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Original Article

Clinical Features and Treatment Response in Chronic Recurrent Erythema Multiforme: Difference Based on the Etiology Related to Herpes Simplex Virus

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ABSTRACT

Background: Erythema multiforme (EM) is typically a self-limited, acute hypersensitivity reaction. However, a subset of patients experiences chronic, recurrent episodes, for which clinical features and treatment strategies differ depending on the underlying etiology, especially in herpes simplex virus (HSV)-associated cases.
Objective: To investigate the clinical and phenotypic features of chronic recurrent EM and assess treatment responses, with a focus on differences based on HSV association.
Methods: This retrospective study included pathology-confirmed cases of suspected EM from 2010 to 2023. Forty patients with chronic EM (≥3 recurrences or persistent disease for ≥12 months) were included. Clinical, histopathologic, and serologic data were analysed. Patients were stratified into herpes simplex virus-associated erythema multiforme (HAEM) and non-HAEM groups. Clustering analysis was performed to identify clinical phenotypes. Treatment responses to antivirals and immunomodulators were evaluated.
Results: Of the 40 patients, 24 (60%) were classified as HAEM. HAEM patients showed more mucosal involvement, smaller targetoid lesions, and acral predominance, while non-HAEM patients had larger, coalescing lesions with more trunk involvement. Cluster analysis supported HSV as the major discriminating factor. Antiviral agents were effective in 87.5% of HAEM cases but ineffective in 76.9% of non-HAEM patients. Immunosuppressants such as cyclosporine and mycophenolate mofetil showed variable responses. Baricitinib induced complete remission in all 3 refractory cases.
Conclusion: HSV association defines a distinct clinical subtype of chronic recurrent EM, with differences in lesion morphology, distribution, and treatment response. Recognizing these patterns may guide targeted therapeutic strategies, including the potential use of Janus kinase inhibitors in refractory cases.

Keywords: Cluster analysis; Erythema multiforme; Herpes simplex virus; JAK inhibitor

INTRODUCTION

Erythema multiforme (EM) is an immune mediated hypersensitivity disease characterized by mucocutaneous involvement with erythematous papules, concentric changes preferentially occurring on extremities[1,2]. EM is usually considered an acute, self-limited disease, however, some patients experience multiple events of flares. The most common cause of EM is known as infections; representatively herpes simplex virus (HSV), *mycoplasma pneumoniae*, however, it is still unknown why some patients have recurrent flares and whether this 'rare' progression is a distinct phenotype of disease[3]. Also, little is known about clinical features of chronic EM so there remain questions such as 'clinical features of chronic EM,' 'the association of HSV,' and the 'treatment response.' Therefore, the aim of our study was to retrospectively elucidate the clinical features of patients with chronic EM, including the pattern of mucocutaneous manifestations, as well as onset, disease duration, association with HSV and therapeutic response.

MATERIALS AND METHODS

Study setting and retrieval of clinical information

This study utilized a retrospective cohort design and employed the Severance Clinical Research Analysis Portal version 2.0 at Severance Hospital for data collection. We identified a total of 713 patients who underwent skin biopsy due to a clinical suspicion of EM between 2010 and 2023 at the Severance Hospital. Detailed reviews were conducted on the medical records of patients who received a confirmed diagnosis of EM based on both clinical evidence and histopathological findings. This study was approved by the Institutional Review Board (IRB) at Severance Hospital, Seoul, Korea (IRB No. 4-2020-0027) and was conducted in accordance with the principles expressed in the Declaration of Helsinki.

Data assessment

Clinical diagnosis of EM was based on the presence of targetoid/non-targetoid erythema with or without mucosal involvement, and corroborated by histopathological evidence of lichenoid inflammation, basal vacuolar change, apoptotic keratinocytes, and epidermal necrosis[4]. Among 713 retrieved cases, 220 patients who fulfilled EM criteria based on these clinical and pathological definitions. Then, we excluded non-relapsing cases and obviously drug-induced EM-like eruptions. We defined chronic EM as a condition presenting with more than 3 times of recurrence or persistent eruption of EM for at least 12 months. Persistent disease was defined as continuous or nearly continuous presence of lesions for ≥12 months without complete resolution periods exceeding 4 weeks. These patients formed the primary subjects of our investigation (**Fig. 1**). The following parameters were evaluated for each patient: age, disease onset, disease duration, mucocutaneous manifestations, serologic test results, lesion distribution, and lesion size. Mucocutaneous manifestations were evaluated according to the following criteria: i) presence of a typical target lesion with concentric color variations, ii) distribution of skin and mucosal involvement and predominance of lesions (specifically oral mucosa, palms and soles), iii) lesion size concurrently considering the presence or absence of coalescing lesions. Lesion distribution analysis was based on cumulative involvement patterns documented throughout the entire disease course. Each anatomical site was recorded as involved if affected during at least one documented episode, with preference given to acute flare documentation when multiple records were available. Patients were evaluated for the potential cause of recurrent EM and classified as herpes simplex virus-associated erythema multiforme (HAEM) according to clinical and serological findings[5,6]. HSV association was determined based on reproducible temporal patterns of EM flares following HSV reactivation, combining patient history, physical examination findings, and laboratory results when available. This included temporal relationship (HSV preceding EM by 3–14 days), positive HSV serology (28/40 tested), recurrent herpes history, antiviral response, and exclusion of other triggers.

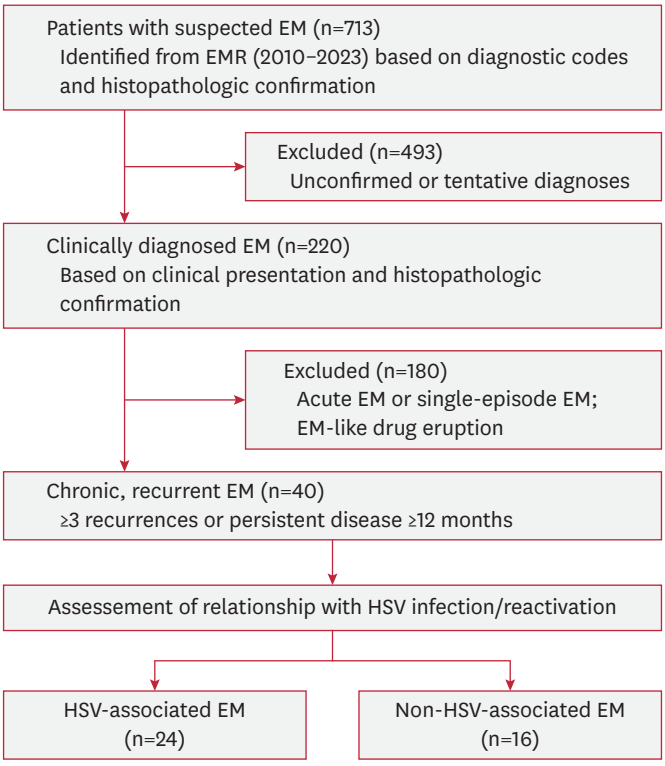

Fig. 1. Study flow and selection of chronic erythema multiforme patients. EM: erythema multiforme, EMR: electronic medical recode, HSV: herpes simplex virus.

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Treatment response assessment

Patients' responses to therapeutic interventions, which encompassed antiviral agents and other immunomodulators, were carefully assessed and classified into the following categories: i) complete response (CR): total resolution of pre-existing lesions without any recurrence, ii) partial response (PR): a reduction in the frequency of EM outbreaks and/or a decrease in the number of lesions, iii) no response (NR): the persistence of lesions with no discernible change in the frequency of outbreaks and/or the count of lesions. Treatment responses were assessed on a per-patient basis, representing overall therapeutic outcomes rather than episode-specific responses. Response duration was evaluated over a minimum follow-up period of 6 months.

Statistics

Categorical data are summarized and presented as frequencies and percentages, and were analysed using Fisher's exact test. Continuous variables are expressed as the means with standard deviations or as medians with interquartile ranges, and were compared using either Student's t-test for normally distributed variables or the Mann-Whitney U test for variables exhibiting a non-normal distribution. To elucidate the characteristic clinical feature of chronic EM, we assessed the association between each clinical feature using Fisher's exact test (α=0.05; 2-sided) and the following features were evaluated. In addition, to explore unbiased grouping patterns among patients, we performed an unsupervised clustering analysis using Gower's distance metric, incorporating both categorical and continuous variables, including mucosal involvement, lesion size, lesion shape, and acral predominance. The optimal number of clusters was determined based on silhouette width analysis. Differences in clinical characteristics between the clusters were then evaluated.

RESULTS

Demographics of chronic EM patients

During the study period (2010–2023), 40 patients were diagnosed clinically and histologically with chronic, persistent EM (**Table 1**). Among them, 27 (67.5%) patients were female and 13 (32.5%) were male which was consistent with previous studies[7]. The mean age of onset was 44.74 years (range 15–82 years), with a mean disease duration of 4.99 years (range 1–20 years). Of the 40 patients, 24 patients were clinically related to HSV infection/reactivation. None of the patients had clinical evidenced of *mycoplasma pneumoniae* nor hepatitis virus infection. Therefore, the patients were grouped into 2 subsets; 24 as HAEM and the remaining 16 as non-HAEM. Although the HAEM group had a longer mean disease duration compared to the non-HAEM group (5.43 vs. 4.34 years), the difference was not statistically significant (p=0.173, **Table 1**). However, this trend may suggest a possible association between HSV infection and prolonged disease persistence in chronic EM.

Table 1. Baseline characteristics of chronic recurrent erythema multiforme patients and distribution of skin lesions

Variables	Total	HAEM	Non-HAEM	*p*-value
No. of patient	40	24	16	
Onset age (yr)	44.74±17.44	47.33±19.78	40.60±12.37	0.246
Duration of disease*	4.99±4.25	5.43±4.38	4.34±4.11	0.173
Sex, female†	27 (68.5)	16 (66.7)	11 (68.8)	0.647
Serology for HSV				
IgG for HSV	21/28 tested	13/15 tested	5/13 tested	
IgM for HSV	5/26 tested	4/14 tested	0/12 tested	
Distribution†				
Face		2 (8.3)	3 (18.8)	0.373
Neck		2 (8.3)	3 (18.8)	0.373
Proximal arm		5 (20.8)	4 (25.0)	1.000
Distal arm		12 (50.0)	12 (75.0)	0.210
Hand		12 (50.0)	11 (68.8)	0.396
Chest		0	0	1.000
Abdomen		1 (4.2)	5 (31.2)	0.029
Back		2 (8.3)	4 (25.0)	0.195
Buttock		6 (25.0)	2 (12.5)	0.439
Inguinal		1 (4.2)	2 (12.5)	0.553
Thigh		4 (16.7)	5 (31.2)	0.441
Lower leg		11 (47.8)	10 (62.5)	0.564
Foot		8 (33.3)	4 (25.0)	0.729

Values are presented as number (%) or mean ± standard deviation.
HAEM: herpes simplex virus-associated erythema multiforme, HSV: herpes simplex virus.
*Mann-Whitney U test, †Fisher's exact test.

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Mucocutaneous clinical manifestations

To characterize the dermatologic manifestations of chronic EM, we evaluated the distribution of lesions across various body regions. Distribution of lesions of skin were evaluated by separation into 13 separate compartments: facial, neck, proximal arm, distal arm, hand, chest, abdomen, back, buttock, inguinal, thigh, lower leg and feet (**Table 1**). Interestingly, although abdominal involvement was observed significantly more frequently in non-HAEM patients compared to HAEM patients (31.2% vs. 4.2%, p=0.029), it remained a relatively minor proportion of the total lesion distribution. No other anatomical sites showed statistically significant differences in skin lesion distribution between the 2 groups. Of the 40 patients, 28 (70.0%) patients exhibited mucosal involvement, with the oral mucosa being the most frequently affected (62.5%). Four patients (10.0%) showed all 3 types (oral, genital, ocular) of mucosal involvement, all of whom were in the HAEM group (**Tables 2** and **3**).

Association with HSV as a predominant discriminating factor

We next conducted an unsupervised clustering analysis to gain unbiased insight into the dermatologic clinical features of chronic

Table 2. Mucocutaneous characteristics of chronic, recurrent erythema multiforme according to clinical clusters

Variables	Total (n=40)	Cluster 1 (n=14)	Cluster 2 (n=26)	*p*-value
Sex, female (%)		9 (64.3)	18 (69.2)	1.000
Onset age (yr)		36.46±12.66	48.88±18.22	0.034
Duration (yr)		4.21±4.08	5.42±4.36	0.401
Association with HSV	24 (60.0)	3 (21.4)	21 (80.8)	<0.01
Mucosal involvement				
Oral mucosa	25 (62.5)	6 (42.9)	19 (73.1)	0.123
Genital mucosa	10 (25.0)	2 (14.3)	8 (30.8)	0.226
Ocular involvement	5 (12.5)	1 (7.1)	4 (15.4)	0.418
All 3 mucosa (oral, genital, ocular)	4 (10.0)	0 (0.0)	4 (15.4)	0.160
Cheilitis with hemorrhagic crusts	6 (15.0)	1 (7.1)	5 (19.2)	0.299
Skin only	12 (30.0)	7 (50.0)	5 (19.2)	0.042
Lesion characteristics				
Predominant acral involvement	17 (42.5)	3 (21.4)	14 (53.8)	0.100
Predominant bullous lesion	12 (30.0)	7 (31.8)	5 (31.2)	0.063
Typical targetoid lesion	23 (57.5)	1 (7.1)	22 (84.6)	<0.001
Size of lesion				<0.001
Mostly small lesions (<3 cm)	26 (65.0)	2 (14.3)	24 (92.3)	
A few large lesions	10 (25.0)	8 (57.1)	2 (7.7)	
Confluent large lesions (>5 cm)	4 (10.0)	4 (28.6)	0 (0.0)	
Coalescence	12 (30.0)	10 (71.4)	2 (7.7)	<0.001

Values are presented as number (%) or mean ± standard deviation.
HSV: herpes simplex virus.

Table 3. Mucocutaneous characteristics of chronic, recurrent erythema multiforme based on HSV association

Variables	Total (n=40)	HAEM (n=24)	Non-HAEM (n=16)	*p*-value
Mucosal involvement	28 (70.0)	21 (87.5)	7 (43.8)	<0.01
Oral mucosa	25 (62.5)	18 (75.0)	7 (43.8)	0.956
Genital mucosa	10 (25.0)	9 (37.5)	1 (6.2)	0.030
Ocular involvement	5 (12.5)	4 (16.7)	1 (6.2)	0.631
All 3 mucosa (oral, genital, ocular)	4 (10.0)	4 (25.0)	0 (0.0)	0.171
Cheilitis with hemorrhagic crusts	6 (15.0)	6 (25.0)	0 (0.0)	0.065
Skin only	12 (30.0)	3 (12.5)	9 (56.3)	<0.01
Lesion characteristics				
Predominant acral involvement	17 (42.5)	14 (58.3)	3 (18.8)	0.031
Predominant bullous lesion	12 (30.0)	7 (31.8)	5 (31.2)	1.000
Typical targetoid lesion	23 (57.5)	18 (75.0)	5 (31.2)	0.016
Size of lesion				<0.001
Mostly small lesions (<3 cm)	26 (65.0)	21 (87.5)	5 (31.2)	
A few large lesions	10 (25.0)	1 (4.2)	9 (56.2)	
Confluent large lesions (>5 cm)	4 (10.0)	2 (8.3)	2 (12.5)	
Coalescence	12 (30.0)	3 (12.5)	9 (56.2)	0.005

Values are presented as number (%).
HAEM: herpes simplex virus-associated erythema multiforme.

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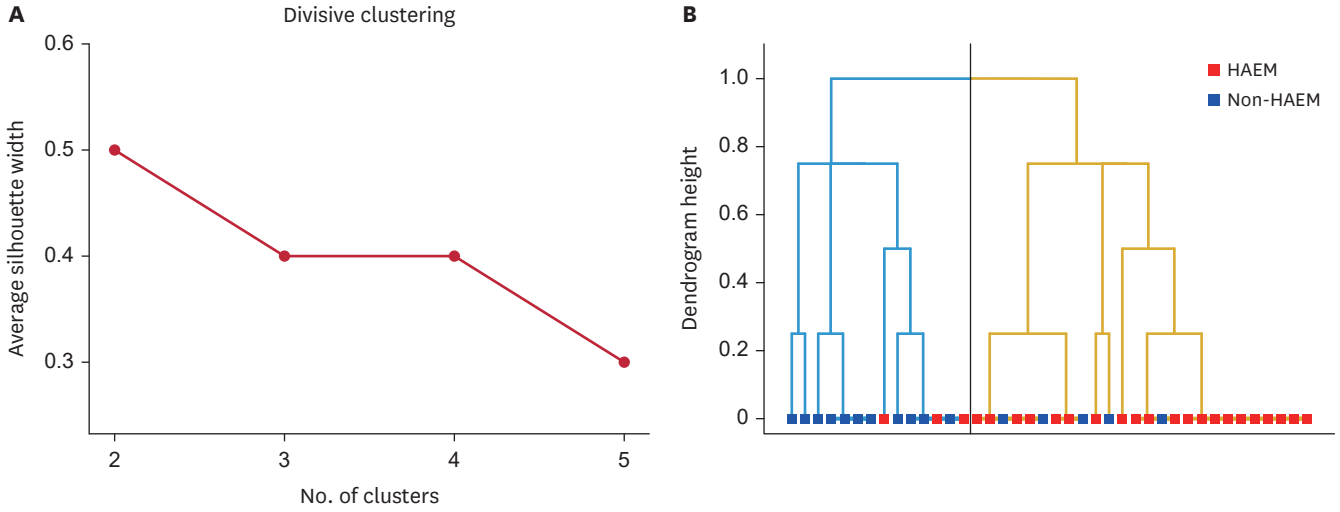

Fig. 2. Clustering analysis of patients based on clinical manifestations. (A) Silhouette width analysis for determining the optimal number of clusters. (B) Hierarchical clustering analysis of chronic erythema multiforme patients based on clinical variables. Dendrogram constructed using Gower's distance clustering, illustrating 2 primary clusters.
HAEM: herpes simplex virus-associated erythema multiforme.

EM. We used Gower's distance approach, incorporating 4 factors: i) mucosal involvement, ii) lesion size (specifically, whether the largest lesion size was above 3 cm), iii) lesion shape (if it was typical targetoid), and iv) acral predominance. Based on silhouette width analysis, we determined that 2 clusters (k=2) were optimal (**Fig. 2A**). Notably, the main distinguishing factor between 2 clusters was the relationship to HSV. Cluster 1 was predominantly composed of non-HAEM patients, while cluster 2 included a high proportion of HAEM patients (p<0.01) (**Fig. 2B**). Cluster 1 patients typically exhibited skin-dominant phenotypes, with less mucosal involvement and more acral lesions with atypical, non-targetoid features. The size of lesions in cluster 1 patients were typically larger than 3 cm, often leading to coalescence between neighbouring lesions (**Table 2**).

Different clinical features of non-HAEM and HAEM

Since the relationship to HSV was a dominant factor distinguishing between cluster1 and 2, we then evaluated the clinical differences between HAEM and non-HAEM (**Table 3**). As expected based on cluster analysis, HAEM patients had more mucosal involvement with predominant acral lesions. The lesions in HAEM were more targetoid, reflecting traditional characteristics of EM. Smaller lesions were more common among HAEM patients, whereas non-HAEM patients typically exhibited larger, coalescing lesions.

Distribution of lesions showed that chronic HAEM patients had more involvement on the peripheral area compared to central trunk which is consistent with the fact that lesion of EM is generally peripherally distributed on the limbs and acral portion (**Table 3**). However, non-HAEM patients had more involvement on the abdomen and back (**Table 1**), suggesting that it may be a distinctive distribution identifying the cause between HAEM and non-HAEM. Notably, 6 cases in the HAEM group exhibited severe hemorrhagic crusting that extended beyond the intraoral mucosa to involve the vermilion border, highlighting a potentially distinctive clinical feature of HAEM (**Table 3**).

Treatment response

The median follow-up duration was 24 months (range: 6–84 months) with 32/40 patients (80%) having ≥12 months follow-up. Most patients (92.5%) enrolled in this study had been treated with continuous or intermittent oral antiviral treatment (acyclovir, valacyclovir, famciclovir). As expected, HAEM patients showed greater response to antiviral agents (87.5%) and most non-HAEM patients did not show any effect to antiviral agents (76.9%) (**Table 4**). A total of 24 patients (14 [58.3%] in HAEM, 13 [81.3%] in non-HAEM) required immunosuppressants even with PR to antiviral agents. Since no standardized treatment guidelines exist for chronic EM and a wide range of immunosuppressants have been reported, we comprehensively evaluated the therapeutic responses of various immunomodulatory agents used in our cohort. Among them, cyclosporine and colchicine were the most frequently prescribed. Although CR was not achieved in any case treated with cyclosporine, the majority of patients demonstrated a PR, indicating its potential role in disease control. In contrast, colchicine exhibited limited efficacy, with a higher proportion of patients showing NR. These findings suggest that cyclosporine may be more effective than colchicine in attenuating disease activity, particularly in patients who fail to respond to antiviral therapy alone.

Table 4. Treatment modalities and response in chronic erythema multiforme

Variables	Total (n=40)	HAEM (n=24)	Non-HAEM (n=16)	*p*-value
Antiviral agents (%)				<0.001
No effect	12 (32.4)	2 (8.3)	10 (76.9)	
Partial response	15 (40.5)	12 (50.0)	3 (23.1)	
Complete response	9 (24.3)	9 (37.5)	0 (0.0)	
Adverse event	1 (2.7)	1 (4.2)	0 (0.0)	
Immunosuppressants	27 (67.5)	14 (58.3)	13 (81.3)	0.177
Colchicine (%)	15 (37.5)	11 (45.8)	4 (25.0)	1.000
No effect	9 (60.0)	7 (63.6)	2 (50.0)	
Partial response	6 (40.0)	4 (36.4)	2 (50.0)	
CSA (%)	14	4	10	0.580
No effect	2 (14.3)	1 (25.0)	1 (10.0)	
Partial response	10 (71.4)	2 (50.0)	8 (80.0)	
Complete response	1 (7.1)	0 (0.0)	1 (10.0)	
Adverse event	1 (7.1)	1 (25.0)	0 (0.0)	
Mycophenolate mofetil (%)	8	5	3	0.292
No effect	1 (12.5)	1 (20.0)	0 (0.0)	
Partial response	4 (50.0)	2 (40.0)	2 (66.7)	
Complete response	1 (12.5)	0 (0.0)	1 (33.3)	
Adverse event	2 (25.0)	2 (40.0)	0 (0.0)	
Azathioprine (%)	7	3	4	0.525
No effect	1 (14.3)	0 (0.0)	1 (25.0)	
Partial response	3 (42.9)	2 (66.7)	1 (25.0)	
Complete response	1 (14.3)	0 (0.0)	1 (25.0)	
Adverse event	2 (28.6)	1 (33.3)	1 (25.0)	
Dapsone (%)	7	3	4	0.030
Partial response	3 (42.9)	0 (0.0)	3 (75.0)	
Complete response	1 (14.3)	0 (0.0)	1 (25.0)	
Adverse event	3 (42.9)	3 (100.0)	0 (0.0)	
JAK inhibitor	3 (100.0)	1 (100.0)	2 (100.0)	1.000
Complete response	3 (100.0)	1 (100.0)	2 (100.0)	

Values are presented as number (%).
HAEM: herpes simplex virus-associated erythema multiforme, CSA: cyclosporine A, JAK: Janus kinase.

Mycophenolate mofetil, which was generally used as a third-line agent, demonstrated favorable outcomes in non-HAEM patients, with all 3 individuals showing either partial or CR. This success rate was notably higher than previously reported in general EM populations. In contrast, 5 HAEM patients received mycophenolate mofetil, and the treatment was unsuccessful in one patient, requiring escalation to other immunosuppressive therapies. Azathioprine also yielded clinical benefit in our cohort, with 4 patients (2 in the HAEM group and 2 in the non-HAEM group) showing partial or CR. Among the 24 patients treated with immunosuppressants, 3 continued to experience recurrent flares despite PRs, highlighting the need for alternative strategies in refractory cases. Given emerging evidence that Janus kinase (JAK) inhibitors can modulate cytotoxic lymphocyte activity implicated in EM pathogenesis, we administered baricitinib to 3 patients (1 HAEM and 2 non-HAEM). All 3 achieved CR and remained stable during follow-up, suggesting that JAK inhibition may represent a promising therapeutic option in chronic EM.

Short-term systemic corticosteroids used for acute flare management were permitted but not included in the treatment response analysis, which focused on maintenance therapies for chronic disease control and recurrence prevention.

DISCUSSION

Due to the diverse phenotypes and variable prognosis of EM, along with the rarity of progression to chronic, recurrent EM, limited studies have been conducted to understand the distressing disease. The clinical characteristics and management strategies are not well defined in recurrent EM and are based on small studies which in some cases encompass acute EM[8]. Some tried to classify separate EM into typical EM (typical targets on extremities) and atypical EM (extensive distribution, atypical, larger targets, involving skin around the mouth and eyes), but these classifications are not linked to clinical parameters such as prognosis (acute vs. chronic), demographic characteristics nor therapeutic strategies[9]. Also some studies include Stevens/Johnsons disease, toxic epidermal as part of the EM spectrum, leading to vague classification[6]. Therefore, this study is of value as it evaluates the clinical and phenotypic characteristics of recurrent EM patients.

Though the number of patients enrolled in this study was small, we have identified that recurrent EM patients were generally related to HSV or idiopathic[5]. *Mycoplasma pneumoniae* infection was not a leading cause of chronic EM[10,11]. Females were more

included in this study, suggesting that chronicity may be related to gender, which contrasts with previous studies reporting male predominance[12].

To focus on the skin manifestation of chronic EM, we have obtained dermatologic characteristics (shape, size, distribution, and mucosal involvement) to dissect differences among the cohort. Unexpectedly 2 clusters were identified and were dependent on HSV relationship (p<0.01). Patients who were classified as cluster 2 generally showed relationship to HSV. The HAEM patients showed aggravation related to HSV infection/reactivation, with greater mucosal involvement, typical targetoid lesions, and acral predominance[13]. Non-HAEM patients on the other hand had less mucosal involvement, and rather had large coalescing lesions. In general, extremities were more commonly involved than central trunk areas, which is consistent with previous acknowledgements. Non-HAEM, on the other hand relatively showed more involvement of central trunk, especially the abdomen area. Adding up these results confirm that the distribution is consistent with generally known concept that EM is more dominant in the peripheral area[1,3,6]. However, it seems that identification of the cause of EM may help understand the distribution more clearly, and can classify the distribution between HAEM and non-HAEM. This study cannot explain why the phenotype and allocation of lesions are different, however, it suggests that future studies should focus on identifying the underlying triggers of disease flares. Regarding the treatment aspect, as expected, patients who were identified HAEM generally showed a favorable response to antiviral treatment[5,8,14,15]. The poor or PR of antiviral agents necessitated the use of immunosuppressants[2,8]. The most selected 2nd line medications were colchicine and cyclosporine, which showed variable response[16]. Colchicine, as previously reported, was largely ineffective, while cyclosporine showed a modest therapeutic benefit[8]. Azathioprine, mycophenolate mofetil, and dapsone, though used in a limited number of patients, demonstrated encouraging results in chronic EM[15,17,18]. However, 1 in HAEM group and 2 in non-HAEM group did not show CR to traditional immunomodulators. Recent studies had shown promising results of JAK inhibitors in chronic EM, and therefore we have administered baricitinib to 3 patients[19]. All showed CR without any adverse events, confirming the potential therapeutic role of JAK inhibitors. Despite concerns regarding the risk of viral reactivation, baricitinib did not exacerbate HSV-related disease, suggesting that JAK inhibition may be safely and effectively used even in HAEM.

The key strength of our study is that we have precisely investigated the clinical aspects of chronic recurrent EM especially focused on the mucocutaneous factors. Also, patients included in this study were pathologically confirmed for EM, and had alternative diagnoses carefully excluded. Previous studies have shown characteristics of recurrent EM, however, this study has strength in that in focuses on the dermatologic characteristic scope and identification of difference focused on HSV. Overall, despite the limitations, our findings demonstrating the clinical distinctions between HSV-related and non-HSV-related chronic EM may facilitate deeper understanding of the pathophysiological basis of EM and guide more tailored treatment approaches.

Several limitations should be acknowledged. The small sample size (n=40) limits statistical power and generalizability, though our cohort represents one of the largest chronic recurrent EM series. The retrospective design introduces inherent biases, which we minimized through strict histological confirmation and standardized data collection. HSV association was determined using clinical criteria rather than PCR confirmation, though our multi-criteria approach aligns with established practice and the 87.5% antiviral response rate supports classification validity. Treatment heterogeneity reflects real-world practice but complicates efficacy interpretation. Finally, the minimum 6-month follow-up may be insufficient for long-term assessment. Despite these limitations, our findings provide valuable insights into chronic EM phenotypes and targeted treatment approaches. Future research directions should include prospective multi-center studies with standardized HSV diagnostic criteria, longer follow-up periods, and randomized controlled trials of emerging therapies like JAK inhibitors. Molecular studies investigating the pathophysiological differences between HAEM and non-HAEM subtypes may provide insights into targeted therapeutic approaches. Additionally, development of validated scoring systems for chronic EM severity and treatment response would facilitate standardized outcome assessment across studies.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

DATA SHARING STATEMENT

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

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