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BRIEF REPORT

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The frequency of peripheral blood eosinophilia and its clinical significance in patients with dermatomyositis

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Abstract: In connective tissue diseases, eosinophil is thought to varying extents to be involved in the pathogenesis. Increased eosinophils in the skin tissues of patients with dermatomyositis (DM) have been reported, but there have been no investigations of blood eosinophilia in patients with DM. This study is the aim of determining the frequency of peripheral blood eosinophilia and elucidating its clinical significance. We retrospectively collected the clinical records of 48 patients (15 men and 35 women) who were diagnosed with classical DM (n = 34), ADM (n = 13), and JDM (n = 1), on the basis of the 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies. Eosinophil count ≥ 400/mm^3 was observed in 14.6% (n = 7) of the patients, while 4.2% (n = 2) of patients had eosinophil counts >1,000/mm^3. Regarding the clinical significance of peripheral blood eosinophilia in DM patients, in seven patients with increased blood eosinophil counts, the prevalence of Gottron's sign/papules, heliotrope rash, V-neck sign, shawl sign, pruritus, internal malignancy, and positive anti-TIF1-γ antibody were more frequent than in those without (85.7% , 85.7%, 71.4%, 71.4%, 85.7%, 42.9%, 28.6% *vs.* 92.7% p = 0.48, 61.0% p = 0.40, 36.6% p = 0.11, 39.0% p = 0.22, 36.6% p = 0.034, 19.5% p = 0.33, and 19.5% p = 0.63, respectively). Among them, pruritus was more common in patients with elevated eosinophil counts with statistical significance. The activity of eosinophilia and severity of skin eruptions also tended to be correlated. In summary, our study suggests that blood eosinophilia is correlated with the presence of pruritus, but not disease-associated autoantibodies or internal malignancy.

***Keywords*:** dermatomyositis, eosinophilia, peripheral blood, pruritus, rash

Introduction

Idiopathic inflammatory myopathies are heterogeneous autoimmune disorders that include polymyositis, dermatomyositis (DM) and inclusion body myositis (*1*). Among them, the 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies distinguished between classical DM, amyopathic DM (ADM) and juvenile DM (JDM).

As representative skin manifestations of DM, heliotrope rash and Gottron's sign/papules are included in the diagnostic criteria, and they are thought to be induced by chronic physiological stimuli (*2*). V-neck sign and shawl sign may be induced by the photosensitivity characteristic of this disease. In addition, vasculopathy including skin ulcers is also seen in DM, especially in patients with anti-melanoma differentiation-associated gene 5 (MDA5) antibody (*3*). These skin eruptions are often accompanied by pruritus, which is more common in patients that are positive for anti-transcriptional intermediary factor (TIF) 1-γ antibody (*4*).

Eosinophils have diverse roles in human diseases. They express various pattern recognition receptors, including toll-like receptors, nucleotide-binding oligomerization domain-like receptors, and G protein-coupled, Fc, chemokine, adhesion, and cytokine receptors (*5*). Stimulation of these receptors induces degranulation of toxic granule proteins such as eosinophil peroxidase, eosinophil cationic protein, eosinophil-derived neurotoxin, and major basic protein. Synthesis of nitric oxide, the release of cytokines or chemokines, and cell trafficking are also activated. Through these processes, eosinophils contribute to host defense as innate immune cells. In connective tissue diseases, eosinophil is thought to varying extents to be involved in their pathogenesis. For example, eosinophils play significant roles in the

pathogenesis of systemic vasculitis such as eosinophilic granulomatosis with polyangiitis or eosinophilic fasciitis.

On the other hand, peripheral blood eosinophilia can be primary or secondary, and most cases are secondary (*e.g.*, drug, bronchial asthma, atopic dermatitis, parasitic infections, malignant tumors, and autoimmune diseases). Among autoimmune diseases, several studies have focused upon blood eosinophilia in primary biliary chlangitis, found in more than 50% of patients (*6*). Eosinophilia in rheumatoid arthritis (RA) has been reported, and the frequency of eosinophilia in Argentinian patients with RA was 7% (*7*). In the peripheral blood of patients with systemic sclerosis (SSc), an eosinophil count of > 300/mm^3 or > 1,000 mm^3 can be seen in 16% or 1% of patients, respectively (*8,9*). We previously analyzed the correlation between vascular abnormalities and peripheral blood eosinophils in SSc patients; the timing of the emergence of the maximum blood eosinophil counts was related to ulcer development (*10*).

There can also be increased eosinophils in the skin tissues of patients with DM (*11*). However, there has not yet been a proper investigation of blood eosinophilia in DM patients. In the present study, we performed a retrospective analysis to determine the frequency of peripheral blood eosinophilia and to elucidate its clinical significance in DM patients.

Patients and Methods

Patient material and clinical assessment

This study was conducted in 2022 by retrospectively collecting the clinical records of 48 patients (15 men and 35 women) who were diagnosed with classical DM (n = 34), ADM (n = 13), and JDM (n = 1), on the basis of the 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies between 2009 and 2021 (*1*).

We excluded patients who lacked laboratory data, whose treatment (*e.g.*, immunosuppressive agents, glucocorticoids) had already been initiated, who already administrated anti-histamine drugs, who were accompanied by hematopoietic disorders, and who had complications that may alter peripheral blood eosinophil number (*e.g.*, allergic disorders).

Clinical and laboratory data were obtained at the time of the first visit to our hospital (Table 1). The average age of patients or duration of disease was 57.0 ± 16.2 years or 7.0 ± 12.8 months, respectively. Antinuclear antibodies (ANA) were detected by indirect immunofluorescence using HEp-2 cells as the substrate. Also, dermatomyositis-specific autoantibodies were examined by enzyme-linked immunosorbent assay (ELISA) or immunoprecipitation (IP) assay. The presence of clinical features including pruritus was determined by the description in medical records. Pruritus due to skin rash of dermatomyositis was focused, and those due to other diseases (*e.g.* urticaria) or drug-induced itchiness were excluded.

This study was approved by the Wakayama Medical University Institutional Review Board (No.3423) and written informed consents were obtained before patients were entered into this study, which was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analysis was assessed by Mann-Whitney *U*-test or Fisher's exact probability test for comparison of medians or percentages, respectively. Correlations were evaluated by Pearson's correlation. P values < 0.05 were considered to be statistically significant.

Results and Discussion

Clinical features of patients in this study

Forty-eight patients with classical DM (n = 34), ADM (n = 13), and JDM (n = 1) were retrospectively collected in this study. The clinical characteristics of patients

Table 1. Summary of clinical/serological features in patients with dermatomyositis (DM, n = 48)

Features	Values
Age at the first visit (mean years ± SD)	57.0 ± 16.2
Duration of disease (mean months ± SD)	7.0 ± 12.8
Type (classical DM:ADM:JDM)	34:13:1
CLINICAL FEATURES	
Gottron's sign/papules (%)	91.7
Heliotrope rash (%)	64.6
V-neck sign (%)	41.7
Shawl sign (%)	43.8
Pruritus (%)	43.8
Internal malignancy (%)	22.9
LABORATORY FEATURES	
CK (U/L)	1,302 ± 2,740.8
AST (U/L)	122.2 ± 130.9
ALT (U/L)	72.8 ± 71.7
LDH (U/L)	454.6 ± 235.1
ANA (> ×80)	37.5
anti-ARS antibody (%)	10.4
anti-MDA5antibody (%)	41.7
anti-TIF1-γ antibody (%)	20.8
anti-Mi2 antibody (%)	2.1
anti-NXP2 antibody (%)	2.1
Others (%)	22.9
ORGAN INVOLVEMENT	
Muscle (%)	70.8
Lung (%)	64.6
Dysphasia (%)	20.8
Joint (%)	35.4

Unless indicated, values are average ± standard deviation. DM, dermatomyositis; ADM, amyopathic dermatomyositis; JDM, juvenile dermatomyositis; CK, creatin kinase; ANA, antinuclear antibody; ARS, aminoacyl-tRNA synthetase antibody; MDA5, melanoma differentiation-associated gene 5 antibody; TIF1-γ, transcriptional intermediary factor 1-γ antibody; NXP-2, nuclear matrix protein. *p < 0.05, versus patients with normal blood eosinophil counts using Fisher test.

included in this study are shown in Table 1. As a result, the prevalence of patients with Gottron's sign/papules, heliotrope rash, V-neck sign, shawl sign, pruritus, and internal malignancy were 91.7%, 64.6%, 41.7%, 43.8%, 43.8%, and 22.9%, respectively. About 50% of patients with DM reportedly have moderate to severe pruritus, which is consistent with the present study (*12*).

Regarding autoantibodies associated with DM, the positivity of anti-aminoacyl-tRNA synthetase (ARS) antibody, anti-MDA5 antibody, anti-TIF1-γ antibody, anti-Mi2 antibody, and anti-nuclear matrix protein (NXP-2) antibody were 10.4%, 41.7%, 20.8%, 2.1%, and 2.1%, respectively. The most common organ involvement was skeletal muscle myopathy (70.8%), followed by interstitial lung disease (64.6%).

Correlation between serum eosinophil counts and clinical/serological features in patients with DM

In patients included in the present study (n = 48), blood eosinophil counts were 0-1,013/μl (average ± standard deviation = 184.7 ± 252.6/μl), whereas eosinophil percentages were 0-20% (2.93 ± 3.64%). Eosinophil count ≥ 400/mm^3 was observed in 14.6% (n = 7) of the patients, whereas 4.2% (n = 2) of patients showed eosinophil counts > 1,000/mm^3.

We examined the correlation of blood eosinophil counts with clinical and serological features in patients with classical DM/ADM/JDM (Table 2). If eosinophil count ≥ 400 /μl is defined as a significant increase, in seven patients with increased blood eosinophil counts, the frequency of Gottron's sign/papules (85.7%) was comparable with that in the patients with normal eosinophil counts (92.7%). In contrast, the prevalence of heliotrope rash, V-neck sign, shawl sign, pruritus, and internal malignancy were more frequent in patients with increased blood eosinophil counts (85.7%, 71.4%, 71.4%, 85.7% and 42.9% *vs.* 61.0%, 36.6%, 39.0%, 36.6%, and 19.5%, respectively). Among them, only the difference in frequency of pruritis was statistically significant (p = 0.034 by Fisher's exact probability test).

As for muscle involvement, levels of creatin kinase were not significantly higher in patients with elevated eosinophil counts than in those with normal eosinophil counts (1,732.9 ± 1,704.3 *vs.* 1,228.4 ± 2,874.3 U/L). Among disease-associated autoantibodies, the percentage of anti-MDA5 antibody was slightly lower and anti-TIF1-γ antibody higher in patients with increased blood

Table 2. Correlation of blood eosinophil levels with clinical/serological features in patients with dermatomyositis (DM, n = 48)

Features	Blood eosinophil counts		p value
	Patients with elevated (≥ 400/μL) eosinophil counts (n = 7)	Patients with normal (< 400/μL) eosinophil counts (n = 41)	
Age at the first visit (mean years ± SD)	59.0 ± 10.1	57.0 ± 16.8	
Duration of disease (mean months ± SD)	9.0 ± 16.1	6.0 ± 12.1	
Type (DM:ADM:JDM)	6:1:0	28:12:1	
CLINICAL FEATURES			
Gottron's sign/papules (%)	85.7	92.7	0.48
Heliotrope rash (%)	85.7	61.0	0.40
V-neck sign (%)	71.4	36.6	0.11
Shawl sign (%)	71.4	39.0	0.22
Pruritus (%)	85.7*	36.6	0.03
Internal malignancy (%)	42.9	19.5	0.33
LABORATORY FEATURES			
CK (U/L)	1732.9 ± 1704.3	1228.4 ± 2874.3	0.25
AST (U/L)	170.0 ± 156.4	114.0 ± 124.2	0.41
ALT (UL)	116.3 ± 124.7	65.4 ± 55.4	0.40
LDH (U/L)	519.6 ± 149.4	443.5 ± 245.1	0.12
ANA (> ×80)	71.4	28.6	0.09
anti-ARS antibody (%)	14.3	9.8	0.56
anti-MDA5antibody (%)	14.3	46.3	0.21
anti-TIF1-γ antibody (%)	28.6	19.5	0.63
anti-Mi2 antibody (%)	0	2.4	1.00
anti-NXP2 antibody (%)	14.3	0	0.15
Others (%)	28.6	22.0	0.65
ORGAN INVOLVEMENT			
Muscle (%)	85.7	68.3	0.66
Lung (%)	42.9	68.3	0.23
Dysphasia (%)	28.6	19.5	0.63
Joint (%)	14.3	39.0	0.40

Unless indicated, values are average±standard deviation. DM, dermatomyositis; ADM, amyopathic dermatomyositis; JDM, juvenile dermatomyositis; CK, creatin kinase; ANA, antinuclear antibody; ARS, aminoacyl-tRNA synthetase antibody; MDA5, melanoma differentiation-associated gene 5 antibody; TIF1-γ, transcriptional intermediary factor 1-γ antibody; NXP-2, nuclear matrix protein. *p < 0.05, versus patients with normal blood eosinophil counts using Fisher test.

eosinophil counts compared with those with normal eosinophil counts (14.3 and 28.6% *vs*. 46.3 and 19.5%, respectively).

DM patients with anti-TIF1-γ antibody or internal malignancy have been thought to be correlated with pruritic skin rash (*13,14*). However, in this study, the percentage of internal malignancy and positive anti-TIF1-γ antibody was slightly elevated in patients with increased blood eosinophil counts, but without statistically significant difference. Taken together, our study suggests that blood eosinophilia is correlated with the presence of pruritus, but not disease-associated autoantibodies or internal malignancy.

Clinical course and images of patients with increased blood eosinophil counts

Among the seven patients with increased blood eosinophil counts, the clinical courses of five patients were recorded (Figure 1). According to longitudinal data, the timing of emerging the increased eosinophil counts tended to be similar to that of the skin eruptions, before and after the treatment with glucocorticoid and/or immunosuppressive agents.

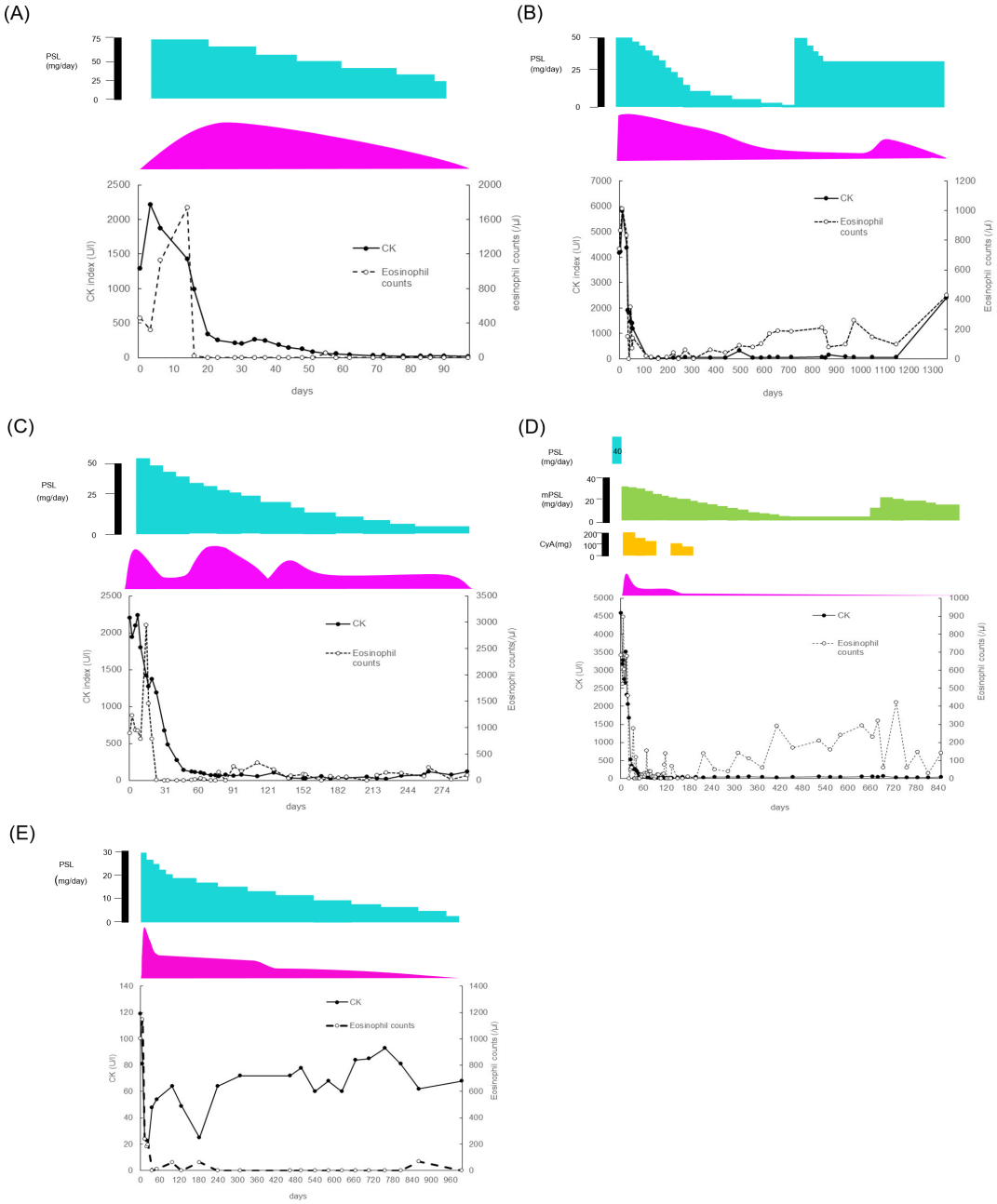

Figure 1. The clinical course of five patients with increased peripheral blood eosinophilia. CK, creatine kinase; PSL, prednisolone; DXS, dexamethasone; BMS, betamethasone; mPSL, methyl-prednisolone; CyA, Cyclosporin A; TAC, tacrolimus; IVCY, intravenous cyclophosphamide. Solid lines; serum CK levels, dotted lines; eosinophil counts. The severity of skin rash is indicated by the red graph.

A representative clinical picture of one of the seven patients with increased eosinophils (case A in Figure 1) is shown in Figure 2. The classical DM patient was positive for anti-NXP2 antibody, and skin manifestations included shawl sign, Gottron's sign, and periungual erythema. Blood eosinophil counts and CK levels at the initial visit were 459/μl (7.0%) and 1,287 U/l. The treatment with glucocorticoids rapidly reduced CK levels, blood eosinophil counts, and severity of skin eruption.

Our study indicated that there tends to be correlation between activity of eosinophilia and severity of skin eruptions in DM patients. We previously demonstrated that the timing of emerging of the maximum eosinophil counts was correlated with the ulcer development in SSc, and suggested the possibility that eosinophils may be involved in the pathogenesis of vascular dysfunction (*10*).

Eosinophils have reportedly been found in 10–20% of biopsies of DM skin lesions (*11,15,16*). Actually, eosinophils are one of the sources of IL-31, a cytokine that bridges inflammation and pruritus (*17*). Expression of IL-31 and IL-31 receptors in DM skin lesions were reported to be up-regulated compared with normal skin (*12*). Accordingly, eosinophils in the skin may be involved in the cause of pruritus in patients with DM. However, although skin biopsy specimen was available in five out of the seven patients with increased blood eosinophil counts, eosinophil infiltration in the dermis was not found in the five patients histopathologically. Thus, we could not prove the association between peripheral blood eosinophilia and eosinophil infiltration in skin tissue. Notably, Kumamoto *et al.* reported that eight out of 680 muscle biopsies of polymyositis patients were identified with > 0.3 eosinophils/mm^3 in the inflammatory infiltrate without concomitant peripheral eosinophilia (*18*). These patients tended to show a marked elevation of serum creatine kinase. Therefore, eosinophil infiltration in each tissue and peripheral blood is unlikely to correlate directly.

This is a pilot study with a small number of samples. To obtain more accurate and reliable data, a larger number of samples are necessary in future studies.

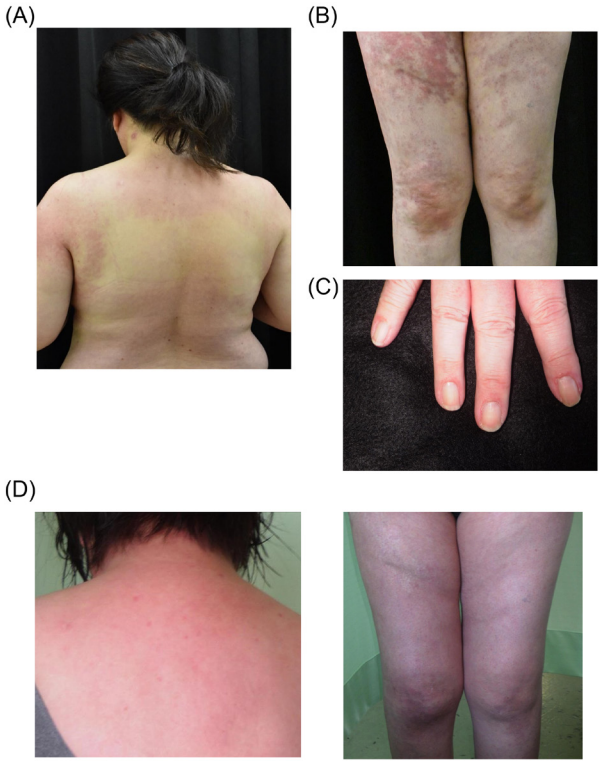

Figure 2. Clinical pictures of anti-NXP2 antibody-positive patients with classical DM (with clinical course shown in Figure 1A). (A) Shawl sign on the upper back and erythema on the lumbar region before treatment; **(B)** Erythema on the thighs and Gottron's sign on the knees before treatment; **(C)** Periungual erythema before treatment; **(D)** Eruption of the upper back and lumbar region after treatment on day 100; **(E)** Eruption of the thighs and knees after treatment on day 100.

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

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