526 hemangiomas found that patients reached the late proliferative stage at a mean (SD) age of 6.2 (2.5) months, whereas the lesions reported herein grew until a mean (SD) age of 17.3 (8.0) months (range, up to 44 months).

All of the hemangiomas in this series were classified as segmental or indeterminate, a contrast to their incidence in a large prospective study in which only 453 of 1530 (29.6%) were classified as segmental or indeterminate. Segmental hemangiomas have been found to have higher rates of complications and need for treatment, and segmental morphologic characteristic is the single greatest predictor of risk of complications and need for treatment. Segmental hemangiomas are on average 10 times larger than lo-
Table. Characteristics of Infantile Hemangiomas With Prolonged Growth (PG)

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Location&amp;</th>
<th>Size, cm²b</th>
<th>Seg or Ind</th>
<th>S, D, or C</th>
<th>ASIc</th>
<th>Ulc</th>
<th>GF</th>
<th>AcS or EAc</th>
<th>Age at LDG, mo</th>
<th>Part of Lesion With PG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>L S1, B S3</td>
<td>NA</td>
<td>Seg C</td>
<td>Parotid</td>
<td>Y</td>
<td>Y</td>
<td>None</td>
<td></td>
<td>11</td>
<td>Parotid (D)</td>
</tr>
<tr>
<td>2/F</td>
<td>Partial L S2</td>
<td>6</td>
<td>Ind C</td>
<td>None</td>
<td>Y</td>
<td>Y</td>
<td>None</td>
<td></td>
<td>12</td>
<td>Lip (D)</td>
</tr>
<tr>
<td>3/F</td>
<td>B S3, upper back</td>
<td>NA</td>
<td>Seg C</td>
<td>Parotid, airway</td>
<td>N</td>
<td>Y</td>
<td>Heart failure, pulmonary hypertension, L eye blindness</td>
<td>14</td>
<td>Back and diffuse beard area (D)</td>
<td></td>
</tr>
<tr>
<td>4/F</td>
<td>L S2</td>
<td>22.5</td>
<td>Seg C</td>
<td>None</td>
<td>N</td>
<td>N</td>
<td>None</td>
<td></td>
<td>10</td>
<td>D malar</td>
</tr>
<tr>
<td>5/F</td>
<td>R S3</td>
<td>72</td>
<td>Seg C</td>
<td>Parotid</td>
<td>N</td>
<td>N</td>
<td>None</td>
<td></td>
<td>19</td>
<td>Parotid (D)</td>
</tr>
<tr>
<td>6/F</td>
<td>S4</td>
<td>10</td>
<td>Seg C</td>
<td>None</td>
<td>Y</td>
<td>N</td>
<td>None</td>
<td></td>
<td>13</td>
<td>Nose (D) and upper lip (C)</td>
</tr>
<tr>
<td>7/F</td>
<td>B S1/S2</td>
<td>315</td>
<td>Seg C</td>
<td>None</td>
<td>Y</td>
<td>N</td>
<td>PHACES (cerebellar hypoplasia, large cisterna magna, arterial anomalies)</td>
<td>14</td>
<td>R occipital scalp (D)</td>
<td></td>
</tr>
<tr>
<td>8/F</td>
<td>R S3/S4</td>
<td>300</td>
<td>Seg C</td>
<td>Parotid</td>
<td>Y</td>
<td>N</td>
<td>None</td>
<td></td>
<td>11</td>
<td>Overall enlargement (D)</td>
</tr>
<tr>
<td>9/F</td>
<td>L medial upper eyelid</td>
<td>8.75</td>
<td>Ind D</td>
<td>None</td>
<td>N</td>
<td>N</td>
<td>Anisometropia</td>
<td>18</td>
<td>Medial upper eyelid (D)</td>
<td></td>
</tr>
<tr>
<td>10/F</td>
<td>R anterior neck</td>
<td>144</td>
<td>Ind C</td>
<td>None</td>
<td>Y</td>
<td>N</td>
<td>None</td>
<td></td>
<td>12</td>
<td>Neck (D)</td>
</tr>
<tr>
<td>11/F</td>
<td>Partial R S2</td>
<td>5</td>
<td>Ind D</td>
<td>None</td>
<td>N</td>
<td>N</td>
<td>None</td>
<td></td>
<td>14</td>
<td>Cheek (D)</td>
</tr>
<tr>
<td>12/F</td>
<td>R medial upper eyelid</td>
<td>NA</td>
<td>Ind D</td>
<td>None</td>
<td>N</td>
<td>N</td>
<td>None</td>
<td></td>
<td>13</td>
<td>Medial upper eyelid (D)</td>
</tr>
<tr>
<td>13/M</td>
<td>R S3</td>
<td>181</td>
<td>Seg D</td>
<td>Parotid</td>
<td>N</td>
<td>N</td>
<td>None</td>
<td></td>
<td>14</td>
<td>Parotid (D)</td>
</tr>
<tr>
<td>14/M</td>
<td>L S3</td>
<td>121</td>
<td>Seg D</td>
<td>Parotid</td>
<td>N</td>
<td>Y</td>
<td>None</td>
<td></td>
<td>15</td>
<td>Parotid (D)</td>
</tr>
<tr>
<td>15/M</td>
<td>R S3</td>
<td>247</td>
<td>Seg C</td>
<td>Parotid NA</td>
<td>Y</td>
<td>None</td>
<td></td>
<td>25</td>
<td>Parotid (D)</td>
<td></td>
</tr>
<tr>
<td>16/F</td>
<td>R S1</td>
<td>214</td>
<td>Seg C</td>
<td>Orbit</td>
<td>N</td>
<td>N</td>
<td>None</td>
<td></td>
<td>16</td>
<td>Medial upper eyelid (D)</td>
</tr>
<tr>
<td>17/M</td>
<td>R S2</td>
<td>60</td>
<td>Seg C</td>
<td>Orbit, soft palate</td>
<td>Y</td>
<td>N</td>
<td>Slight astigmatism</td>
<td>13</td>
<td>Intra-orbital (D)</td>
<td></td>
</tr>
<tr>
<td>18/F</td>
<td>B S3</td>
<td>176</td>
<td>Seg D</td>
<td>Parotid</td>
<td>Y</td>
<td>N</td>
<td>None</td>
<td></td>
<td>24</td>
<td>Lip (C) and parotid (D)</td>
</tr>
<tr>
<td>19/F</td>
<td>Occipital/posterior neck</td>
<td>165</td>
<td>Seg D</td>
<td>None</td>
<td>N</td>
<td>N</td>
<td>Asymptomatic spinal cord compression</td>
<td>14</td>
<td>Neck (D)</td>
<td></td>
</tr>
<tr>
<td>20/F</td>
<td>L S2</td>
<td>90</td>
<td>Seg C</td>
<td>None</td>
<td>Y</td>
<td>N</td>
<td>PHACES (ventriculomegaly, mild bony overgrowth of face PHACES (bilateral eyelid ptosis, exophthalmos, airway involvement, cardiomyopathy)</td>
<td>14</td>
<td>Cheek (D)</td>
<td></td>
</tr>
<tr>
<td>21/F</td>
<td>B S3</td>
<td>NA</td>
<td>Seg C</td>
<td>Parotid, oral mucosa, airway</td>
<td>Y</td>
<td>Y</td>
<td>None</td>
<td></td>
<td>30</td>
<td>Cheeks (C)</td>
</tr>
<tr>
<td>22/F</td>
<td>B S3</td>
<td>NA</td>
<td>Seg C</td>
<td>None</td>
<td>Y</td>
<td>N</td>
<td>None</td>
<td></td>
<td>28</td>
<td>Lips and right preauricular (C)</td>
</tr>
<tr>
<td>23/F</td>
<td>B S1/S2/S3</td>
<td>NA</td>
<td>Seg C</td>
<td>Airway</td>
<td>Y</td>
<td>N</td>
<td>PHACES (medial raphe, sternal aplasia, arterial anomalies, and cardiac defects)</td>
<td>44</td>
<td>Chin, lips, gums (1° superficial)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AcS, additional complications; ASI, adjacent structures involved; B, bilateral; C, combined; D, deep; EAs, extracutaneous abnormalities; GF, growth failure; Ind, indeterminate; L, left; LDG, last documented growth; NA, not available; PHACES, syndrome of posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities, sternal defects and/or supraumbilical raphe; R, right; S, superficial; Seg, segmental; Ulc, ulceration.

* S1 through S4 refer to facial segmental patterns of infantile hemangiomas as described by Haggstrom et al.4

* Size reported was maximal area of cutaneous involvement measured by a physician.

* Adjacent structures based on clinical examination and/or imaging studies.

* Multiple lesions on magnetic resonance imagining, including 1 extending into the mediastinum and 1 surrounding the thoracic spinal cord.

* The patient subsequently developed 3 new hemangiomas on the back.

Calized hemangiomas,4 and our cases were no exception, with a mean (SD) area of involvement of 125 (103) cm². The size and patterns of segmental hemangiomas on the face respect anatomic boundaries corresponding to embryologic neuroectodermal derivatives, suggesting an error in development as early as 6 to 8 weeks of gestation.4 Their more aggressive clinical behavior may hypothetically be attributed to a more pervasive developmental defect not present in localized hemangiomas.

In a recent prospective study,5 53% of hemangiomas had only a superficial component (Anita N. Haggstrom, MD, e-mail communication, November 2007), yet in our study all were either deep or both superficial and deep. Previous studies2,4,5 have suggested that deep hemangiomas may have a longer proliferative phase. In our cases, the component subjectively assessed to have prolonged growth was typically the deep component (Table and Figures 1-3). Our series also had an overrepresentation of hemangiomas involving the parotid gland (39%). Some authors10-12 have asserted that parotid hemangiomas involute more slowly and are more resistant to systemic therapy than other hemangiomas. The findings in our
cases support the concept of true differences in behavior in deep hemangiomas, including those with parotid involvement, rather than simply being an observational bias, and raise the question of whether the milieu in deeper sites is more permissive for growth than in more superficial sites. Parotid glands may have a higher-than-normal rate of blood flow, and Blei and Rutkowski noted high blood flow in hemangiomas at certain sites, particularly the parotid gland, but also the upper extremity, upper lip, and scalp, and suggested that they are “transiently arterialized,” causing slower involution than at other anatomic sites.

Nearly all patients were treated with systemic CS, and a substantial minority received other systemic treatments. Most responded initially to CS but had rebound growth during or after steroid taper. This occurred despite treatment with CS for prolonged periods of time; the mean duration of treatment was 11 months—substantially longer than in other reported case series in which the mean duration of treatment was 6 to 8 months. Although the mechanisms of action of CS are only partially understood, Ritter et al proposed that infantile hemangioma involution stems from immune recognition of the aberrant hemangioma vascular phenotype, inciting an immune response targeted at hemangioma endothelial cells. Based on this model and our findings, we hypothesize that segmental hemangiomas represent a more fundamental developmental defect than localized hemangiomas and that those involving deeper tissues, particularly the parotid gland, are more impervious to immune recognition and sustained involution.

Identifying a therapy that would function by triggering immune recognition of hemangioma endothelial cells may be a possible therapeutic strategy.
Most infantile hemangiomas follow a well-described natural history of proliferation within the first 5 to 6 months of life, followed by slow, gradual involution. Some hemangiomas, however, demonstrate a more prolonged growth pattern and pose distinct clinical challenges. In this study, prolonged growth was observed primarily in hemangiomas with a deep component and segmental morphologic characteristics, types of hemangiomas that, although not rare, are present in a minority of cases. Although most infantile hemangiomas with these characteristics have typical growth patterns, this case series emphasizes that a small but clinically important subset will continue to grow. Recognition of this subset can alert parents and health care providers to consider more aggressive treatment for these hemangiomas. In addition, infantile hemangiomas with prolonged growth may provide clues to the pathogenesis of hemangiomas and the mechanisms of their involution, and therefore warrant further investigation.

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Author Contributions: Drs Brandling-Bennett and Frieden had full access to all 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: Brandling-Bennett and Frieden. Acquisition of data: Brandling-Bennett, Metry, Baselga, Lucky, Adams, Cordisco, and Frieden. Analysis and interpretation of data: Brandling-Bennett, Metry, Lucky, and Frieden. Drafting of the manuscript: Brandling-Bennett and Frieden. Critical revision of the manuscript for important intellectual content: Brandling-Bennett, Metry, Baselga, Lucky, Adams, and Cordisco. Statistical analysis: Cordisco. Study supervision: Adams, Cordisco, and Frieden.

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REFERENCES

Type 2 Segmental Acanthosis Nigricans: A Historical Case Explained by a New Concept

In 1936, Curth\(^1\) reported a remarkable case of acanthosis nigricans (AN) with both unilateral linear and symmetrical nonlinear changes. Herein, arguments are presented for the concept that early loss of heterozygosity (LOH) caused the segmental skin lesions in this case, which were superimposed on less pronounced nonsegmental AN.

A 15-year-old boy presented with symmetrical lesions of AN “with exception of the strictly unilateral manifestation on the right side of the abdomen and the right groin”\(^1\) that had been present since birth (Figure 1). None of his family members was affected with AN. Bilateral, nonsegmental AN involving wide areas of the patient’s body appeared when he was 10 years old (Figure 2). In 1939, Curth\(^2\) stated that “these symmetric changes completely subsided after puberty,” whereas “a large acanthotiform nevus, strictly confined to the right side of the abdomen, has been present since birth and has not undergone any changes at any period of his life.”

Biopsy specimens demonstrated “histological identity of a unilateral epidermal naevus with symmetrical benign acanthosis nigricans although, clinically, the two eruptions showed differences.”\(^3\) In a specimen of segmental AN, the epidermal proliferation was “more marked” than that noted in a nonsegmental lesion “but was much of the same character.”\(^4\) Helen Olendorff Curth, who joined the faculty at Columbia University in New York, New York, in 1931, was fascinated by this unusual observation. During a 40-year period, she revisited the case in several publications.\(^2,3\) Apparently, she felt that this case was an insoluble riddle: “This interesting association invites some speculation as to the relationship of the two conditions to each other. The possibility of the association being fortuitous is remote since it seems improbable that the unilateral naevus, histologically identical with a subsequent symmetrical eruption of a rare dermatosis, occurred by chance.”\(^3\) In 1939, she came close to the presently proposed explanation by expressing the following thought: “As the symmetric variety has been recognized as a genodermatosis, it seems justified to conclude that both the unilateral and the symmetric eruptions were caused by the same abnormal gene.” But being uncertain, she continued, “It must be kept in mind, however, that certain nongenetic factors may have played a role in the determination of the unilateral distribution.”\(^2\)

This unusual case can be explained as a type 2 segmental manifestation as previously proposed for autosomal dominant skin disorders such as neurofibromatosis 1, epidermolytic hyperkeratosis of Brocq, Darier disease, or Hailey-Hailey disease.\(^4\) In an embryo heterozygous for a given trait, postzygotic LOH occurring at an early developmental stage would give rise to a cell clone being either homozygous or hemizygous for the mutation. Dorsoventral outgrowth of this clone would result in pronounced segmental involvement superimposed on less marked nonsegmental lesions of the same phenotype.

Acanthosis nigricans is an autosomal dominant trait that is caused by an\(^5\) mutation.\(^5\) The patient would have been heterozygous for the mutation, and an early event of LOH would have given rise to rather pronounced congenital segmental lesions superimposed on the symmetrical lesions of AN that appeared later. Molecular studies may support this explanation. For example, a 16-year-old girl who had a linear AN form of epidermal nevus involving a thigh at birth and who later developed typical bilateral AN\(^6\) could have DNA analysis results that might corroborate the theory of type 2 segmental AN reflecting LOH at the\(^5\) locus.

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Figure 1. A “14-year-old patient with unilateral epidermal nevus present since birth and symmetric benign acanthosis nigricans present since puberty.”\(^2\)

Figure 2. “Acanthosis nigricans in the right axilla.”

\(^1\) Curth HO. Benign type of acanthosis nigricans: etiology. Arch Dermatol. 1936;34:353-368.


