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Title:

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Date:

2017-01-01

Citation:

Ma, E. H., Robertson, S. J., Chow, C. W. & Bekhor, P. S. (2017). Infantile Hemangioma with Minimal or Arrested Growth: Further Observations on Clinical and Histopathologic Findings of this Unique but Underrecognized Entity. *Pediatric Dermatology*, 34 (1), pp.64-71. <https://doi.org/10.1111/pde.13022>.

Persistent Link:

<https://hdl.handle.net/11343/292151>

Received Date : 21-Sep-2015

Revised Date : 27-Jul-2016

Accepted Date : 09-Aug-2016

Article type : Original Articles

Infantile Haemangiomas with Minimal or Arrested Growth: Further observations on clinical and histopathologic findings of this unique but under-recognized entity

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/pde.13022](https://doi.org/10.1111/pde.13022)

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Word Count:

Abstract: 226

Text: 1982

Abstract

Introduction:

Infantile Haemangiomas with Minimal or Arrested Growth (IH-MAG) is an entity becoming increasingly recognized in the literature. It is important to be aware of its existence, as the correct diagnosis is essential for prognostication, treatment and in the case of facial segmental lesions, direction of further investigations, if PHACE syndrome versus Sturge-Weber syndrome is suspected. Although the clinical and

histological characteristics of IH-MAG resemble capillary malformations the positive GLUT-1 status is a delineating feature.

Materials and Methods:

We reviewed 9 cases of infants who presented after the year 2000 with birthmarks showing unique clinical features suggestive of a special variant of infantile haemangioma. All patients had serial photographs performed, demonstrating resolution of the birthmark over time. Five of these cases had skin biopsy performed, all of which confirmed GLUT-1 positivity.

Results:

This photographic series of IH-MAG demonstrates their unique clinical, histological and immunochemistry features. They were nearly fully formed at birth and their common clinical features included telangiectasia, venules, and matte erythema with light and dark areas. Spontaneous resolution over time without cosmetic disfigurement was the observed natural history in the majority of cases.

Conclusions:

IH-MAG is a unique clinical subset of haemangioma where close observation is the preferred treatment. When in doubt, a biopsy for histology and GLUT-1 status may be needed to confirm diagnosis before embarking on unnecessary laser treatment or medical interventions.

Introduction

Infantile Haemangiomas with Minimal or Arrested Growth (IH-MAG) is an emerging entity which is being gradually recognized in the literature.^{1,2} We present a photographic series of IH-MAGs showing clinical and histological characteristics

resembling capillary malformations or congenital haemangioma however the GLUT-1 status confirmed haemangiomas. It is important to be aware of the existence of this entity with its unique features, as the correct diagnosis is essential for prognostication and treatment. We present a detailed photographic series demonstrating resolution of this group of haemangioma. The histology and immunochemistry will also be discussed.

Case Series

Case 1

A 5 month-old boy was noted to have a bruise-like patch on the dorsum and palm of left hand at birth (Fig1a). The initial colour was bright red with telangiectasia; this grew darker in the following months but did not elevate. The clinical features included light and dark erythematous areas with a dull/matte appearance, telangiectasia, and in some sections a peripheral darker edge.

The parents were keen to confirm the diagnosis and consider early laser treatment if this was capillary malformation. The biopsy showed a few moderately dilated, superficial, thin-walled blood vessels which were lined by bland endothelial cells that were positive for GLUT-1 and CD34, and negative for D2-40.

This child was observed and the area almost completely cleared spontaneously by the age of 18 months (Fig1b).

Case 2

A 7 week-old girl presented with a macular erythematous birthmark on the left hand (Fig1c). Clinically it demonstrated a deeply erythematous and matte appearance with alternating dark and light areas in the centre. There was a certain degree of peripheral darkening and some brightly erythematous macules at the periphery measuring 1-2mm in diameter. The area did not appear to grow or elevate. A skin biopsy demonstrated features identical to those seen in case 1.

The area was observed and gradually faded over the following months (Fig1d).

Case 3

A 6 month-old girl presented with multiple erythematous birthmarks over her back, neck, cheek and lip. The back and neck lesions were nearly fully formed at birth with only mild increase in size in the postnatal period and with no elevation. The features resembled the previous cases with deep erythema and dull/matte appearance over the lower back with alternating lighter and darker parts and peripheral pallor. The neck and cheek lesions showed prominent venules and telangiectasia especially posterior to the ear. Interestingly, the lower lip lesion became slightly elevated after birth requiring laser treatment and a new area developed over the anterior lower gum after birth although this did not proliferate further.

A biopsy taken from the back demonstrated a moderate number of small vessels in the papillary dermis, lined by flat endothelial cells. Some of these had a thin wall and others had slightly thickened hyaline wall. There was no obvious increase in blood vessels in the reticular dermis or subcutis. Immunostaining showed GLUT-1 positivity, and CD 34 showed a double contour appearance similar to an involuting infantile haemangioma (IH).

Following observation the areas slowly faded as expected.

Case 4

A 4½ month-old girl presented with a birthmark on the left upper thigh, which was noticed at day 2 after birth (Fig2a). Clinically it demonstrated an erythematous patch with light and dark areas, telangiectasia, venules and peripheral pallor. In spite of the mild increase in diameter in the following months, the area did not elevate clinically and gradually cleared by the age of three years (Fig2b).

A skin biopsy showed features similar to those in Case 1.

Case 5

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This 3 month-old female presented with vascular lesions over left lower limb which started as mottled, bluish discoloration with superimposed bright red papules over upper thigh at birth; this was associated with the development of leg length discrepancy which peaked at the age of 2 (Fig2c). This case was previously reported as segmental haemangioma of infancy with skeletal overgrowth.³ Although it was more extensive in distribution and included limb overgrowth in comparison with the above cases, it did demonstrate some striking similarities in appearance. It showed a deep matte erythematous background with alternating light and dark areas, venules and telangiectasia with additional features of brightly erythematous papules at proximal margin resembling cherry angiomas. Spontaneous ulceration was also a feature in this case.

Punch biopsy from the area of matte erythema showed features similar to those in Case 1. A further biopsy from the bright nodules showed focal lobules of small vessels within the superficial dermis, similar to those in IH. Immunostaining showed GLUT-1 positivity of these vessels in both the macular and nodular areas.

The dark matte erythematous discolouration over the lower limb gradually faded since birth. The bright red papules grew until approximately 10 months of age and started to regress at the age of 15 months. Ulceration occurred over 2 areas which were then treated with pulsed dye laser with good result. (Fig2d)

Case series without biopsies

Cases 6-9 (Fig 3,4) represent infants who presented with birthmarks of similar clinical features and did not require biopsies. They slowly faded over the following months to years under clinical observation, and key features are listed in Table 1.

Discussion

❖ Clinical features

This group of haemangiomas have been described as Infantile Haemangiomas with Minimal or Arrested Growth (IH-MAGs).^{1,2} They are mostly fully formed at birth, and they do not fit in the definition of congenital haemangioma due to different morphological and immunostaining patterns. We present this series with more detailed descriptions of the clinical features and photographs demonstrating clinical resolution – an essential feature for the diagnosis of Infantile Haemangioma (IH). Classical IHs have been described as tumours usually absent at birth or present as precursor lesions followed by proliferative phase and subsequent involution.⁴⁻⁶ Most IH growth occurs before 5 months age, and the first few weeks to months are critical for growth.⁷ In contrast, the haemangiomas presented here were noted to be mostly fully formed at birth with minimal further growth in size and minimal tendency to proliferate above the level of skin surface, other than occasional cherry angioma-like lesions at the peripheral margin.

All the lesions were noted to be present either at birth or a few days after birth. The presence of telangiectasia, venules, and matte or dull erythema with light and dark areas were features common to all cases in this series. Other features occurring at the periphery of the lesions include peripheral bright red papules, dusky erythema, and rarely, ulceration (case 5). The deep erythema and onset at birth can clinically resemble capillary malformation (CM) and this may be diagnosed inadvertently. Distribution of lesions were 56% on the lower limbs, 33% on hands/distal forearm and only 11% had lesions on head, neck and trunk. IH-MAG may also be associated with development of typical IH at other sites, and this was observed in case 3 and 5 (Table 1).

It is important to distinguish between IH-MAG and CM when segmental lesions present on the face, as a segmental facial IH-MAG may warrant workup for PHACE syndrome, whereas CM on the face may require evaluation for Sturge-Weber syndrome. Additionally, the presence of a segmental IH-MAG involving the lumbosacral or perineal region may require workup for LUMBAR/PELVIS syndrome.

❖ Histology

The histology of the typical IH of the proliferative phase in young infants shows well-circumscribed lobules of cellular masses of capillaries with small lumens lined by plump endothelial cells. As the lesion evolves the capillaries become more dilated, sometimes with thickened hyaline walls.

In contrast, the histology of this group of IH-MAG demonstrated different and highly characteristic features. A number of moderately dilated small vessels were present in the superficial dermis. The endothelial cells were flat and appeared inactive. The walls of the vessels were very thin (Fig5a). There was no epidermal atrophy, fibrosis or fibroadipose tissue. On histology alone the features more closely resembled capillary malformations in which dilated thin-walled vessels within the superficial dermis were the main feature. Immunohistochemistry was positive for GLUT-1 (Fig5b). In cases 3 and 5, the endothelial cells were surrounded by a prominent layer of hyaline material (Fig5c). Immuno-histochemistry showed the endothelial cells were again positive for GLUT-1, but also a double contour appearance with CD34 (Fig5d). This was very similar to the appearance of IHs in the later stages of development, especially with involution.

GLUT-1 positivity demonstrates a clear distinction between IH and capillary malformations. GLUT-1, an erythrocyte-type glucose transporter protein, is a highly selective and diagnostically important marker for IH, and GLUT-1 is negative in vascular malformations and congenital haemangiomas.⁸ The GLUT-1 positivity made it clear that these vascular lesions in our series were infantile haemangiomas.

❖ Pathogenesis

The pathogenesis of IHs has been evolving, and to date there is no universally accepted model.⁹ Previous theories have suggested a relationship between haemangioma and the placenta, and fetal placental progenitor was suggested to be the cell type of origin for IH.^{10,11} However studies in areas of vasculogenesis and angiogenesis demonstrated the significant role of local tissue hypoxia and subsequent

release of mediators of vasculogenesis, with oestrogen's potentiating effect, in proliferating IHs.¹²⁻¹⁴

The isolation of multipotent progenitor cell capable of de novo blood vessel formation has suggested that IH may be a result of pathologic vasculogenesis.¹² Tissue ischaemia leads to upregulation and stabilization of hypoxia inducible factor-1 α (HIF-1 α) which increases the production of mediators upregulating mobilization of bone marrow derived endothelial progenitor cells (EPCs) to the ischaemic tissue promoting vasculogenesis and hence proliferation of haemangioma. Kleinman's study showed children with proliferating haemangioma had significant elevation of circulating mediators of EPCs. Oestrogen may have a promoting effect in hypoxia included mitosis of endothelial cells and may hence be a modulator of EPC trafficking.¹³ Therefore it is possible, in IH-MAGs, the degree of vasculogenesis mediators release and the cascade effect was somehow less active with less tissue damage compared to the rapidly proliferating IH.

Another possibility is the degree of local tissue hypoxia may determine the downstream effect of vasculogenesis mediator release and hence the severity of tissue damage as a result of endothelial cell proliferation.^{13,14} This also leads to the hypothesis that propranolol may play a role in dampening the effect of vasculogenesis mediators resulting in reduction of further proliferation and less tissue damage. It is also interesting to note propranolol treatment often results in incomplete resolution to a level that resembles IH-MAG.

Further study of quantitative comparison between IH-MAGs and rapidly proliferating IH may be able to identify their biochemical differences at the level of mediators released, as well as oestrogen level; this could offer further understanding in their pathogenesis and treatment.

❖ **Clinical implication**

The combination of features described above makes this group of IH a distinct subgroup of superficial IHs. The recognition of this entity has demonstrated the usefulness of biopsy and immunostaining when the clinical diagnosis is in doubt as

they can be mimickers of CMs or congenital haemangiomas. GLUT-1 positivity makes the distinction clear. A recent article has suggested dermoscopy as an additional diagnostic modality for IH-MAGs with the features of oval erythema, reddish telangiectasia, large network of bluish vessels and greyish-white areas.¹⁵

There is a trend toward early laser treatment of CMs. The correct diagnosis will therefore avoid unnecessary laser treatments for infants with IH-MAG.

Conclusion

We present this photographic series of IH-MAG to demonstrate their unique clinical, histological and immunochemical features. Spontaneous resolution over time is the natural history for these lesions. Active intervention is not usually required unless the area involved is cosmetically disfiguring or ulceration occurs. Close observation of the IH-MAG is recommended to exclude the possibility of delayed evolution into a more typical haemangioma. When the diagnosis is in doubt, particularly if the area involved is large, segmental or the possibility of an underlying syndrome exists, a biopsy for histology and GLUT-1 status may be indicated.

Acknowledgement:

The authors thank the photography department of Skin and Cancer Foundation Inc, Victoria, for their assistance with the image production of this publication.

Table 1.

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 |
|--------------|----------|-----------|-------------------|---------------------------|------------|------------|----------------|----------|----------|
| Age of Onset | At birth | At birth | At birth | Noticed day 2 after birth | At birth | At birth | At birth | At birth | At birth |
| Gender | Male | Female | Female | Female | Female | Male | Female | Male | Female |
| Site | Hand | Hand | Head, Neck, Trunk | Lower limb | Lower limb | Lower limb | Buttock, Calf. | Hand | Foot |
| Approximate | 12 | 12 months | Involuting | 3 years | Involuting | 12 months | 3 years | 4-5 | 15 |

| Time to Resolution | months | | at 9 months review | | after 18 months | | | years | months |
|---------------------------|-----------------|-----------------|--|-----------------|-----------------|----------|------------|----------|----------|
| Clinical features: | | | | | | | | | |
| Telangiectasia | + | + | + | + | + | + | + | + | + |
| Venules | + | + | + | + | + | + | + | + | + |
| Matte erythema | + | + | + | + | + | + | + | + | + |
| Light and dark areas | + | + | + | + | + | + | + | + | + |
| Peripheral pallor | - | - | + | + | - | - | + | - | - |
| Peripheral bright Papules | + | + | - | - | + | + | - | - | - |
| Darker at Periphery | + | + | + | - | + | - | - | + | + |
| Ulceration | - | - | - | - | + | - | - | - | - |
| Associated Typical IHs | - | - | Only in lip/ mucosal areas. None in cutaneous areas. | - | + | - | Upper limb | - | - |
| Associated overgrowth | - | - | - | - | + | - | - | - | - |
| Immuno-staining | GLUT-1 positive | GLUT-1 positive | GLUT-1 positive | GLUT-1 positive | GLUT-1 positive | Not done | Not done | Not done | Not done |

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Legends for Figures and Table

Figure 1:

1 a (case 1 at presentation)

1 b (case 1 at resolution)

1 c (case 2 at presentation, M: Matte erythema with light and dark areas)

1 d (case 2 at resolution)

Figure 2 :

2 a (case 4 at presentation, T: areas of telangiectasia, V: venules),

2 b (case 4 at resolution)

2 c (case 5 at presentation)

2 d (case 5 at resolution)

Figure 3 :

3 a (case 6 at presentation)

3 b (case 6 at resolution)

3 c (case 7 at presentation)

3 d (case 7 at resolution)

Figure 4 :

4 a (case 8 at presentation)

4 b (case 8 at resolution)

4 c (case 9 at presentation)

4 d (case 9 at resolution)

Figure 5 :

5 a (H&E at low power showing moderately dilated small vessels in the papillary dermis, flat and inactive looking endothelial cells and thin walled vessels)

5 b (immunohistochemistry positivity for GLUT-1 at low power)

5 c (H+E at high power showing endothelial cells surrounded by a prominent layer of hyaline material)

5 d (immunohistochemistry positivity for CD34 at high power showing a double contour appearance)

Table 1 .

A summary of clinical features with immunochemistry staining status of all cases.

Table 1.

A summary of clinical features with immunochemistry staining status of all cases.

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 |
|---------------------------------------|-----------|-----------|--|---------------------------|----------------------------|------------|----------------|-----------|-----------|
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| Gender | Male | Female | Female | Female | Female | Male | Female | Male | Female |
| Site | Hand | Hand | Head, Neck, Trunk | Lower limb | Lower limb | Lower limb | Buttock, Calf. | Hand | Foot |
| Approximate Time to Resolution | 12 months | 12 months | Involuting at 9 months review | 3 years | Involuting after 18 months | 12 months | 3 years | 4-5 years | 15 months |
| Clinical features: | | | | | | | | | |
| Telangiectasia | + | + | + | + | + | + | + | + | + |
| Venules | + | + | + | + | + | + | + | + | + |
| Matte erythema | + | + | + | + | + | + | + | + | + |
| Light and dark areas | + | + | + | + | + | + | + | + | + |
| Peripheral pallor | - | - | + | + | - | - | + | - | - |
| Peripheral bright Papules | + | + | - | - | + | + | - | - | - |
| Darker at Periphery | + | + | + | - | + | - | - | + | + |
| Ulceration | - | - | - | - | + | - | - | - | - |
| Associated Typical IHs | - | - | Only in lip/ mucosal areas. None in cutaneous areas. | - | + | - | Upper limb | - | - |
| Associated overgrowth | - | - | - | - | + | - | - | - | - |

| | | | | | | | | | |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|----------|----------|----------|----------|
| Immuno-staining | GLUT-1 positive | GLUT-1 positive | GLUT-1 positive | GLUT-1 positive | GLUT-1 positive | Not done | Not done | Not done | Not done |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|----------|----------|----------|----------|

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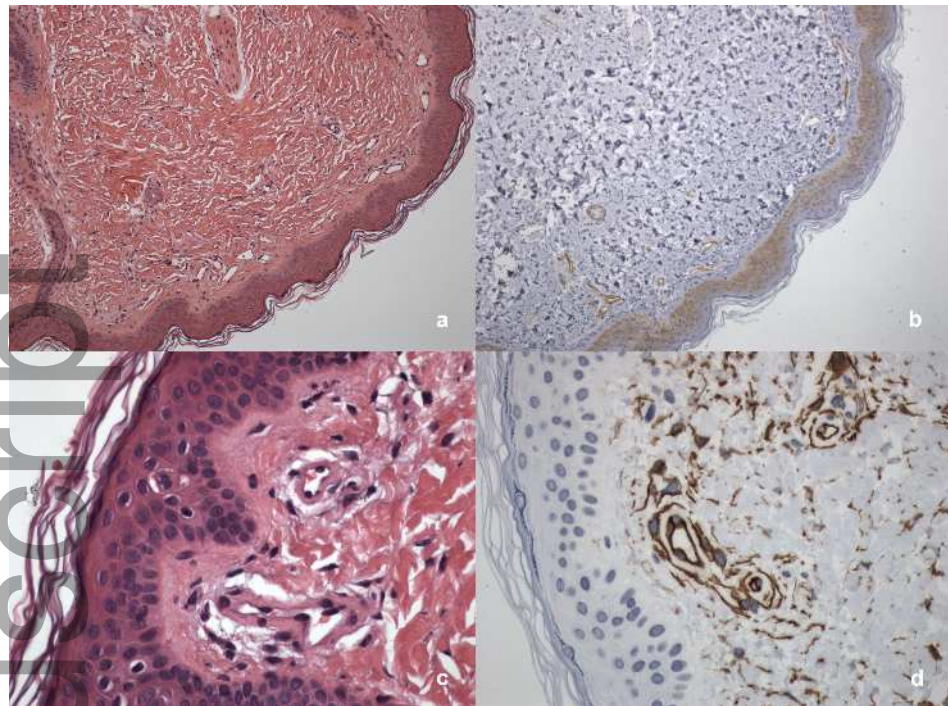
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