STUDY

Infantile Hemangiomas With Minimal or Arrested Growth

A Retrospective Case Series

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Objective: To describe clinical characteristics of infantile hemangiomas with minimal or arrested growth (IH-MAGs).

Design: Retrospective case series.

Setting: Ambulatory referral center at the University of California, San Francisco.

Patients: Infantile hemangiomas with minimal or arrested growth were defined as infantile hemangiomas with a proliferative component equaling less than 25% of their total surface area. The patients must have been at least age 2 months at the initial visit or on follow-up. Forty-two eligible patients with 47 IH-MAGs were included in the study.

Main Outcome Measures: Medical record review was performed for demographic and gestational information, lesion size, and clinical appearance, presence of proliferation, complications, coexisting classic infantile hemangiomas, and morphologic subtype classified as localized, segmental, or indeterminate.

Results: Infantile hemangiomas with minimal or arrested growth manifested most commonly as fine or coarse telangiectatic patches. Proliferation was present in 30% (14 of 47 IH-MAGs), usually as small papules at the periphery of these hemangiomas. Sixty-eight percent (32 of 47 IH-MAGs) of them were present on the lower body. Seventeen patients had classic infantile hemangiomas at another body site. Comparison of distribution of sites of IH-MAGs showed a 26-fold (95% confidence interval, 1.9-351.5; $P = .01$) likelihood of having IH-MAGs on the lower body compared with classic infantile hemangiomas.

Conclusions: Infantile hemangiomas with minimal or arrested growth have a distinct clinical appearance and a unique predilection for the lower body. Recognition of IH-MAGs will help in more accurate diagnosis of vascular birthmarks of infancy, and the presence of IH-MAGs in an individual patient does not exclude the proliferative potential of other infantile hemangiomas that may be present.

Arch Dermatol. 2010;146(9):971-976

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GROWTH IS ONE OF THE most characteristic features of infantile hemangiomas (IHs) and so distinctive a clinical feature that it is often helpful in diagnosis. Most IHs arise on normal skin or grow from a premonitory mark, with a growth phase characterized by rapid proliferation from a few days or weeks until several months of age.[1] Premonitory marks are evident in up to half of the cases[2] and are often recognizable as a well-demarcated patch of pallor on which IH growth occurs or alternatively as a telangiectatic or bruiselike patch.[3-5]

However, a minority of IHs have minimal or arrested growth beyond the stage resembling premonitory marks. These IHs have been variously described in the literature as "abortive," "precursor," or "minimal growth" hemangiomas; "macular hemangioma with port-wine stain–like appearance"[6]; "reticular infantile hemangioma"[7]; or "plaque-telangiectatic hemangiomas."[8] A 2008 case series confirmed that these vascular lesions are IHs rather than other vascular anomalies, as their blood vessels stain positively for glucose transporter protein 1 expression.[9] How these hemangiomas differ from those with more typical growth characteristics has not been well studied. Moreover, because of their flat telangiectatic appearance, they are sometimes mistaken for vascular malformations such as port-wine stains. To better understand their clinical characteristics, we retrospectively reviewed the medical records and photographs of patients at the University of California, San Francisco, with infantile hemangiomas with minimal or arrested growth (IH-MAGs) identified over a 4-year period at the University of California, San Francisco.

METHODS

STUDY DESIGN

A search was performed of a large University of California, San Francisco, pediatric dermatology photographic archives dating from September 2005 to March 2009. The search was based on labeling of photographs as "abortive" or "premonitory."

Table 1. Clinical Characteristics of Infantile Hemangiomas With Minimal or Arrested Growth (IH-MAGs) Among 42 Infants

Characteristic	Value
Sex, No. (%)	
Female	27 (64)
Male	15 (36)
Race/ethnicity, No. (%)	(n=22)
White non-Hispanic	17 (77)
Hispanic	2 (9)
Asian	2 (9)
Middle Eastern	1 (5)
Gestational age, wk, No. (%)	(n=30)
<37	4 (13)
≥37	26 (87)
Birth weight	(n=13)
Mean, lb (kg)	6.6 (3.0)
Median (range), lb	6.9 (3.3-7.5)
Age at presentation, mo	
Mean	6
Median	6
Age when IH-MAG was first noted, No. (%)	(n=32)
At birth	25 (78)
Later [range]	7 (22) [1 wk to 3 mo]
Morphologic subtype, No. (%)	(n=47)
Localized	30 (64)
Segmental	14 (30)
Indeterminate, partial segmental	3 (6)
Presence of proliferation, No. (%)	(n=47)
Yes	14 (30)
No	33 (70)
Presence of ulceration, No. (%)	(n=47)
Yes, all on anogenital IH-MAG	4 (9)
No	43 (91)

SI conversion factor: To convert pounds to kilograms, multiply by 0.45.

An IH-MAG was defined as an IH with a proliferative component equaling less than 25% of its total surface area. Any component that appeared bright red, papular, plaquelike, or nodular was deemed proliferative. The visual inspection was corroborated by the physical examination findings documented in the patient's medical records. The IH-MAG had to be diagnosed in an infant of at least age 2 months at the initial visit or on follow-up past age 2 months. Approval for the study was obtained from the committee on human research at the University of California, San Francisco.

All available medical records were reviewed, and information was gathered regarding sex, gestational age, birth weight, race/ethnicity, age when the IH-MAG was noted, and age at presentation to the clinic. Photographs of individual lesions and written descriptions were used to determine size, location, clinical appearance, and morphologic subtype. Size dimensions were used to calculate the approximate surface area. The surface areas were then categorized as follows: less than 5 cm^2, 5 to less than 10 cm^2, 10 to less than 50 cm^2, or 50 cm^2 or more. The morphologic subtypes were noted as localized, segmental, or indeterminate using previously defined criteria.[8] The presence of proliferation or ulceration was also noted.

For those patients who had follow-up visits, the subsequent photographs of individual IH-MAGs and written descriptions were used to determine change in size and clinical appearance. Any coexisting IHs that were photographed and documented were also noted.

The clinical appearance of each IH-MAG was noted for the following features: fine telangiectasias, coarse telangiectasias, bruiselike areas, and vasoconstricted areas. The anatomical distribution was categorized as follows: upper body for hemangioma on the head, neck, upper torso or upper extremities; or lower body for hemangioma involving the lower torso (below the umbilicus), buttocks, genital area, or lower extremities.

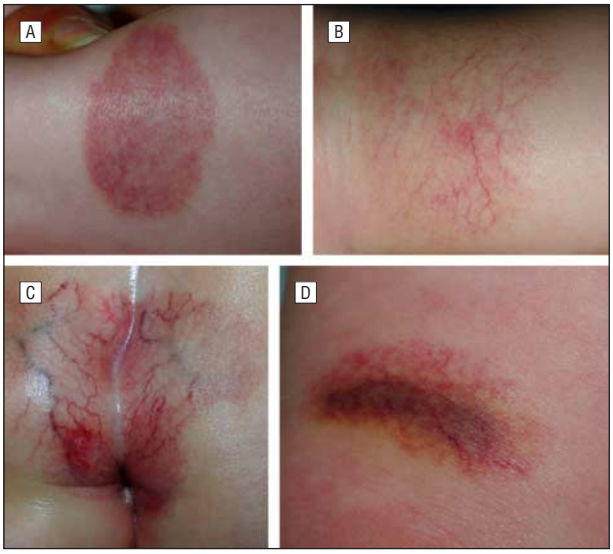

Figure 1. Infantile hemangiomas with minimal or arrested growth are commonly characterized by fine telangiectasias (A), coarse telangiectasias (B), or both (C); they may also feature a bruiselike appearance (D).

STATISTICAL ANALYSIS

Statistical analysis was conducted by an independent statistician. Generalized estimating equation methods were used.

RESULTS

Forty-four patients with 49 IH-MAGs were identified. One patient was excluded because the medical record could not be located. A second patient was excluded because on follow-up her presumed IH-MAG had a proliferative component exceeding 25% of the total surface area. Therefore, data were collected for 42 patients with 47 IH-MAGs (**Table 1**).

Twenty-seven patients (64%) were female. Seventeen patients (77%) were of white non-Hispanic race/ethnicity. Information on gestational age was available for 30 patients, of whom 4 (13%) were born at fewer than 37 weeks. Birth weight was available for 13 patients, of whom 2 (15%) had low birth weight, defined as 1500 to 2499 g. The mean and median birth weights were 3.0 and 3.1 kg, respectively. Information on when the IH-MAG was first noted was available for 32 patients, of whom 25 (78%) had their IH-MAG noted at birth, while 7 (22%) had their IH-MAG noted at an older age, ranging from 1 week to 3 months. The mean age at first visit was 6 months (median age, 6 months; age range, 5 weeks to 17 months).

The most common appearance was that of fine or coarse telangiectatic patches (**Figure 1**). Many were within a vasoconstricted patch or displayed a vasoconstricted halo (**Figure 2**). If a proliferative component was present, it most often was small bright red papules at the periphery of the IH-MAGs (**Figure 3**). A minor proliferative component was present in 14 IH-MAGs (30%), whereas proliferation was absent in 33 (70%). Thirty IH-MAGs (64%) were localized, 14 (30%) were segmental, and 3 (6%) were indeterminate (partial seg-

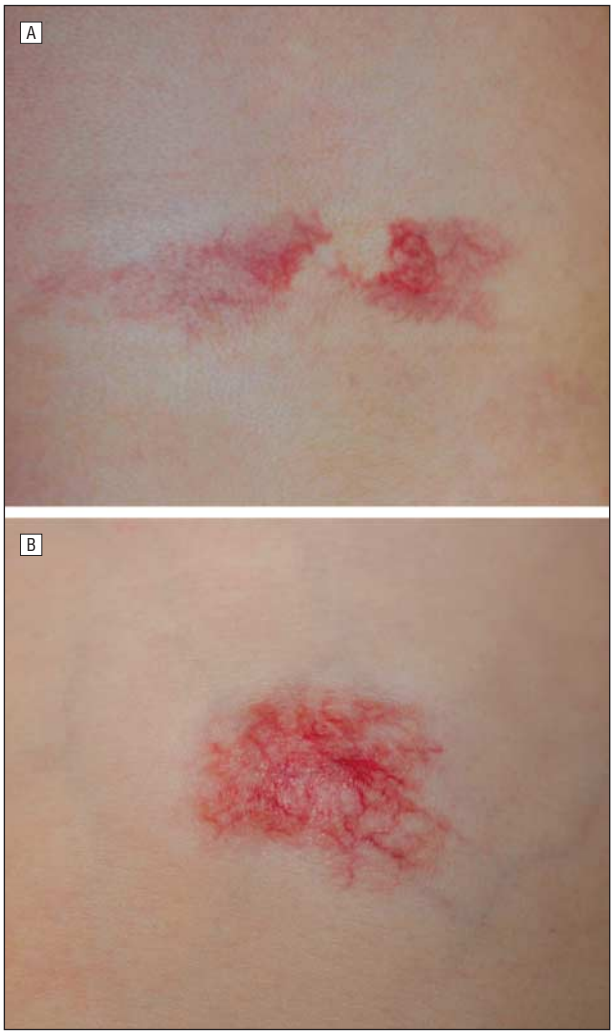

Figure 2. Infantile hemangiomas with minimal or arrested growth are commonly seen within a vasoconstricted patch (A) or with an associated vasoconstricted halo (B).

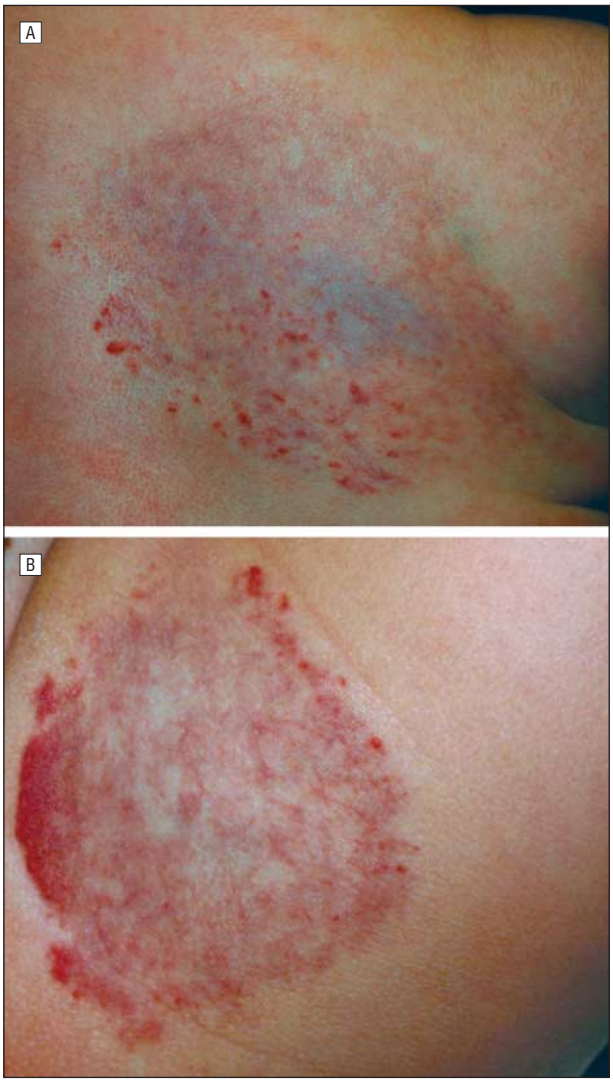

Figure 3. When a proliferative component was present, it was usually in the form of small papules in the periphery of the infantile hemangioma with minimal or arrested growth (A and B), sometimes forming a confluent rim (B).

mental) (Table 1). Twenty-one (45%) IH-MAGs were smaller than 5 cm^2, 6 (13%) were 5 to less than 10 cm^2, 13 (28%) were 10 to less than 50 cm^2, and 7 (14%) were 50 cm^2 or more. The median surface area of IH-MAGs was between 5 and 10 cm^2.

Fifteen IH-MAGs (32%) were on the upper body, while 32 (68%) involved a site below the waist (lower body). Because 17 patients had 1 or more classic IHs at another body site, we compared the sites of distribution between IH-MAGs and IHs. Twenty-six IHs (90%) involved the upper body, and 3 (10%) were located below the waist. Statistical analysis comparing sites of anatomical distribution of hemangiomas in all patients revealed a 26-fold (95% confidence interval, 1.9-351.5; $P = .01$) likelihood of having IH-MAGs on the lower body compared with classic IHs (**Figure 4**). This marked difference was also found when analyzing only patients with both IH-MAG and IH, whose sites of predilection could arguably be considered controls for IH-MAG vs IH (odds ratio, 23; 95% confidence interval, 3.3-159.3, $P = .002$). Ulceration developed in 4 IH-MAGs (**Figure 5**), all of which were in the anogenital area, with 2 being localized and 2 being segmental. Follow-up information was available in 13 patients, of whom 8 showed noticeable fading of the IH-MAG (**Figure 6**). **Table 2** summarizes the clinical and demographic features of IH-MAGs and compares them with previously published results of IHs.

COMMENT

To our knowledge, this study is the largest case series of IH-MAGs reported. In addition to the unique clinical characteristics of these hemangiomas, a striking difference between IH-MAGs and IHs was anatomical distribution: 32 of 47 IH-MAGs (68%) appeared on the lower half of the body in our case series, and this is in contrast to 62% of IHs that involved the head and neck or face in a 2006 large prospective study.[10] In our study, IH-MAGs were 26 times more likely than IHs to appear on the lower half of the body compared with the upper half of the body. Infantile hemangiomas with minimal or arrested growth also shared demographic similarities with IHs in that they tended to occur most often in infants of white non-Hispanic race/

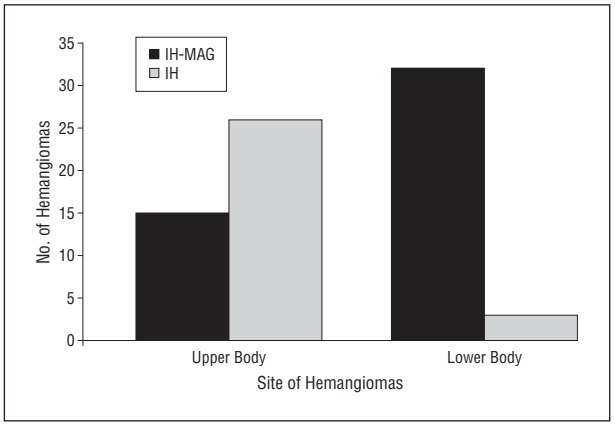

Figure 4. Numbers of infantile hemangiomas with minimal or arrested growth (IH-MAG) and classic infantile hemangiomas (IH) on the upper body and lower body. Statistical analysis revealed a 26-fold likelihood of having an IH-MAG on the lower body compared with an IH.

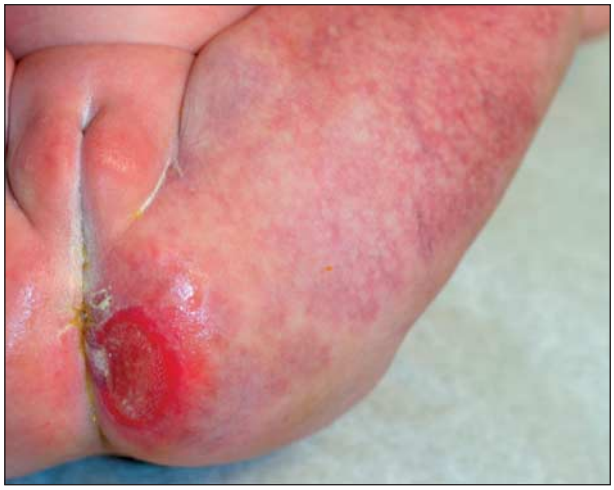

Figure 5. Segmental infantile hemangioma with minimal or arrested growth and ulceration in the perianal region. Note that the ulcer edge shows hyperemia rather than proliferation.

ethnicity. In addition, the reported ratio of girls to boys in IH-MAGs (1.8:1.0) was within the lower range compared with that of IHs in other series (range, 1.5:1.0 to 3.5:1.0).[8,11,12] The association with prematurity was somewhat less striking than with ordinary IHs: 4 of 30 patients (13%) having IH-MAGs were born at fewer than 37 weeks' gestation compared with 20% in a 2007 large prospective study[12] of IHs (Tables 1 and 2). The mean and median birth weights in our patients were comparable to those reported in patients with IHs.[12] However, the small number of patients makes it difficult to determine whether these differences are truly significant.

In IHs and IH-MAGs, localized hemangiomas predominated over segmental or indeterminate hemangiomas. Ulceration occurred as a complication in 4 of 47 IH-MAGs (9%), a slightly lower rate than that of 15% to 23% reported in several previous studies[8,10,13] of IHs. Four of 8 anogenital IH-MAGs ulcerated, comparable to the 50% rate of ulceration observed at this site in a 2007 prospective study.[13] However, the fact that ulceration occurred at all deserves comment. Ulceration has been observed to occur more commonly during the late proliferative phase of IH. Ulceration in an IH-MAG suggests that proliferation alone may not be the sole reason and that other mechanisms such as hypoxia or local environmental factors (friction or exposure to a specific microbial microenvironment) may have a role. The edges of ulcerated IH-MAGs showed some evidence of hyperemia and questionable minimal proliferation after ulceration (Figure 6) but in a pattern differing from the minimal proliferation seen in other IH-MAGs, which almost always occurred at the edge of the hemangioma.

As mentioned, some patients in our series also had typical IHs, underscoring that the presence of an IH-MAG is not predictive of the proliferative fate of other hemangiomas that may be present in the same individual. We have noted this phenomenon in other patients who were not seen during the study period who had clinically typical IH-MAGs on the face and at the same time had bulkier proliferative IHs at other sites such as in the airway or involving the orbit or parotid gland.

Not all patients had follow-up in this study because IH-MAGs are medically low risk for complications such as ulceration. The question of further proliferation in those IH-MAGs without follow-up can be raised. However, significant proliferation is unlikely in our patients for the following reasons. Recent investigations of IH growth have shown that superficial proliferation is an early event, and in fact IHs reach 80% of their final size by age 3 months.[1] Most important, superficial aspects of IHs manifest early and grow rapidly in the first few weeks of life. Therefore, our inclusion criteria for the study (the infant had to be at least age 2 months at the initial visit or had to have follow-up past age 2 months) are a reasonable way to identify IH-MAGs. Only 4 patients were seen before age 3 months (age range, 2-2½ months) without subsequent follow-up visits. The remainder were seen past age 3 months, which is well beyond the rapid proliferative stage of IHs.

The reason for the lack of a growth phase in IH-MAGs is unclear. The differences in anatomical distribution suggest that local factors such as a denser underlying vasculature (eg, as would be present in the head and neck region)[14] may have a role in hemangioma growth. Some authors have proposed that the pathogenesis of hemangiomas may be a response to a locally hypoxic environment, leading to recruitment of endothelial progenitor cells and subsequent vasculogenesis.[15-17] Speculatively, the absence of robust recruitment for such an endothelial progenitor cell may result in an IH-MAG with reduced blood flow in the lower half of the body, dampening the effects of growth factors such as hypoxia-inducible growth factor 1α, vascular endothelial growth factor, and stromal derived factor 1α, which are known to be involved in the proliferation of hemangiomas.[15-17] This hypothesis could provide the basis for future studies as the pathogenesis of IHs continues to be unraveled.

The natural history of IH-MAGs seems similar to that of IHs. Because this was a retrospective study of a subtype of hemangiomas that has a low risk for complications, not all patients had follow-up visits. Among the patients who did, approximately half had appreciable fading of their IH-MAGs. The period of follow-up varied, ranging from age 5 months to 3 years. Therefore, based on these limited data, it is likely that IH-MAGs roughly follow the time frame of involution observed in IHs, but

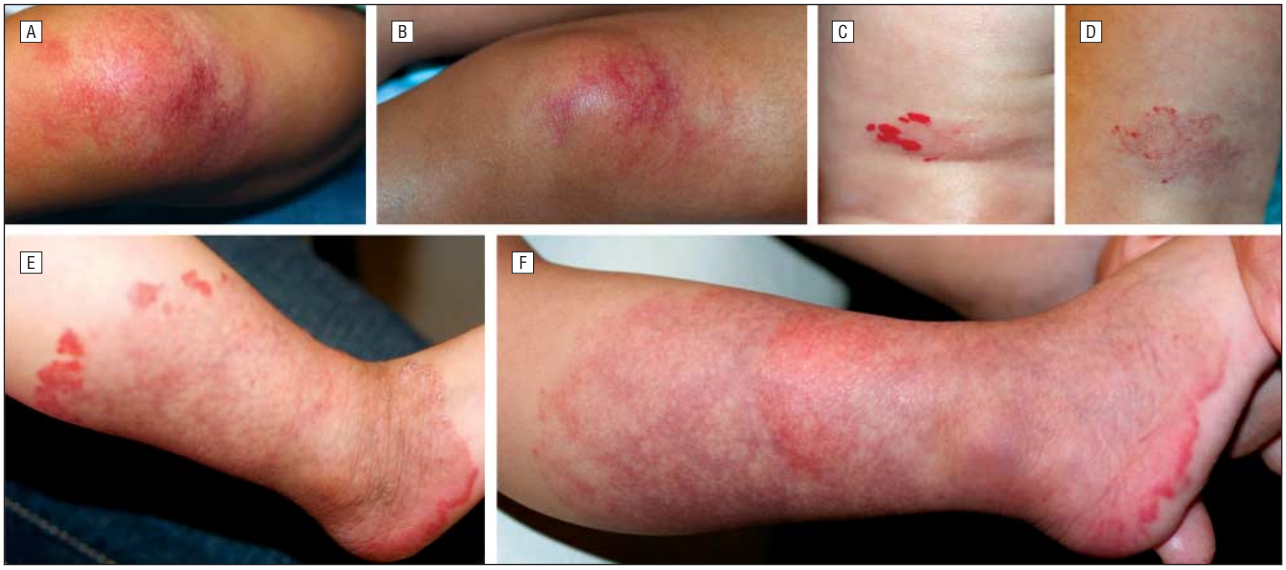

Figure 6. Infantile hemangiomas with minimal or arrested growth show fading over time. On knee at age 14 months (A) and age 27 months (B). On back at age 5 months (C) and age 12 months (D). On right leg at age 6 months (E) and age 12 months (F).

Table 2. Comparison of Clinical and Demographic Features Between Infantile Hemangiomas[2,8,10-13] and Infantile Hemangiomas With Minimal or Arrested Growth (IH-MAGs) in the Present Case Series

Feature	Infantile Hemangiomas	IH-MAGs
Most common clinical appearance	Red plaques or nodules	Fine or coarse telangiectatic patches
Morphologic subtype, %		
Localized	67	64 (30 of 47)
Segmental	13	30 (14 of 47)
Partial segmental	16	6 (3 of 47)
Multifocal	4	0
Predilection for location, %		
Face, head, neck	Approximately 60	11 (5 of 47)
Arms and trunk	Not stated	21 (10 of 47)
Lower body	Not stated	68 (32 of 47)
Ratio of girls to boys	Range, 1.5:1.0 to 3.5:1.0	1.8:1.0
White non-Hispanic race/ethnicity, %	Approximately 70	77 (17 of 22)
Gestational age <37 wk, %	Approximately 20-35	13 (4 of 30)
Birth weight, mean (median), kg	3.1 (3.2)	3.0 (3.1)
Patients whose hemangioma was noted at birth, %	Approximately 35	78 (25 of 32)
Presence of ulceration, %		
Overall	Approximately 15	9 (4 of 47)
Anogenital hemangioma with ulceration	Approximately 50	50 (2 of 4)

a larger prospective study will be needed to more definitively address this.

Just as segmental facial IHs have been associated with structural anomalies in PHACE (posterior fossa anomalies, hemangioma, arterial abnormalities, cardiac anomalies/aortic coarctation, and eye anomalies) syndrome,[18] segmental IHs of the lumbosacral area have been associated with spinal dysraphism and urogenital and anorectal anomalies as seen in PELVIS (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag) and SACRAL (spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization) syndromes.[19,20] Large segmental IH-MAGs (referred to by Mulliken et al[7] as "reticular infantile hemangiomas") that extensively involved the lower limb and perineum have also been reported to be associated with urogenital and anorectal structural anomalies and severe complications such as deep ulcers and life-threatening cardiac overload. Although these serious complications are important to note, they seem to represent a subset that ranges from uncommon to rare. In our case series, only 1 patient with a segmental IH-MAG on the lumbar area was found to have spinal dysraphism on magnetic resonance imaging, and none had deep or recalcitrant ulcerations.

Diagnosis of IH-MAGs can be difficult, even for experienced clinicians. They are often mistaken for port-wine stains, and this error in diagnosis can become medically significant, particularly if misdiagnosis occurs in a segmental IH-MAG involving the upper face and forehead, leading to unnecessary concern and workup for Sturge-Weber syndrome, while at the same time ignoring the potential for PHACE syndrome. Some IH-MAGs are initially difficult to differentiate from port-wine stains, par-

ticularly if they are small, but the presence of a more blotchy distribution of color, as well as both fine and coarse telangiectasias, particularly in the context of a vasoconstricted background, is helpful in diagnosis. A small peripheral proliferative component, if present, facilitates diagnosis, but this is present in less than one-third of cases. Two other conditions may also pose diagnostic confusion. Noninvoluting congenital hemangioma may manifest as a solitary patch with coarse telangiectasias admixed with small venules and vasoconstriction in its periphery. Most noninvoluting congenital hemangiomas have a subtle palpable component, are warm to palpation, and have distinct imaging characteristics that are not evident in IHs or IH-MAGs.[21] Another possible misdiagnosis is the condition known as capillary malformation (CM)–arteriovenous malformation, in which *RASA1* mutations result in multifocal cutaneous CMs and fast-flow vascular anomalies. Capillary malformations associated with *RASA1* mutations share characteristics of IH-MAGs; their round-to-oval telangiectatic appearance is often associated with a vasoconstricted halo.[22] These CMs are usually multifocal and randomly distributed, can increase over time, and have autosomal dominant inheritance, which are features that may help in distinguishing them from IH-MAGs.[22,23]

In most cases, diagnosis of IH-MAG is a clinical one, but a skin biopsy may be useful in selected cases, as GLUT-1 expression in the vessels would help to distinguish it from other vascular anomalies.[9,24] Skin biopsies were not performed for histopathologic confirmation of GLUT-1 positivity in our patients, and this may be a limitation of the study. However, because IH-MAGs were clinically recognized as low-risk variants of IHs, biopsy was not found to be clinically necessary or ethically justifiable.

Characteristics that are helpful in recognizing IH-MAGs are red-blue overtones and peripheral blanched halos, which are presumably caused by vasoconstriction. In addition, coarser and more arborizing telangiectasias can be important clues to distinguish IH-MAGs from port-wine stains, as can fading or clearance over time. Although long-term prospective studies regarding the natural history of IH-MAGs have not been performed to date, 8 patients in our study seen in follow-up displayed at least some degree of fading over time.

In conclusion, this is the largest case series to date describing the clinical features of IH-MAGs and emphasizes their characteristic clinical features and unique predilection for the lower body. Recognition of IH-MAGs will help in more accurate diagnosis of vascular birthmarks of infancy, and the presence of an IH-MAG in an individual patient does not exclude the proliferative potential of other cutaneous or extracutaneous IHs that may be present.

Accepted for Publication: January 12, 2010.
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Author Contributions: Drs Suh and Frieden 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*: Suh and Frieden. *Acquisition of data*: Suh and Frieden. *Analysis and interpretation of data*: Suh and Frieden. *Drafting of the manuscript*: Suh and Frieden. *Critical revision of the manuscript for important intellectual content*: Suh and Frieden. *Administrative, technical, or material support*: Suh and Frieden. *Study supervision*: Suh and Frieden.
Financial Disclosure: Dr Frieden is a consultant for Pierre Fabre Dermatology.
Additional Contributions: Alan G. Bostrom, PhD, contributed to the statistical analysis.

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