



## ORIGINAL ARTICLE

# Infantile Hemangiomas with Minimal and Arrested Growth: Clinical Features and Treatment Outcomes with 0.5% Topical Timolol Maleate

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**Background:** A minority of infantile hemangiomas showing minimal or arrested growth (IH-MAGs) have been recognized in the literature. Nevertheless, the clinical features and treatment outcomes of IH-MAGs have not been well investigated. **Objective:** This study aimed to understand the clinical characteristics of IH-MAGs better and their response to treatment with topical timolol maleate. **Methods:** We retrospectively reviewed medical records and clinical images of patients with IH-MAGs. Treatment response with topical timolol was assessed in both IH-MAGs and classic infantile hemangiomas (IHs) groups. **Results:** Of the 1,038 patients with IHs, only 31 (3.0%) were diagnosed with IH-MAGs. Lesions with non-proliferative components were more frequently distributed in the lower half of the body (61.5%) than those with proliferative components (16.7%). In 14 patients treated with topical timolol, the global assessment scale showed more significant and rapid improvement than in those with classic IHs. **Conclusion:** Although the prevalence of IH-MAGs may be relatively low, understanding their clinical features will help in differential diagnosis. Furthermore,

these type of lesions might be more responsive to topical timolol than classic IHs. (**Ann Dermatol 33(5) 448 ~ 455, 2021**)

## -Keywords-

Blood vessel tumors, Infantile hemangioma, Infantile hemangioma with minimally and growth, Timolol

## INTRODUCTION

Infantile hemangiomas (IHs) could be classified based on morphologic characteristics, involved anatomical area, or skin level to which the tumor infiltrates<sup>1</sup>. Each clinical subset of IHs has a different clinical progression and response to treatment. Apart from "classic" IHs, there is one subtype of IHs that has distinctive clinical features, known as infantile hemangiomas with minimal or arrested growth (IH-MAGs). This noteworthy type has recently been noticed by clinicians and is characterized by two distinguishable features: 1) morphologically, it has proliferative lesions (such as papules or plaques) covering less than 25% of the total area and 2) it has a proliferative phase with only a limited amount of growth or nearly unchanged progression<sup>2</sup>. With these distinctive findings and recent reports, IH-MAGs are now included in the International Society for the Study of Vascular Anomalies classification and have garnered increasing attention. Nevertheless, the rarity of the disease and under-recognition of this entity have made it difficult to outline suitable diagnostic approaches and appropriate management. Despite promising reports of the clinical characteristics of IH-MAGs, there remains a lack of large scale studies. Furthermore, there has been no established report on the treatment of IH-MAGs.

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We retrospectively investigated all patients with IHs and identified subgroups diagnosed with IH-MAGs at the Pusan National University Yangsan Hospital (PNUYH) to analyze the characteristic clinical features and evaluate outcomes following topical timolol treatment.

## MATERIALS AND METHODS

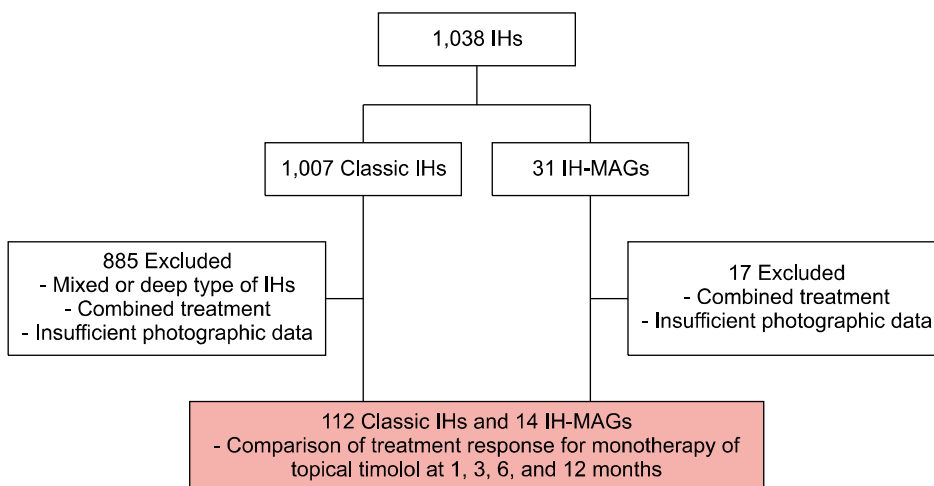
### Patients and methods

This study obtained approval from the institutional review board of PNUYH (IRB no.05-2019-064). We retrospectively identified subjects diagnosed with IH-MAGs between July 2012 and October 2018 using our patient record database. The diagnosis of IHs was based on medical history, physical examination, and clinical images. Additionally, we established the following inclusion criteria for identifying the "IH-MAGs" subgroup: 1) age at initial visit >3 months (given the fact that the morphological features of IH-MAGs are similar to those found in the very early phase of classic IHs [known as "premonitory mark"], the time period in which the initial proliferations were considered to have sufficiently elapsed was judged to be 3 months; 2) proliferative lesions should account for <25% of the total lesioned area; 3) because of similar clinical features with capillary malformation (especially when primary lesion has no or only few proliferative superficial components), other distinct findings (blotchy and pale-pink color, overlying fine telangiectatic patch, color tone that gradually fades over time, response to beta-blocker) were strictly applied for differential diagnosis; 4) no previous treatment history; and 5) presence of definite growth history (change in color or increasing diameter or thickness) after birth perceived by parents or physicians. For an accurate diagnosis, all patients who did not have a clinical image or whose data were not clearly described in the medi-

cal records were excluded. Skin biopsy was not performed in all patients. Clinical data were collected including demographic characteristics (sex, age at visit, gestational age, birth weight), lesion features (size, distribution, presence of ulcerative lesions, concomitance of classic IHs, presence of other anomalies), and treatment response to 0.5% topical timolol (Rysmon TG<sup>®</sup> 0.5%; Wakamoto Pharmaceuticals Co. Ltd., Kanagawa, Japan) monotherapy. Size was evaluated as an approximate surface area and divided into four groups (<5 cm<sup>2</sup>, 5~<25 cm<sup>2</sup>, 25~<100 cm<sup>2</sup>, ≥100 cm<sup>2</sup>). Multiple lesions were considered as the sum of each lesion. Anatomical areas were divided into head and neck, trunk, upper extremities, and lower extremities. In addition to the overall morphological features of the individual lesions, each lesion was examined and categorized as having telangiectatic patches, pale red- to pink-colored patch, bluish discoloration, or peripheral halo. The proportion of each individual finding was analyzed. Because the degree of involvement of proliferative lesions is an important criterion in diagnosing IH-MAGs, we performed further analyses of clinical features (demographic factors, size, and distribution) according to the presence (grouped as "pIH-MAGs") or absence (grouped as "nIH-MAGs") of proliferative lesions.

### Assessment of the outcomes with topical timolol maleate

To assess responses to topical treatment and exclude other implicated factors, patients with IH-MAGs were allocated as a "treatment group" if they were treated using topical timolol monotherapy. Furthermore, to evaluate the treatment response chronologically, we included only those patients who had clinical images from at least 1, 3, 6, and 12 months after starting treatment. Several instruments used to evaluate IHs treatment outcomes, such as the Hemangioma Severity Score, Hemangioma Activity and



**Fig. 1.** Flow chart of patients selection for assessment of treatment response with topical timolol maleate in classic infantile hemangiomas (IHs) and infantile hemangiomas with minimal or arrested growth (IH-MAGs).

Severity Index, and Hemangioma Activity Score, have limited application to IH-MAGs<sup>3-5</sup>. Therefore, the global assessment score (GAS), used to grade lesions more generally by investigators, was applied to evaluate the treatment response at each time point<sup>6,7</sup>. Two investigators compared clinical photographs from each time point with those from the baseline visit and assessed improvement based on the entire lesion area and color and decrease in size of proliferative lesions. After scoring each clinical photograph, the mean GAS (mGAS) was utilized to evaluate topical timolol maleate treatment outcomes. To compare treatment efficacy, we additionally subdivided patients with classic IHs from the initially collected patients and designated them as the control group. Furthermore, to ensure the consistency of the clinical characteristics of the control group, we included patients whose lesions presented as localized superficial classic IHs of similar size. None received any treatment except topical timolol. Finally, we only included patients whose treatment course could be evaluated by clinical images and medical records from visits at 1, 3, 6, and 12 months after commencing treatment (Fig. 1). The mGAS of the IH-MAGs group and classic IHs group at each period was evaluated.

### Statistical analysis

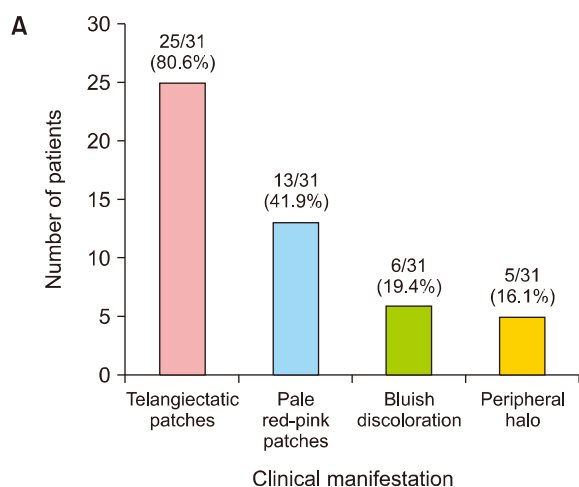
Statistical analyses were performed using IBM SPSS ver. 21 (IBM Corp., Armonk, NY, USA). When comparing clinical features of patients with and without proliferative lesions, we used the Mann-Whitney test for unpaired values and Fisher's exact test for non-numeric data. Mean scores at each time point following treatment in both groups were compared using the Mann-Whitney test. *p*-values

less than 0.05 were considered statistically significant.

**Table 1.** Demographic and clinical characteristics of patients with IH-MAGs

Parameter	Value
Investigated patients with IHs	1,038
Patients with IH-MAGs	31 (3.0)
Sex ratio	
Male:female	1:2.1
Gestational age (wk)	38.8±1.0 (29.0~40.0)
Age at visit (mo)	6.2±2.8 (5.0~19.0)
Birth weight (kg)	3.0±0.5 (1.3~4.0)
Presence of proliferative component	
Yes	18 (58.1)
No	13 (41.9)
Size (cm <sup>2</sup> )	
< 5	10 (32.3)
5 ~ < 25	11 (35.5)
25 ~ < 100	5 (16.1)
≥ 100	5 (16.1)
Distribution	
Head and neck	8 (25.8)
Trunk	9 (29.0)
Upper extremities	8 (25.8)
Lower extremities	9 (29.0)
Presence of concomitant classic IHs	6 (19.4)
Presence of ulcerative change	1 (3.2)
Presence of congenital anomaly	0 (0.0)

Values are presented as number only, number (%), or mean± standard deviation (range). IH-MAGs: infantile hemangiomas with minimal and arrested growth, IHs: infantile hemangiomas.



**Fig. 2.** Characteristic clinical appearance of infantile hemangiomas with minimal or arrested growth (IH-MAGs) and representative photographs of each characteristic finding. (A) Proportion of individual morphologic features of IH-MAGs. (B) Telangiectatic patch. (C) Pale-red patch. (D) Bluish discoloration. (E) Peripheral halo.

## RESULTS

### Demographics and morphologic features

Of 1,038 patients with IHs, 31 (3.0%) were classified with IH-MAGs. Twenty patients were female and the mean age at the initial visit was 6.2 months (Table 1). The mean gestational age and birth weights were 38.8 weeks and 3.0 kg, respectively. Most patients had no significant birth history except for three low birth weight (LBW) patients. Clinically, every patient had localized or segmental IH-MAGs and the size of the lesions in most patients did not exceed 25 cm<sup>2</sup>. Lesions were found to occur most frequently in the lower limb and trunk (both 29.0%) but, overall, were uniformly distributed across the body without any remarkable difference between regions. Eighteen patients (58.1%) had gross proliferative lesions. Concomitant classic IHs were found in six patients (19.4%). Ulcerative change developed in one patient whose lesion was on the lower lip. Associated anomalies were not found in all patients.

### Characteristic clinical findings

Lesion-related features included telangiectatic patches (80.6% of lesions), pale red- to pink-colored patches (41.9%), bluish discoloration (19.4%), and peripheral halo (16.1%) (Fig 2). Some of these overlapped in lesions. Comparing the pIH-MAGs and nIH-MAGs groups (Table 2), there were no significant differences in demographic factors or birth profile. However, when patients were classified according to lesion size, 10 patients (55.6%) with pIH-MAGs had a lesion ≥25 cm<sup>2</sup>, whereas none of the patients from the nIH-MAGs group had a lesion ≥25 cm<sup>2</sup> (p=0.010). Furthermore, most lesions were located on the upper body of pa-

tients with pIH-MAGs, whereas they were predominantly found on the lower body in the nIH-MAGs group (p=0.021).

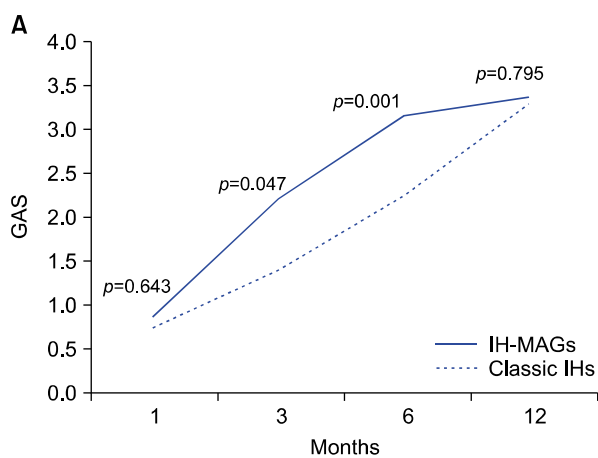
### Treatment outcomes with 0.5% topical timolol maleate

Of the 31 patients with IH-MAGs, only 14 patients had a treatment history of 0.5% topical timolol maleate monotherapy (Fig. 3, 4). Of the 1,007 patients with classic IHs, only 122 patients were included in the control group, i.e., they had a superficial-type lesion and received the same treatment as that by the IH-MAGs group. In the first month after topical timolol maleate treatment, the mGAS was similar in both the IH-MAGs and control groups (0.86 ±

**Table 2.** Comparison of clinical features of patients with proliferative (pIH-MAGs) and without proliferative lesions (nIH-MAGs)

Parameter	pIH-MAGs	nIH-MAGs	p-value
Sex			>0.05
Male:female	1:2.6	1:2.25	
Gestational age (wk)	39.1±2.8	36.5±5.1	>0.05
Age at visit (mo)	7.4±4.1	5.5±2.4	>0.05
Birth weight (kg)	3.1±0.6	2.8±0.8	>0.05
Size (cm <sup>2</sup> )			0.010
<25	8 (44.4)	13 (100)	
≥25	10 (55.6)	0 (0)	
Distribution			0.021
Upper half of the body	15 (83.3)	5 (38.5)	
Lower half of the body	3 (16.7)	8 (61.5)	

Values are presented as ratio, mean ± standard deviation (range), or number (%). nIH-MAGs: non-proliferative infantile hemangiomas with minimal and arrested growth, pIH-MAGs: proliferative infantile hemangiomas with minimal and arrested growth.

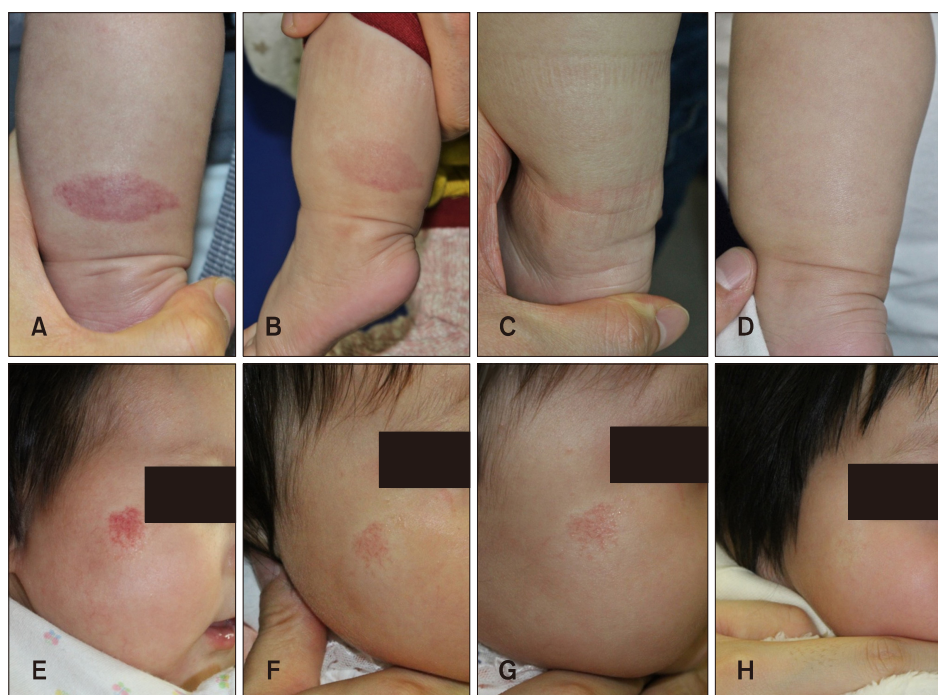


GAS	1 month	3 months	6 months	12 months
IH-MAGs	0.86±0.23	2.21±0.37	3.14±0.31	3.36±0.29
Classic IHs	0.75±0.40	1.40±0.72	2.24±0.85	3.28±0.62

### B

GAS	Improvement (%)*	Meaning
-1	<0	Worse
0	0	No change
1	0~24	Minor improvement
2	25~49	Good improvement
3	50~74	Considerable improvement
4	75~100	Nearly complete healed state

**Fig. 3.** Comparison of treatment response between classic infantile hemangiomas (IHs) and infantile hemangiomas with minimal or arrested growth (IH-MAGs). (A) Mean GAS score for each treatment period in both IH-MAGs group (n=14) and classic IHs group (n=122). (B) Degree of proportional improvement with descriptive meaning for each score of the GAS: global assessment scale. \*Color and size were assessed in comparison with the photograph from the initial visit.



**Fig. 4.** Treatment outcomes of infantile hemangiomas with minimal or arrested growth (IH-MAGs) with 0.5% topical timolol maleate. (A~D) Representative photographs showing the favorable progression for IH-MAGs appearing on the face of a 4-month-old female infant and (E~H) the lower leg of a 3-month-old female infant. (B, F) Mild improvement of color and induration of the entire lesion in both patients at 3 months. (C) Subsequent more prominent clearance of the lesion on the lower leg, (G) while the facial lesion persists at 6 months. (D, H) Almost complete healing of the lesions at both sites at 12 months.

0.23 vs.  $0.75 \pm 0.40$ ;  $p=0.643$ ). However, the control group showed significantly better improvement at 3 ( $2.21 \pm 0.37$  vs.  $1.40 \pm 0.72$ ;  $p=0.047$ ) and 6 months after initiating treatment ( $3.14 \pm 0.31$  vs.  $2.24 \pm 0.85$ ;  $p=0.001$ ). However, at the end of the 12-month evaluation period, there was no significant difference between the two groups ( $3.36 \pm 0.29$  vs.  $3.28 \pm 0.62$ ;  $p=0.795$ ).

## DISCUSSION

The prevalence of IH-MAGs has not yet been investigated. Our study suggests that IH-MAGs occur uncommonly, with 3.0% of patients with IHs having IH-MAGs. No congenital anomaly or associated disease was found and only three patients had prenatal problems. The most distinctive feature of IH-MAGs is that the characteristic proliferative phase of IHs is barely observed or stops prematurely. In the case of classic IHs, the characteristic proliferative phase initiates within the early weeks after birth and almost all patients have a noticeable progressive change in the tumor within 3 months after birth. However, this characteristic feature is hardly noticeable in patients with IH-MAGs<sup>2</sup>. Furthermore, as in our series, the morphologic feature of IH-MAGs were not consistent with those of classic IHs, which are specifically determined by the age of the patients. Rather, it is similar to the premonitory mark seen in classic IHs<sup>8</sup>. Because IH-MAGs could resemble the clinical features of the premonitory mark of IHs, it is necessary to discriminate the IH-MAGs from classic IHs based

on the time of the occurrence of lesion and age of the patient.

There was a significant sexual difference, as IH-MAGs in girls were twice of that in boys. Female dominance was somewhat lower than that for classic IHs, where the female:male patient ratio is 3.5:1. One previous study on IH-MAGs reported a sex ratio of 1.8:1, similar to our data;<sup>2</sup> However, another reported a ratio of 3.3:1<sup>9</sup>. In addition, it has been reported that IHs occur frequently in premature infants or those with LBW<sup>8</sup>. However, we found only one patient (3.2%) with preterm birth and three patients (9.7%) with LBW. The less significant association with prematurity in IH-MAGs was also reported in other series, ranging from 0.0% to 13.0%<sup>2,9,10</sup>. Prematurity or LBW account for a significant number of patients with classic IHs, because the hypoxic environment plays an important role in triggering the development of IHs. Either prematurity or LBW is at risk of hypoxic condition, and it can be seen that the expression of GLUT1, insulin-like growth factor and other angiogenic factors, which is increased by hypoxia, leads to abnormal vasculogenesis of infantile hemangioma. The pathomechanism of IH-MAG has not been well elucidated. However, the fact that their growth stops and regresses earlier than IHs means that they are less exposed to hypoxic events, which is an important stimulus for vasculogenesis, and so we could assumed that this is in line with the result that IH-MAG is less associated with prematurity or LBW.

More than half of our patients (67.8%) had lesions <25

cm<sup>2</sup> and lesions were distributed relatively equally across patients. Proliferative lesions were grossly identified in 18 patients (58.1%), similar to that in previous reports, ranging from 30% to 64%<sup>2,10</sup>. Differences may have been caused by factors, such as race, as well as the small number of investigated patients; hence, further study is warranted.

We identified a difference in lesion size and location between the pIH-MAGs and nIH-MAGs groups. nIH-MAGs showed significantly smaller size than pIH-MAGs, and we speculated that the size was smaller because the proliferative components may reflect increased internal blood flow or proliferation of vascular structure, which could be directly related to the size of lesion. There might be more attributable factor to the size of lesion (demographic factors such as birth weight or gestational age). Although data for interpretation of this result is insufficient, it is possible to find more factors associated with the size difference through future study. Non-proliferative lesions were found more frequently on the lower body, similar to reports from other studies<sup>2,9</sup>. Although this study did not reveal a significant difference in the anatomical location of the lesions of total IH-MAGs, it is worth noting that there was a marked predominance of non-proliferative lesions on the lower body. Because there is a difference in the distribution of blood vessels between anatomical regions, some authors suggest that this leads to differences in IHs growth patterns<sup>1</sup>. The predominance of non-proliferative lesions, which are speculated to receive limited blood supply, in the lower body may be associated with the decreased blood flow or reduced vascular density in this region. Given that previously identified distribution-related features were more prominent in non-proliferative lesions, we cautiously suggest that there is a pathophysiologic relationship between the distribution of the vasculature or blood flow according to the anatomical location and the occurrence of IH-MAGs. Telangiectatic patches are the most common diagnostic clinical feature of IH-MAGs, alongside blotched color distribution and vasoconstricted halos<sup>2</sup>. Additional findings, such as oval-shaped erythema, a large network of bluish vessels, and atrophic ecchymotic plaques, could also be helpful<sup>11,12</sup>. Our study analyzed the proportion of each characteristic finding among lesions, most of which presented with a mixed appearance. However, given this clinical diagnostic approach may not be apparent, the history of the previous growth phase, onset of disease and response to topical beta-blocker treatment could differentiate IH-MAGs from other vascular anomalies, such as congenital hemangiomas or capillary malformation.

The prognosis and management of IH-MAGs have not yet been clarified. There is no significant difference in their

natural progression from that of classic IHs, where fading or resolution occurs in only approximately half of patients over various observation periods<sup>1</sup>. Although there is a limit to the comprehensive interpretation of cases of IH-MAGs because of the difference in the follow-up periods, one report<sup>11</sup> showed that eight out of nine patients experienced spontaneous resolution with different response rates, while others showed that all lesions persisted without any change in natural progression<sup>13</sup>. Among the treatment options, oral propranolol was mostly used in patients with ulcers or large lesions; although the treatment duration varied, treatment responses were relatively good<sup>9,14</sup>. There was one case report of oral propranolol applied to non-ulcerative IH-MAGs overlying eczema leading to rapid improvement<sup>15</sup>. Because IH-MAGs follow the natural course of classic IHs, there are few reports related to topical treatment of IH-MAGs. Nevertheless, in one report, two of 13 patients were treated with topical timolol, resulting in progressive fading of the lesion<sup>9</sup>. As in our series, the efficacy of topical timolol for treatment of IH-MAGs (3 patients with nIH-MAGs and 11 patients with pIH-MAGs were included) was relatively favorable, but the question of the need for treatment remains. For decisions regarding local treatment for IHs, treatment guidelines are not well established compared to those for oral formulations. However, safety and substantial therapeutic efficacy have already been demonstrated in a large body of literature.

In our study, we were able to identify a comparable level of early responses in many patients with subsequent resolution over a 12-month period. There was an idea that the treatment response might not be clear compared to the classic IHs in which the proliferative lesion (therapeutic target) is more pronounced, but as our result, the overall improvement was faster and more pronounced in IH-MAGs. One of the plausible reasons for this therapeutic response could be attributed to differences in the qualitative or quantitative expression of the beta-adrenergic receptor (ADBR). To date, the ADBR is a well-known receptor for propranolol in various vascular tumors<sup>16</sup>; however, the difference in the response to propranolol of individual subtypes (ADBR1, ADBR2, and ADBR3) has not been clearly established. Previous reports have suggested that the level of ADBR1 mRNA expression in proliferative lesions was greater than in involuted or propranolol-responsive lesions, whereas the expression of ADBR3 protein was more prevalent in propranolol-responsive lesions than in proliferative lesions<sup>17</sup>. It could be assumed that the ADBR3 is more likely to be expressed in IH-MAGs. In addition, we carefully speculated that the beta-blockers could play a role in boosting the process of rapidly progressing aborting or regression phase. However, further studies are

needed because there are limited data regarding the precise relationship or mechanism associated with the expression of receptors. Moreover, there is a doubt about the need for unnecessary intervention for IH-MAGs. However, considering the fact that some patients have the lesion for years without any regression and that a reliable relationship with the caregiver of the patient needs to be maintained, topical treatment could be worthwhile, trying selectively with sufficient explanation.

Our study was limited by its retrospective design and small sample size. Furthermore, we could not collect more supportive data, such as histologic features identified using glucose transporter-1 staining, dermoscopic features, or additional laboratory data, which could be helpful in a more comprehensive analysis. Additionally, the evaluation of treatment outcomes was based solely on the subjective assessment of investigators because of the limited utilization of other formal scoring systems and clinical heterogeneity with the inclusion of classic IHs. Further research with large scale long-term clinical trials is necessary to better understand and confirm our results.

This study sufficiently showed the prevalence of IH-MAGs among patients diagnosed with IHs. Although we analyzed the proportion of characteristic findings that would help in the diagnosis of IH-MAGs, further studies are needed to determine the clinical significance of these individual findings. Finally, although there has been no established consensus regarding the treatment of IH-MAGs, we could demonstrate a considerable response to topical treatment relative to that of classic IHs. There are now many studies exploring this arising entity, so we believe that our study will help clarify various clinical aspects of IH-MAGs, together with future studies.

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The patients in this manuscript have given written informed consent to publication of their case details including photography.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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## DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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