Association of Solitary, Segmental Hemangiomas of the Skin With Visceral Hemangiomatosis

Denise W. Metry, MD; Aimee Hawrot, MD; Carolyn Altman, MD; Ilona J. Frieden, MD

Background: Multiple hemangiomas of the skin have traditionally been recognized as a clue to potential visceral hemangiomas. Recently, hemangiomas have been recognized to have subcategories, localized and segmental, which correlate with risk of complications. While less common, segmental hemangiomas of the skin have a higher risk of being life- or function-threatening and/or having associated structural anomalies such as those that occur in PHACE (posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities) syndrome (PHACES, if sternal clefting/supraumbilical raphe is included). However, the potential association of solitary, segmental hemangiomas of the skin with visceral hemangiomatosis has not been previously emphasized.

Observations: A total of 47 cases of segmental hemangiomas of the skin in association with visceral hemangiomatosis were found. The location of the cutaneous hemangiomas most commonly, but not exclusively, involved the face (37 cases [79%]). The most common site of internal organ involvement was the liver (20 cases [43%]), followed by the gastrointestinal tract (16 [34%]), brain (16 [34%]), mediastinum (9 [19%]), and lung (7 [15%]). The percentages of reported cases of hemangiomas of the pancreas, spleen, bones, or kidneys were 6% or less. Forty percent of patients met criteria for the diagnosis of PHACE(S) syndrome. In this subgroup, internal organ hemangiomas were most commonly found in the brain or mediastinum (18 cases [53%]). Overall, 12 patients (25%) died during infancy, most commonly because of gastrointestinal involvement or congestive heart failure secondary to liver involvement.

Conclusion: Segmental hemangiomas of the skin have an associated risk of visceral hemangiomatosis, with the potential of causing vital organ compromise.

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HEMANGIOMAS OF INFANCY (HOI) are the most common benign tumors of childhood. Unique in their behavior, HOI classically undergo an initial phase of proliferation, followed by slow involution and often complete regression. Demonstrating a striking predilection for the head and neck region, HOI occur in 2 morphologic forms. Most are localized, tumor-like lesions, with a relatively low risk of associated complications. Less common, HOI are of “segmental” morphology, which are generally larger, involving a region or territory of skin. Many, but not all, segmental hemangiomas have a more plaquelike morphology. It is now recognized that segmental HOI have a higher risk of causing life- or function-threatening complications and of having associated structural anomalies. For example, PHACE (Online Mendelian Inheritance in Man [OMIM] 606519) is a neurocutaneous syndrome in which segmental hemangiomas, most commonly of the face, are associated with 1 or more of the following anomalies: posterior fossa brain malformations, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities (called PHACES if ventral developmental defects such as sternal clefting and/or supraumbilical raphe are included). In contrast, multifocal cutaneous hemangiomas (generally defined as 5 or more) have a “localized” type of morphology and a well-recognized potential for concomitant visceral hemangiomas. The term “disseminated neonatal hemangiomatosis” has been used to describe the uncommon presentation of several to hundreds of small, multifocal hemangiomas of the skin in association with extracutaneous hemangiomas, most commonly hepatic. In this article, we report 4 cases and present data from 43 additional reports of segmental hemangiomas of the skin asso-
associated with visceral hemangiomas, emphasizing the potential of extracutaneous hemangiomas in this setting.

METHODS

We retrospectively reviewed the records of 4 patients with both segmental cutaneous and visceral hemangiomas. In addition, a PubMed search using the key words hemangiomatosis, large hemangioma, and hemangioma AND liver, hepatic, gastrointestinal, brain, cardiac, pancreas, spleen, thyroid, mediastinum, bone, and trachea was performed, and each discovered case was then cross-referenced. Reports of ocular and/or airway hemangiomas, as well as cases of visceral involvement due to contiguous extension from the skin, were excluded. The 130 cases of PHACE(S) syndrome detailed by us in 2001, as well as 31 additional cases since reported, were also reviewed for the presence of internal organ involvement.

REPORT OF CASES

CASE 1

A 2-month-old white female infant presented to the pediatric dermatology service for multiple facial hemangiomas that had progressively developed over her first month of life. She was also known to have a large perimembranous ventricular septal defect, a small secundum atrial septal defect, and pulmonary stenosis, and thus met criteria for PHACE(S) syndrome. On examination, she had multiple erythematous papules in a bilateral, segmental distribution involving her temples, eyelids, and lower lip (Figure 1). No extrafacial cutaneous hemangiomas were present. Prednisolone treatment (2 mg/kg per day) was initiated because of right visual obstruction and she was immediately evaluated by an ophthalmologist. However, after 6 weeks, the treatment was rapidly tapered owing to poor weight gain and progressive cardiac compromise.

Brain magnetic resonance imaging (MRI) performed when she was 4 months old showed a large right orbital hemangioma, a hemangioma in the deep parotid space, and angiomatous thickening along the seventh and eighth cranial nerves and internal auditory canal. No structural malformations of the brain were present. Brain magnetic resonance angiography demonstrated anomalous cerebral vasculature with persistent fetal circulation and an essentially absent internal carotid artery on the right side; anomalous fenestration and duplication of the cavernous internal carotid artery on the left side; enlarged external carotid branches on the right side; and an enlarged right ophthalmic artery. Although many of her small cutaneous facial hemangiomas had resolved, the right periorbital lesion was continuing to enlarge. An intrallesional steroid injection was performed and patching of the left eye was recommended.

At 5 months of age she was admitted to Texas Children’s Hospital in Houston for progressive failure to thrive. Chest radiographs demonstrated cardiomegaly and increased pulmonary vascularity. Limited MRI of the chest and abdomen was performed to determine whether hemangiomas were present, which could have complicated an anticipated cardiovascular surgery. The image revealed multiple hepatic hemangiomas mainly involving the right lobe of the liver, with a small focus in the medial segment of the left lobe (Figure 2). There was arteriovenous shunting from the hepatic arterial to the portal venous systems. Abnormal soft tissue was also visualized from the superior mediastinum and lower neck to the thoracic inlet, which corresponded to paratracheal hemangioma although no airway compromise was evident.

Cardiac catheterization indicated that the intracardiac shunt was the most significant. Preoperative laboratory data, which included thyroid function tests, were...
within normal limits except for a slightly elevated serum aspartate aminotransferase level. Cardiac repair included closure of the atrial and ventricular septal defects, right ventricular outflow tract resection, and patch augmentation of the main pulmonary artery. Five weeks postoperatively she had gained weight, and although persistent hepatomegaly and a diastolic inflow rumble were found on examination, furosemide could be discontinued. She has since undergone continuous monitoring by the cardiology, dermatology, hepatology, and neurology services. She has remained stable except for mild bilateral conductive hearing loss, for which she has been fitted with hearing aids. Both her cutaneous and visceral hemangiomas have undergone slow but steady involution.

CASE 2

A 2-month-old African American male infant born 13 weeks prematurely was transferred to Texas Children’s Hospital for the evaluation of multiple medical problems. He was noted to have a right-sided segmental hemangioma of the face and scalp (Figure 3), ventricular septal defect, patent foramen ovale, right-sided aortic arch, and severe pulmonary stenosis, and thus met criteria for PHACE(S) syndrome. Further workup on admission included MRI of the chest and abdomen, which confirmed the known cardiac defects but revealed no visceral hemangiomas. Magnetic resonance angiography of the brain showed an aberrant course of the right internal carotid artery with persistent basilar anastomosis with the fetal carotid. An MRI of the brain did not reveal any structural abnormalities but showed a right cerebellopontine angle mass consistent with an intracranial hemangioma, which extended into the internal auditory canal (Figure 4).

A daily dose of 3 mg/kg of prednisolone was initiated because of right visual axis obstruction and the intracranial hemangioma. However, the patient’s course was further complicated 2 weeks after admission by the development of a methicillin-resistant Staphylococcus aureus sepsis that required rapid tapering of the steroid treatment. His cutaneous hemangiomas are being monitored clinically and his intracranial hemangioma with serial imaging studies.

CASE 3

A white infant girl presented at 7 months of age with a segmental, right-sided hemangioma of the face, scalp, and neck. Mild gastrointestinal bleeding had occurred earlier in infancy, and MRI and endoscopy confirmed the presence of hemangiomas in the gastrointestinal tract. No intervention was required. A complete workup for PHACE(S) syndrome was negative.

CASE 4

A female infant presented at 4 months of age with a segmental hemangioma of the lumbosacral spine and gluteal cleft. During MRI studies evaluating for possible tethered spinal cord (which was not present), an asymptomatic hemangioma of the right lobe of the liver measuring 1.2 cm in diameter was noted.

ADDITIONAL REPORTS

Besides our 4 cases, we discovered 43 additional reports of segmental, cutaneous hemangiomas associated with internal organ involvement15-24 (Table 1). Hemangiomas of the airway and eye were excluded. Most patients were female, and the segmental hemangioma was located on the face in most, and most commonly unilaterally. We found only 1 case with a hemangioma morphology similar to that described in case 1—specifically, with multiple small facial hemangiomas in a segmental distribution.13

Thirty (64%) of the total of 47 cases described only 1 extracutaneous site of visceral hemangioma; 11 patients (23%) had 2 and 6 patients (13%) had 3 or more sites involved. The liver was the most common extracu-
Hemangioma involvement of the internal organs, generally associated with multiple cutaneous hemangiomas, is a known entity distinct from PHACE(S) syndrome. Some authors have used the term “hemangiomatosis” to describe the presence of multiple (>5)
small, generalized hemangiomas, and draw a distinction between “benign” and “disseminated” or “diffuse” hemangiomatosis on the basis of the extent of internal organ involvement and associated morbidity risk.3,25–27 Others have proposed the designation “multiple hemangiomas with or without extracutaneous involvement” as a more appropriate description of the spectrum of possible manifestations.28

It has recently been recognized that “segmental” HOI have a markedly higher risk of being life- or function-threatening and/or having associated structural anomalies, that they generally require more intensive and prolonged therapy, and that they are associated with a poorer outcome.1 Although segmental hemangiomas of the face overlying the mandibular skin and neck (in a so-called beard distribution) have a known risk of noncontiguous hemangiomas of the airway,29 the potential association of a segmental hemangima (in any location) with visceral hemangiomatosis has received much less attention.9 Because HOI, especially those of segmental morphology, show an increased incidence among female infants and are most commonly located in the head and neck,1,30 the female and facial predominance demonstrated in our series were expected findings. More important was the association of internal organ hemangiomas (with or without PHACE[S]) syndrome, with segmental HOI in cutaneous locations other than the face. This finding serves to further support the significance of lesion morphology as a risk factor for potential complications, even independent of hemangima location. Interestingly, the cutaneous and extracutaneous hemangiomas were found to be ipsilateral in most reports in which laterality was noted.

Most our patients were found to have only 1 extracutaneous site of visceral involvement with hemangima. However, this finding, in addition to the general association of segmental hemangiomas of the skin with internal organ hemangiomatosis, is likely underestimated since extensive imaging is not performed in otherwise asymptomatic patients. For example, in 2 of our patients, liver hemangiomas were only discovered upon routine imaging for another indication. Similarly, it is likely that cases of visceral hemangiomatosis in association with solitary cutaneous hemangiomas of localized morphology exist, although the extensive cross-referencing undertaken in our series revealed no such cases. In addition, there is always the possibility of diagnostic heterogeneity in any review of the literature, especially in relation to vascular lesions. The diagnosis of visceral hemangima in our series was often based on characteristic imaging results and/or clinical course, without accompanying histopathologic studies or confirmatory immunostaining with glucose transporter protein 1. Thus, despite the presence of a cutaneous hemangima, we cannot exclude the possibility that the visceral lesions in some of the cases included in our series represented vascular anomalies or other glucose transporter protein 1–negative vascular tumors.

The liver was the most common site of organ involvement with hemangima in our series, followed by the gastrointestinal tract and the brain. These results are similar to those found in patients described under the syndrome of “multiple hemangiomas with extracutaneous involvement.”27 However, we discovered a higher-than-expected number of cases of hemangiomas of the mediastinum and brain. In fact, these were the most common sites of extracutaneous involvement among patients with PHACE(S) syndrome, a finding not appreciated in our previous review of the syndrome but recently noted in a report by Poetke et al.23 However, patients with PHACE are more likely to undergo imaging of the head and neck to look for potential anomalies. Consistent with our previous review of PHACE(S) syndrome, most patients in the present series were noted to have only 1 extracutaneous manifestation of PHACE(S), which supports the concept of this syndrome as a spectrum of disease.29

Approximately one fourth of the patients in our series died in infancy, most commonly from complications related to gastrointestinal bleeding or hepatic involvement—known worrisome locations. Hepatic hemangiomas may manifest with coagulopathy, heart failure, and/or respiratory distress. Internal hemorrhage is also of significant concern with hemangiomas in hepatic or gastrointestinal locations. A recent review of hepatic hemangiomas reported mortality rates between 15% and 43%, depending on the mode of treatment.31 In a recent review by Iyer et al.,32 one third of hepatic hemangiomas were associated with hemangiomas in other sites, and most patients became symptomatic shortly after birth. Therapeutic options for hepatic and gastrointestinal hemangiomas may include surgical resection, embolization, corticosteroids, and interferon alfa.

The small number of deaths noted in our series did not allow for an analysis of mode of treatment. However, it should be noted that 3 of the 12 deaths occurred prior to 1990, a time when systemic therapies with agents such as interferon were not routinely used for life-threatening hemangiomas. However, even with the pres-

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. (%) of Cases</th>
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<tbody>
<tr>
<td>Cutaneous segmental hemangima</td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Chest</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Structural brain malformation</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Cardiac anomalies/coarctation of the aorta</td>
<td>10 (53)</td>
</tr>
<tr>
<td>Arterial anomalies</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Eye anomalies</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Ventral developmental defects</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Visceral hemangima</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>10 (53)</td>
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<tr>
<td>Mediastinum</td>
<td>9 (47)</td>
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<tr>
<td>Gastrointestinal tract</td>
<td>6 (32)</td>
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<tr>
<td>Liver</td>
<td>5 (26)</td>
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<tr>
<td>Lung</td>
<td>3 (16)</td>
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<tr>
<td>Pancreas</td>
<td>1 (5)</td>
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<tr>
<td>Bone</td>
<td>1 (5)</td>
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Abbreviations: PHACE, posterior fossa brain malformations; hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities; PHACE(S), if sternal clefting/supraumbilical raphe is included with PHACE.*

*There were 19 cases of segmental facial hemangima and visceral hemangiomatosis in patients without PHACE(S).
ent availability of such agents, alternatives are sometimes needed for life-threatening hepatic hemangiomas.

The potential presence of extracutaneous hepatic hemangiomas should be considered in patients with segmental hemangiomas, including those with PHACE(S) syndrome. Comprehensive full-body imaging of all patients with segmental hemangiomas is not recommended because of the expense involved and the need for general anesthesia when obtaining magnetic resonance studies in young infants. In addition, it should be noted that many extracutaneous hemangiomas will remain completely asymptomatic. Instead, evaluation should be tailored to other risk factors (depending on the anatomic location of the hemangioma) and other signs and symptoms that may be present.

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Corresponding author: Denise W. Metry, MD, Department of Dermatology and Pediatrics, Texas Children’s Hospital, Houston, 6621 Fannin, CC 620.16, Houston, TX 77030 (e-mail: dmetry@bcm.tmc.edu).

REFERENCES