


RESEARCH ARTICLE

Clinical and pathological differences between skin-limited IgM/IgG vasculitis and skin-limited IgA vasculitis

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Abstract

Objectives: Cutaneous IgM/IgG vasculitis (IgM/IgG V) is characterized by leukocytoclastic vasculitis histologically and by IgM- or IgG- perivascular deposition. However, clinical differences between IgM/IgG V and skin-limited IgA vasculitis (IgA V) have not been fully clarified. In the present study, we assessed the clinical and histopathological differences between IgM/IgG V and IgA V.

Methods: We examined 14 patients with IgM/IgG V and 24 patients with skin-limited IgA V. The cases associated with systemic diseases were excluded. Clinical findings, laboratory data, and histological findings were compared between IgM/IgG V and IgA V groups.

Results: Livedo lesions appeared more often, and palpable purpura less often in IgM/IgG V. Localization of the lesions was more limited to the lower legs in IgM/IgG V. In laboratory data, there were no statistical differences in peripheral blood cell counts, IgG, IgA, and IgM levels between the two groups. Histopathological findings showed less infiltration of neutrophils, CD8+ T cells, and CD3+ T cells, and nuclear dusts in IgM/IgG V. Systemic steroids were administered significantly less frequently in IgM/IgG V cases, but the recurrence rate did not differ.

Conclusions: Based on these results, IgM/IgG V may be a clinically and histologically different entity from IgA V. However, further studies are necessary to define the differences between them more clearly.

KEYWORDS

IgA vasculitis, IgM/IgG vasculitis, livedo lesion, neutrophil, palpable purpura

1 | INTRODUCTION

The 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012) showed the definition of vasculitis.¹ However, CHCC2012 did not explicitly discuss

the presence of skin-limited or skin-dominant forms of vasculitis. Therefore, cutaneous small-vessel vasculitis was defined as a distinct entity differing from systemic vasculitides in the dermatologic addendum to CHCC2012.² Cutaneous IgM/IgG vasculitis (IgM/IgG V) is characterized by a leukocytoclastic pattern histologically,

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and direct immunofluorescence (DIF) studies show IgM- or IgG-dominant or codominant perivascular deposition.

IgA vasculitis (IgA V) is the most common small-vessel leukocytoclastic vasculitis (LCV).^{2,3} However, the clinical differences between skin-limited IgM/IgG V and skin-limited IgA V have not been fully studied.⁴ Thus, in the present study, we assessed the clinical and histopathological differences between IgM/IgG V and IgA V.

2 | METHODS

2.1 | Patients

We examined adult Japanese patients aged > 15 years with skin-limited IgA V and IgM/IgG V, retrospectively. The patients were diagnosed based on clinical and histological findings, and the results of DIF studies in our department from January 2009 to December 2019. Only skin-limited IgA V and IgM/IgG V were enrolled. The cases associated with probable etiologies (eg, infection, malignancy, collagen diseases, or drug-induced) were excluded. Consequently, the IgM/IgG V group included 14 patients (eight men and six women) (50.9 ± 24.9 years) and the IgA V group included 24 patients (three men and 21 women) (49.5 ± 21.1 years).

2.2 | Methods

We compared the types and localization of skin lesions between the two groups. Laboratory data, including peripheral blood counts, serum levels of IgG, IgA, and IgM, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and complement (C3, C4, and CH50), were compared. In addition, the values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, and antistreptolysin-O (ASO) were measured. Systemic therapies and the clinical course were compared.

Histologically, cell infiltration of neutrophils, lymphocytes, eosinophils, and histiocytes, and nuclear dusts in the dermis were evaluated in four different high-power fields (HPF) (400×).

Immunohistochemical staining was performed using monoclonal antibodies against CD3 (LN10, Novocastra), CD4 (SP35, Cell Marque), CD8 (4B11, Novocastra), CD20 (L261.3.4, DAKO), and CD56 (123C3.D5, Novus Bio), and the cell numbers positively stained were determined in four different HPF (400×). DIF study of the lesional skin was performed using polyclonal antibodies to IgG, IgA, IgM, and C3 (Cappel) and monoclonal antibodies to C1q (FMC 75, Novus Bio).

2.3 | Statistical analyses

Statistical analyses were performed using chi-square and two-tailed Student's *t*-tests, and Mann-Whitney *U* test. Statistical significance was defined as a *p* value of < 0.05.

3 | RESULTS

3.1 | Clinical features

Livedo lesions were observed more often in IgM/IgG V than IgA V. Palpable purpura appeared more often in IgA V than in IgM/IgG V patients. However, there were no differences in induration, non-palpable purpura, ulcer, blood blisters, and erythema. Localization of the skin lesions was mostly in the lower legs in both groups. Skin eruptions limited to the lower legs were more frequently in IgM/IgG V (Table 1). The duration from onset to biopsy was not significantly different between the two groups (Table 1).

3.2 | Laboratory data

There were no statistical differences in peripheral blood cell counts between the two groups. IgG levels were higher than normal ranges in six patients of both groups. IgA levels were higher than normal ranges in five out of 24 IgA V (20.8%) and four out of 14 IgM/IgG V (28.6%) patients. IgM levels were higher in three out of 24 IgA V (12.5%) and 2 out of 14 IgM/IgG V (14.3%) patients. There were no differences in IgG, IgA, and IgM levels between the two groups. Serum ASO levels were slightly elevated in two out of 19 IgA V patients tested (11%). However, no antecedent symptoms of upper respiratory inflammation were noticed in these two patients. Serum ASO levels were not elevated in all 3 IgM/IgG V patients tested.

3.3 | Histological findings

Both groups showed damage to the capillaries mainly in the upper dermis (Figure 1). The association between the depth of affecting vessels and clinical features was not found. The numbers of infiltrated neutrophils and nuclear dusts were lower in the IgM/IgG V (Table 1).

Immunohistochemical analyses showed CD3⁺, CD4⁺, and CD8⁺ T cells infiltrated around capillaries in the upper dermis of these two groups (Figure 1), but few CD20⁺ B cells and CD56⁺ cells. The numbers of CD3⁺ and CD8⁺ T cells were significantly higher in IgA V.

Of the 14 IgM/IgG group, 2 were positive for IgG only, 10 for IgM only, and two for both IgG and IgM on the vessels in the upper dermis by DIF study. C3 and C1q deposition was observed in the upper dermis of 10 (71.4%) and 1 (7.1%) of 14 IgM/IgG V cases, respectively. C3 and C1q deposition was observed in the upper dermis of 20 (83.3%) and 1 (4.2%) of 24 IgA V cases, respectively (Table 1).

3.4 | Treatments and clinical courses

Systemic steroids were given to IgA V patients significantly more often (Table 2). Skin eruptions disappeared in all patients of both groups after 2-3 weeks. Afterward, 19 patients with IgA V and 10

TABLE 1 Comparison of clinical findings between IgA vasculitis and IgM/IgG vasculitis

	IgA vasculitis n = 24 (%)	IgM/IgG vasculitis n = 14 (%)	p value
(A) Background			
Gender (woman)	21 (87.5)	6 (42.9)	<0.01**
Age	49.5 ± 21.1	50.9 ± 24.9	1.000
Time from onset to biopsy (day)	10.8 ± 10.2	12.9 ± 11.0	0.682
(B) Skin eruption			
Palpable purpura	24 (100)	5 (35.7)	<0.001***
Non-palpable purpura	18 (75)	10 (71.4)	1.000
Livedo lesion	0 (0)	4 (28.6)	<0.01**
Induration	12 (50)	7 (50)	1.000
Ulcer	3 (12.5)	2 (14.3)	0.875
Blood blister	1 (4.2)	1 (7.1)	0.692
Erythema	1 (4.2)	2 (14.3)	0.264
(C) Localization of skin eruptions			
Only lower legs	7 (29.2)	9 (64.3)	<0.05*
Lower legs and thighs	10 (41.7)	0 (0)	<0.01**
Four extremities	2 (8.3)	2 (14.3)	0.564
Lower extremities and trunk	3 (12.5)	2 (14.3)	0.875
Four extremities and trunk	2 (8.3)	1 (7.1)	0.896
(D) Laboratory examination ^a			
Leukocyte count (/μL)	7993.0 ± 3379.3	7000.4 ± 5165.8	0.470
Neutrophil count (/μL)	5434.5 ± 3180.7	4328.8 ± 3956.9	0.383
IgG (mg/dL)	1447.5 ± 438.4	1734.1 ± 663.3	0.139
IgM (mg/dL)	141.4 ± 107.5	135.9 ± 109.1	0.891
IgA (mg/dL)	309.9 ± 108.5	316.6 ± 179.9	0.893
CRP (mg/dL)	3.42 ± 6.14	3.99 ± 5.94	0.0648
AST (IU/L)	25.5 ± 16.8	30.7 ± 32.8	0.528
ALT (IU/L)	19.3 ± 12.7	22.8 ± 17.0	0.487
BUN (mg/dL)	14.2 ± 4.82	17.5 ± 8.51	0.199
Creatinine (mg/dL)	0.680 ± 0.233	0.791 ± 0.298	0.214
ESR 60 min (mm)	41.0 ± 25.2	31.1 ± 37.8	0.448
(E) Histological findings ^b			
Lymphocytes	62.7 ± 52.1	66.6 ± 40.7	0.808
Eosinophils	0.541 ± 0.8	8.00 ± 8.43	0.0632
Neutrophils	10.5 ± 4.53	1.54 ± 1.23	<0.001***
Nuclear dusts	18.4 ± 11.9	8.71 ± 8.31	<0.001***
CD4 ⁺ Tcells	16.2 ± 1.63	14.7 ± 2.90	0.655
CD8 ⁺ Tcells	6.33 ± 4.28	3.23 ± 3.21	<0.05*
CD3 ⁺ T cells	21.8 ± 2.39	13.9 ± 2.95	<0.05*
Depth of affecting vessels ^c			
Upper dermis	18 (75)	9(64.3)	0.712
Upper to mid-dermis	6 (25)	5 (35.7)	0.712
(E) Deposition by DIF study			
IgA	24 (100)	0 (0)	<0.001***
IgM	0 (0)	12 (85.7)	<0.001***

(Continues)

TABLE 1 (Continued)

	IgA vasculitis n = 24 (%)	IgM/IgG vasculitis n = 14 (%)	p value
IgG	0 (0)	4 (28.6)	<0.01**
IgM + IgG	0 (0)	2(14.3)	0.0571
C3	20 (83.3)	10 (71.4)	0.385
C1q	1(4.2)	1 (7.1)	0.692

Note: Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; DIF, direct immunofluorescence; ESR, erythrocyte sedimentation rate.

aThe data at the first visit.

bThe numbers of cells or nuclear dusts evaluated in high-power fields.

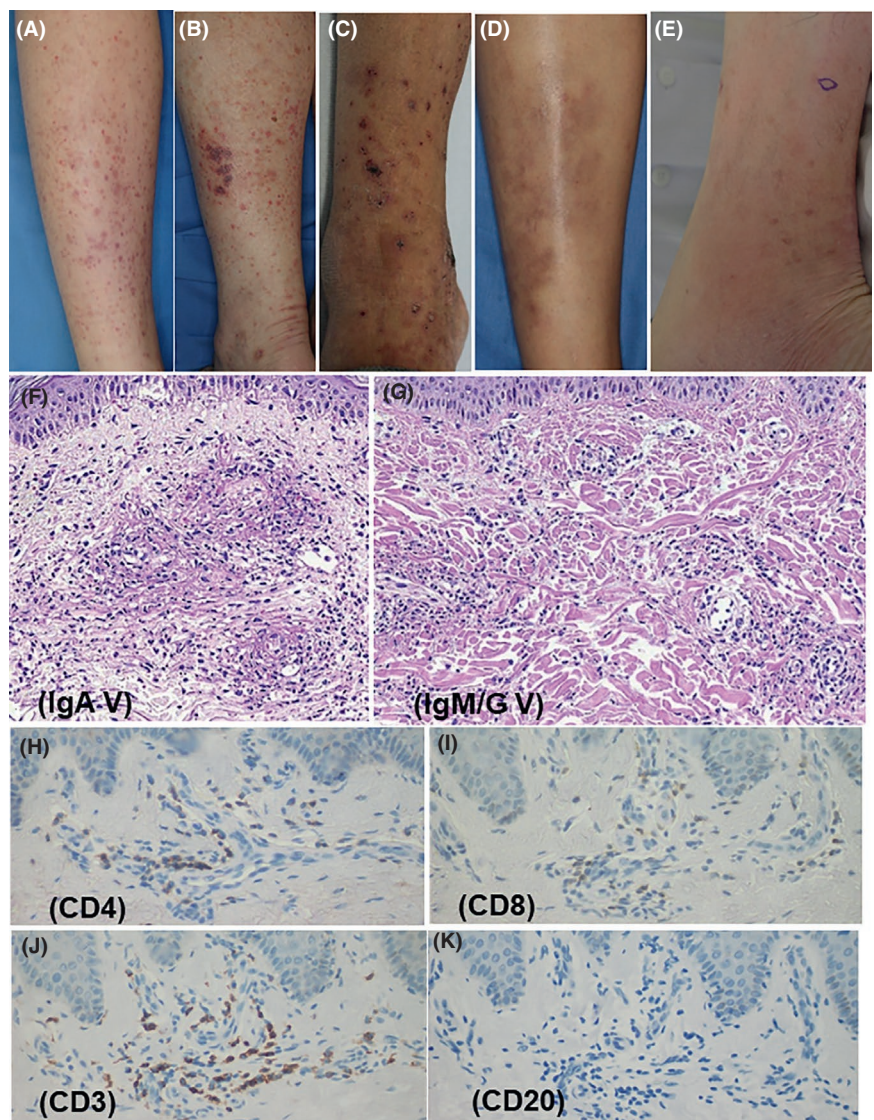
cThe numbers of patients with the depth of mainly affecting vessels in the dermis (%).

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$.

FIGURE 1 Representative clinical findings (A-E), histopathological findings by hematoxylin and eosin stain (F, G), and immunohistochemical stain of the lesion of IgM vasculitis (H-K). A: palpable purpura, B: blood blister and crusts, C: small ulcer, D: induration and livedo lesion, E: erythema. A-C, show IgA vasculitis cases, and D-E show IgM vasculitis cases. F: IgA vasculitis, G: IgM vasculitis. H: CD4, I: CD8, J: CD3, and K: CD20



	IgA vasculitis n = 24 (%)	IgM/IgG vasculitis n = 14 (%)	p value
(A) Treatments			
Corticosteroids	15 (62.5)	4 (28.6)	0.0436*
Vitamin C + Tranexamic acid	6 (25)	3 (21.4)	0.803
Diaphenylsulfone	3 (12.5)	1 (7.1)	0.604
Minocycline	1 (4.2)	0 (0)	0.439
Azathioprine	0 (0)	1 (7.1)	0.185
Aspirin	0 (0)	1 (7.1)	0.185
(B) Time course			
Follow-up period (month)	5.47 ± 3.14	5.95 ± 3.41	0.663
Time from onset to initial remission (day)	25.5 ± 12.4	26.7 ± 13.5	0.809
Recurrence within 6 months (patients)	3/19 (15.8%)	0 (0%)	0.185

Note: $p < 0.05$.

patients with IgM/IgG V were followed for at least 3 months. Three out of 19 IgA V patients (15.8%) had recurrence, but none with IgM/IgG V (Table 2).

4 | DISCUSSION

Skin eruptions of IgA V are characterized mainly by palpable purpura⁵⁻⁸ with a predilection for the lower legs.^{3,4} Although skin involvement is the most frequent in IgA V, systemic involvement is observed in 25%–70% of cases.^{5,9-11} Immune complex-mediated vasculitis is subdivided to LCV with or without deposition of IgA-containing immune complexes; the latter includes IgM/IgG-associated LCV.¹² IgM/IgG V patients do not show any systemic symptoms according to previous reports.^{2,4,12} Thus, IgM/IgG V patients were compared to skin-limited IgA V in our study.

A recent study⁴ has shown that blood blisters are significantly more frequent in IgA V than in IgM/IgG V, as well as targetoid lesions that are absent in IgM/IgG V patients.⁴ This suggests that these two features may help discriminate the two forms.⁴ In our study, livedo lesions appeared more often in IgM/IgG V, and palpable purpura was more common in IgA V (Table 1).

IgM deposition in IgA V lesions is correlated with renal involvement.¹³ However, in our study, IgA V with additional IgM or IgG deposition were excluded to compare between pure skin-limited IgA V and skin-limited IgM/IgG V. Thus, further studies are needed to define the association between the distribution of skin lesions and systemic involvement.

This is the first study which shows histological differences between skin-limited IgA V and IgM/IgG V. Histopathological findings showed more neutrophil infiltration and nuclear dusts in IgA V. In small-vessel vasculitis, CD4⁺ T cells produce cytokines, notably IL-1, interferon- γ , and tumor necrosis factor (TNF)- α and recruit cytotoxic T cells, B cells, and NK cells, which play a part in the inflammatory

TABLE 2 Comparison of systemic treatments and recurrence between IgA vasculitis and IgM/IgG vasculitis

network. There are two distinct cellular patterns in LCV; one rich in neutrophils and another in lymphocytes.¹⁴ The neutrophil infiltrate regresses with the persistence of an infiltrate of mononuclear cells. Thus, the number of infiltrated neutrophils may be associated with histological changes during an earlier period from the onset. Therefore, differences in infiltrating cell counts may depend on when the biopsy is performed. In our study, IgA V showed infiltration with more neutrophils, CD8⁺ T cells, and CD3⁺ T cells in IgA V than IgM/IgG V group. However, the time between onset and biopsy was not significantly different, suggesting other factors for the differences. The profiles of infiltrated cells may be related to the different clinical features between the two groups.

IgA V is usually considered as a self-limited disease with remission within 4–6 weeks in children, though adult patients require more aggressive treatment.⁵ Systemic steroids were administered in 30.8% of IgA V patients as the first-line treatment.⁵ In our study, systemic steroids were administered to more patients with IgA V. According to a previous report,⁴ symptoms recur in 24.4% of patients with IgM/IgG V and 35.7% of those with IgA V, and the time from onset to initial remission is significantly longer in IgA V. In the present study, the IgM/IgG V did not recur, and the time from onset to initial remission did not differ between two groups. As limitations of our study include the small sample size, further studies are required for completely assessing the differences between IgM/IgG and IgA V.

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CONFLICT OF INTEREST

The authors declares no conflict of interest.

DECLARATION SECTION

Approval of the Research Protocol: The study protocol was approved by the ethics committee of Gifu University Graduate School

of Medicine (#2019-285). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki.

Informed Consent: Since this study was a retrospective study, explanations and consents to patients were made by opting out on the Gifu University website.

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