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BRIEF REPORT

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Analysis of infantile hemangioma without proliferation after birth

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Abstract: Infantile hemangiomas (IHs) are the most common benign tumors of infancy, occurring in approximately 5-10% of the population. Among what appear to be typical IHs with proliferative and involuting phases, we noticed that there are also IHs that are already present at birth and regress without proliferating. We therefore aimed to determine the frequency and clinical characteristics of this type of IH. A retrospective study was conducted on 176 lesions of 137 Japanese patients with IH. As a result, six lesions (3.4%) in three patients with IH (2.1%) were already present at birth and lacked subsequent proliferation. Analysis of the clinical characteristics of IHs without proliferation revealed that they are significantly less common in the head and neck region, which is the preferred site of the tumor, than typical IHs with proliferation (0% *vs.* 42.9%, $p < 0.05$ by Fisher's exact test). This suggests that when the clinical course of IH is uncommon, their distribution can also be atypical. Furthermore, all of the IHs without proliferation were superficial types, and there were no deep types in this cohort. This study demonstrates that the clinical course of IH can be diverse, and that very rarely there can be a type of IH that does not grow after birth. It may be necessary to consider conducting a detailed interview for the growth history at the first visit for the possibility of such a type of IH without proliferation, as it is likely that they can be followed up without the need for treatment.

Keywords: pathogenesis, cause, subtype

Introduction

Infantile hemangiomas (IHs) are the most common benign tumors in infancy, occurring in approximately 5-10% of the population (*1*). The typical clinical course is either absent at birth or with precursor lesions, such as erythematous telangiectasias or macules. The lesions thereafter show tumor growth (*i.e.,* proliferation phase) for several months, and in the involuting phase, they gradually disappear over several years. The site of predilection is the head and neck region (*2*). Low birth weight, multiple pregnancies, preterm delivery, progesterone therapy, and family history of IH have all been reported to be associated with the incidence of IH (*1*).

The detailed pathogenesis of IH has yet to be elucidated, but a number of hypotheses exist to explain its unique clinical presentation (*3*). For example, the first hypothesis is placental cell embolism. The gene expression pattern of IH differs from that of endothelial cells in the surrounding skin, resembling the pattern of endothelial cells comprising fetal microvessels in the human placenta (*4*). A second hypothesis is related to hypoxia: Local hypoxia associated with glucose transporter (GLUT)-1 and indoleamine 2,3-dioxygenase may be involved in the pathogenesis (*1*). A third hypothesis concerns endothelial progenitor cells and stem cells. Endothelial progenitor cells derived from IHs have been shown to cause IH-like lesions in immunocompromised mice (*5*).

In addition, according to our previous study, IH is less common in the jaw and cheek regions among the head and neck area, which are less prone to external stimuli (*6*). We therefore hypothesized that physiological events, including perinatal hypoxia or mechanical stress during delivery, may be one of the triggers of hemangioma formation. Recently, among what appear to be typical IHs, we have also noticed that there are IHs that were already present at birth, that do not enlarge thereafter, and then spontaneously involute. Here, we aim to determine the frequency and clinical characteristics of this type of IH.

Patients and Methods

Clinical assessment and patient material

This retrospective study was approved by the Research Ethics Committee of Wakayama Medical University (No. 2730) in accordance with the Declaration of Helsinki. The informed consent was obtained from the

patients' guardians. IH infants who visited Wakayama Medical University Hospital between January 2017 and June 2020 were included in the study. All patients were diagnosed based on clinical symptoms, imaging findings (*e.g.,* ultrasound and MRI), or histopathological findings. Cases with unknown onset were excluded.

The following variables from medical records and clinical photographs were collected for our analysis: date of onset, gender, number of lesions, distribution (head and neck, limbs, trunk), family history, gestational week, birth weight, and clinical subtypes (*7*). The clinical subtype was defined by the depth of soft tissue involvement. Superficial-type IHs involving the skin surface have elevated, lobulated, bright red appearance. Deep-type IHs arise from the reticular dermis and/or subcutaneous layers, and appear as bluish subcutaneous nodules or tumors. Mixed-type IH has features of both subtypes.

Statistical analysis

Statistical analysis was performed using Fisher's exact test for comparison of frequencies; $p < 0.05$ was considered statistically significant.

Results and Discussion

Clinical characteristics of IH patients included in this study

Clinical data were collected on 176 lesions in 137 IH patients (87 females and 50 males). Their mean age at first visit was 2.94 months. The distribution of the 176 lesions was 73 in the head and neck (41%), 42 in the extremities (24%), and 61 in the trunk (35%). No segmental IH was included. The clinical subtypes of the 176 lesions were 113 superficial (64%), 17 deep (10%), and 46 mixed (26%). Multiple lesions were detected in 24 patients (14%). Among the 137 patients, only 5 (4%) had apparent family history. Information on gestational week was available for 74 patients based on medical record, and 14 cases were born earlier than 37 weeks. According to data on birth weight for 70 patients, 15 had low birth weight (< 2,500 g). Because this was retrospective study, information on gestational age or birth weight was sometimes lacking in medical records.

Clinical pictures of IH without proliferation

In our cohort, of the 176 lesions in 137 patients with IH, six lesions (3.4%) in three patients with IH (2.1%) were already present at birth and did not show subsequent proliferation. The information on the presence or absence of proliferation after birth was based on parental observation, but most cases in the present cohort were thought to have proliferative tendencies. The 137 IH patients were then classified into two groups according to the presence or absence of tumor proliferation: Patients with IH already present at birth and without subsequent proliferation (IH without proliferation, $n = 3$), and those with typical IH present at or after birth and subsequently proliferated (IH with proliferation, $n = 134$).

Representative clinical pictures of patients with IH lesions already present at birth and without subsequent proliferation are shown in Figures 1-3. Case 1 was born at 40 weeks and five days with hemangioma of the vulvar region (Figure 1A). Diagnosis of IH was confirmed histopathologically based on the neoplastic proliferation of disorganized vascular channels (Figure 1B) and positive GLUT-1 staining (Figure 1C). Case 2 had a lesion on the thigh (Figure 2), while Case 3 showed multiple IHs on the hand, lower leg, abdomen, and back (Figure 3, A-D).

Each of these patients had typical clinical presentation of IH, but did not proliferate during at least five months of follow-up, and spontaneous involution was confirmed (Table 1), except for the thigh lesion of case 2 and the hand lesion of case 3 which treated with pulsed dye laser

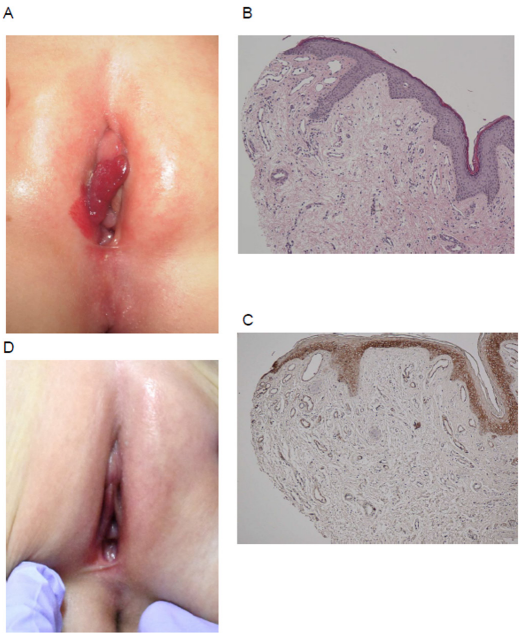

Figure 1. Clinical manifestation of Case 1 without proliferation on the vulva. (A) Clinical finding at the first visit, **(B)** Histological findings of biopsy specimen showing proliferation of disorganized vascular channels, **(C)** GLUT-1 staining, **(D)** involution at 12 months after the first visit.

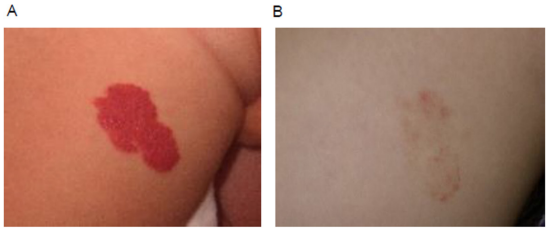

Figure 2. Clinical manifestation of Case 2 without proliferation on the right thigh. (A) Clinical finding at the first visit, **(B)** involution at 10 months after the first visit.

before involuting phase.

Usually, such IH cases without proliferation are considered to be abortive IH, minimal growth IH, or rapidly involuting congenital hemangioma (RICH) as differential diagnosis (*8,9*). However, the clinical presentation and clinical course of the three patients were different.

Analysis of clinical characteristics of IH without proliferation

Differences between the two groups in gender, distribution, clinical subtype, family history, gestational week, and birth weight were analyzed (Table 2). As a result, the distribution of IHs with proliferation was in the head and neck in 73 lesions, the trunk in 58 lesions, and the extremities in 39 lesions (Table 3). As mentioned above, IH was more common in the head and neck region (*10*), but IH without proliferation tended to be found in the other areas, indicating a statistically significant difference in the frequency of head and neck lesions between the two groups (42.9% *vs.* 0%, $p = 0.036$ by Fisher's exact test). IH without proliferation is more likely to occur outside the head and neck region.

Thus, our analysis suggests that when the clinical course of IH is uncommon, the distribution may also be atypical. In our previous study, IH appearing after birth was shown to tend to have multiple lesions more frequently than IH present at birth, suggesting that IH present at birth is caused by local triggers (*7*). In addition to local triggers, multiple IHs appearing after birth may be caused by systemic factors, such as cytokines involved in systemic neovascularization or sensory nerve growth after birth. Actually, several cytokines (bFGF, IFN-γ, IGF-I, and TGF-β1) were higher in the patients with multiple lesions than in those with a single lesion, with statistically significant difference (*11*). The pathogenesis

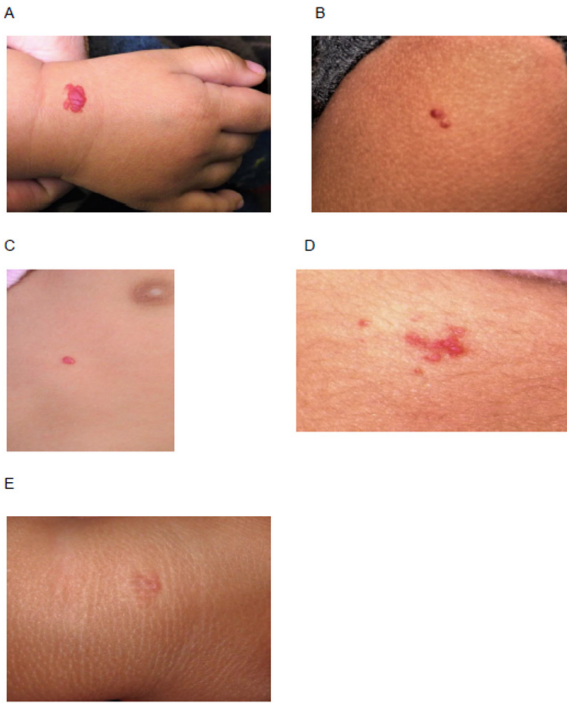

Figure 3. Clinical manifestation of Case 3 without proliferation. (A) right hand at the first visit, **(B)** left lower leg, **(C)** right upper abdomen, and **(D)** back, **(E)** disappearance of right hand lesion at 5 months after the first visit.

Table 2. Clinical characteristics of infantile hemangioma patients included in this study

Characteristics	Number of cases
Gender	
Female	87
Male	50
Distribution	
Head and neck	73
Limbs	42
Trunk	61
(Multiple)	(24)
Clinical type	
Superficial	113
Deep	17
Mixed	46
Family histories	
+	5
–	129
Unknown	3
Gestational week	
< 37 weeks	14
≥ 37 weeks	60
Unknown	63
Birth weight	
Mean weight (kg)	2.84
Low birth weight	15
Proliferation	
+	134
–	3

Table 3. Correlation of onset with distribution

Distribution	Without proliferation	With proliferation	All
Head and neck	0 (0%)	73 (42.9%)	73
Trunk and limbs	6 (100%)	97 (57.1%)	103
All	6	170	176

Table 1. Clinical characteristics of infantile hemangioma without proliferation

Cases	Gestational week	Birth weight	Age at the first visit	Follow-up period	Involution
Case 1	40w, 5d	3,170g	12 months	12 months	+
Case 2	Unknown	Unknown	2 months	10 months	+
Case 3	Unknown	Unknown	11 months	5 months	+

Table 4. Correlation of onset with clinical subtypes

Subtypes	Without proliferation	With proliferation	All
superficial	5	108	113
deep	0	17	17
mixed	1	45	46
All	6	170	176

of IH without proliferation in the present study may be different from such typical IHs, and tumor growth may have already begun before birth, and the tumor may be at its maximum size at birth. However, because gestational weeks were not significantly different between the two groups, the detailed etiology is still to be clarified.

Furthermore, the clinical subtypes of IH lesions without proliferation were five superficial-type (83%), none of deep-type, and one of mixed-type (17%), while those with proliferation were 108 superficial-type (64%), 17 deep-type (10%), and 45 mixed-type (26%). The superficial-type was the most common in both groups, whereas the deep-type was found only in IH with proliferation (Table 4). The deep-type may be difficult to recognize on the day of birth because of the lack of color change on the surface, and this result should be verified through further case series.

Conclusion

This study demonstrates that the clinical course of IH can be diverse, and that very rarely there may be a type of IH that does not grow after birth. It may be necessary to consider conducting a detailed interview for the growth history at the first visit for the possibility of such a type of IH without proliferation, as it is likely that they can be followed up without the need for treatment.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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