

The Serology of Some Microorganisms in Patients with Erythema Multiforme

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Abstract

Background Erythema multiforme (EM) is a mucocutaneous syndrome characterized by typical and/or atypical target-like lesions, with or without mucosal involvement. Etiology is often associated with the herpes simplex virus (HSV) or other microorganisms, rarely due to medication. Many cases have no identifiable cause.

Objective To investigate the seropositivity rates for several microorganisms in EM.

Methods This descriptive cross-sectional study was conducted on 54 EM patients and 30 healthy controls (HCs group). Serology was done by Enzyme Linked Immunosorbent Assay (ELISA) for herpes simplex virus 1/2 (HSV1/2) and *Mycoplasma pneumoniae* (MP), by Chemiluminescent Microparticle Immunoassay (CMIA) for cytomegalovirus (CMV) and Epstein-Barr virus (EBV).

Results There was no significant differences in the rates of IgM and IgG positivity for HSV1/2, CMV, EBV, and *M. pneumoniae* between the EM and HCs groups. Among EM patients, the rates of HSV-1/2-IgM positivity and MP-IgM positivity were higher in the group of under 30 years old compared to the group of ≥30 years old. The rate of positive MP-IgM was higher in the febrile group (77.78%) compared to the non-febrile group (15.56%); in the group with localized, acral lesions, the rate of positive EBV-IgM was higher, but the rate of positive HSV-1/2-IgG was lower compared to the group with diffuse lesions.

Conclusion The role of microorganisms in the pathogenesis of EM remains incompletely understood. However, in younger individuals (<30 years of age), EM may be associated with infection by HSV and/or *M. pneumoniae*. In febrile cases of EM, *M. pneumoniae* infection may be implicated, whereas localized, acral forms of EM may be associated with EBV infection.

Keywords Cytomegalovirus; Epstein-Barr virus; Erythema multiforme; *Mycoplasma pneumoniae*; Herpes Simplex virus.

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Introduction

Erythema multiforme (EM) is a mucocutaneous syndrome first described by Von Hebra in 1860. Characteristic cutaneous lesions include typical and/or atypical target lesions. The disease is

classified into a minor form, characterized by the absence of mucosal involvement with lesions confined to the skin and lips, and a major form, in which mucosal lesions are present.¹⁻³ Currently, EM is recognized as a distinct clinical entity, separate from the Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum, with unique clinical, epidemiological, and pathogenetic characteristics. Although generally benign, EM may recur frequently and result in complications, particularly ocular sequelae and post-inflammatory pigmentary

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changes. Sometimes, EM can be associated with an antibody-mediated disease such as IgM nephropathy. Regarding etiology, EM is most commonly associated with reactivation of herpes simplex virus (HSV) infection and only rarely induced by medications.⁴ Beyond HSV, many cases are associated with infection of *Mycoplasma pneumoniae* (MP). Evidence from previous studies and case reports has also suggested associations between EM and infections caused by COVID-19 vaccination,^{5,6} Orf virus,⁷ Epstein-Barr virus (EBV),^{8,9} cytomegalovirus (CMV).^{10,11} These cases are often characterized by recurrent, persistent, and treatment-resistant disease, showing poor responses to conventional therapies such as systemic corticosteroids and immunosuppressive agents but favorable responses to antiviral medications, including acyclovir and ganciclovir.⁹ In case of persistent EM, dapsone may have efficacy.¹²

In routine clinical practice, a considerable proportion of patients with EM have no identifiable cause, including no history of suspected drug exposure or HSV infection. The potential role of microbial etiologies has not been extensively investigated. Serological testing is a readily available diagnostic tool that is relatively easy to perform, provides rapid results, and may assist in the initial diagnostic evaluation. In contrast, other diagnostic methods, such as polymerase chain reaction (PCR) and microbial culture, require longer processing times, involve greater technical complexity, and may not be available in all healthcare settings. Therefore, this study was conducted to investigate serological evidence of infection with selected microorganisms in patients with EM and to evaluate their associations with disease characteristics.

Methods

This study was conducted among patients with EM treated at the National Hospital of Dermatology and Venereology and a group of healthy controls (HCs) between January to November 2024.

Patients presented with an acute onset of disease occurring after drug exposure, infection, or in the absence of an identifiable triggering factor. Cutaneous lesions consisted of typical target lesions (comprising three concentric zones: a central vesicle or dusky necrotic macule, surrounded by a paler intermediate ring and an outer erythematous raised ring) and/or atypical target lesions (consisting of only two concentric zones). Lesions were distributed predominantly on the acral sites (localized) or more diffusely. Mucosal involvement could be present or absent. The diagnosis of EM was established based on the clinical judgment of at least two physicians from the treating department, as no definitive gold standard currently exists for the diagnosis of EM, including histopathological examination.

In this study, the diagnosis of EM was mainly based on clinical presentation, particularly the presence of typical or atypical target lesions. Histopathological examination was not routinely performed because the clinical features were characteristic, the disease course was acute, and patients generally showed a rapid response to treatment.

Skin biopsy was only performed in patients whose clinical presentation raised suspicion for Sweet syndrome or other conditions in the differential diagnosis, such as bullous pemphigoid or paraneoplastic pemphigus. If the histopathological findings supported one of these alternative diagnoses, the patients were excluded from the study.

Inclusion criteria: Patients with a confirmed diagnosis of EM following diagnostic criteria mentioned above, regardless of age, who provided written informed consent to participate in the study, or whose legally authorized representatives provided written informed consent on their behalf. **Exclusion criteria:** Patients with sepsis (defined as a serum procalcitonin level >2 ng/mL and/ or a positive blood culture); with immunodeficiency disorders.

A total of 30 healthy individuals were recruited as HCs. These participants had no history of drug hypersensitivity and were free from infectious diseases, allergic disorders (including allergic rhinosinusitis, urticaria, vernal conjunctivitis, and bronchial asthma), as well as any other significant medical or surgical conditions.

Study Methods This was a cross-sectional descriptive. Study participants were consecutively enrolled in chronological order. The convenient sample consisted of 54 patients with EM and 30 HCs. All participants underwent medical history taking and clinical examination according to a standardized study case report form.

Serum samples were collected after obtaining written informed consent from patients, HCs, or their legally authorized representatives. For each participant, 4 mL of venous blood was drawn into a tube without anticoagulant for serum separation. Blood samples were kept at room temperature for 10-20 minutes and subsequently centrifuged at 2,000-3,000 r.p.m for 20 minutes. The separated serum was aliquoted and stored at -80°C until microbiological testing was performed.

Serum levels of HSV1/2 IgM and IgG, as well as *M. pneumoniae* IgM and IgG antibodies, were determined using enzyme-linked immunosorbent assay (ELISA). The following commercial ELISA kits were used: HSV1/2 antibodies: SERION ELISA classic Herpes Simplex Virus 1+2 IgG (catalog number: ESR105G); SERION ELISA classic Herpes Simplex Virus 1+2 IgM (catalog number: ESR105M). *Mycoplasma pneumoniae* antibodies: SERION ELISA classic *Mycoplasma pneumoniae* IgG (catalog number: ESR127G); SERION ELISA classic *Mycoplasma pneumoniae* IgM (catalog number: ESR127M).

All ELISA kits were manufactured by Institut Virion/ Serion GmbH (Würzburg, Germany).

Detection of EBV and CMV antibodies was

performed using a two-step chemiluminescent microparticle immunoassay (CMIA) for the qualitative detection of anti-EBV viral capsid antigen (VCA) IgM and IgG antibodies, as well as anti-CMV IgM and IgG antibodies, in human serum and plasma samples. The assay kits were manufactured by Abbott Ireland Diagnostics Division, Finisklin Business Park, Sligo, Ireland.

All serological testing was performed at Medlatec laboratory, Hanoi, Vietnam.

All data were checked and standardized before entry into the study database. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). The Chi-square test and Fisher's exact test were used to compare proportions between groups. A two-sided p-value of < 0.05 was considered statistically significant.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee for Biomedical Research of the National Hospital of Dermatology and Venereology (Approval No. 55/HĐĐĐ-BVDLTW; dated 13.11.2023).

Result

The EM and HCs groups were comparable in terms of age and sex distribution. Among patients with EM, 43 (79.63%) had no identifiable trigger, including no history of suspected drug exposure. Fever was observed in 9 patients (16.67%). Mucosal involvement, including the ocular, oral, and other mucosal sites, was present in 13 patients (24.07%). The majority of patients (48/54, 88.89%) exhibited a generalized distribution of skin lesions, whereas the remaining 6 patients (11.11%) had localized and acral lesions, with or without concomitant mucosal involvement (**Table 1**).

In both groups, the seropositivity rate for MP-IgM was higher than that for MP-IgG. In contrast, for the other microorganisms investigated, IgM

Table 1 Demographic and clinical characteristics of the two groups

Characteristic	EM group (n = 54)		HCs group (n = 30)	
	30	20 - 45	27.50	19 - 45
Age, median (IQR)				
Sex, n (%)				
Male	23	42.59	15	50
Female	31	57.41	15	50
Etiology (suspected medicines), n (%)				
Albendazole	1	1.85	NA	NA
Mifepristone	1	1.85	NA	NA
Dietary supplements	4	7.41	NA	NA
Traditional herbal medicine	1	1.85	NA	NA
Multiple medications	4	7.41	NA	NA
Unknown	43	79.63	NA	NA
Fever present, n (%)	9	16.67	NA	NA
Mucosal involvement present, n (%)	13	24.07	NA	NA
Ocular mucosal involvement, n (%)	2	3.70	NA	NA
Oral mucosal involvement, n (%)	8	14.81	NA	NA
Distribution, n (%)				
Generalized	48	88.89	NA	NA
Localized and acral sites, including mucosal involvement	6	11.11	NA	NA

IQR: interquartile range; NA: Non applicable.

Table 2 Comparison of seropositivity rates for selected microorganisms between patients with EM and healthy controls.

Antibodies	EM group (n = 54)		HCs group (n = 30)		P*
	n	%	n	%	
CMV-IgM	1	1.85	3	10	0.1278
CMV-IgG	54	100	30	100	1
EBV-IgM	5	9.26	1	3.33	0.4138
EBV-IgG	53	98.15	30	100	1
HSV1/2-IgM	12	22.22	2	6.67	0.0668 [†]
HSV1/2-IgG	47	87.04	29	96.67	0.249
MP-IgM	14	25.93	5	16.67	0.33115
MP-IgG	11	20.37	3	10	0.2217 [†]

*Fisher's exact test; [†]Chi-square test; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HSV: Herpes simplex virus; MP: *Mycoplasma pneumoniae*.

seropositivity rates were lower than the corresponding IgG seropositivity rates.

No significant differences in seropositivity rates were detected between patients with EM and HCs for any of the microorganisms examined (**Table 2**).

In the EM group, the seropositivity rates for HSV1/2-IgM and MP-IgM were significantly higher in patients aged <30 years compared with those aged ≥30 years ($P<.05$). In contrast, the seropositivity rate for HSV1/2-IgG was significantly higher in the ≥30-year age group than in the <30-year group ($P<.01$).

In the HCs group, no significant differences in these seropositivity rates were observed between participants aged <30 years and those aged ≥30 years (**Table 3**).

In patients with EM, the group with acral and localized lesions (e.g., lesions involving periorificial areas, hands, feet, knees, elbows, and shoulders) had a significantly higher rate of EBV-IgM seropositivity compared with the group with generalized lesions ($P<.01$). In contrast, the HSV1/2-IgG seropositivity rate was significantly higher in patients with generalized lesions than in those with acral and localized lesions ($P<.05$) (**Table 4**).

In the EM group, the seropositivity rate for MP-IgM was significantly higher in patients with fever (77.78%) than in those without fever (15.56%) ($P<.001$) (**Table 5**).

Discussion

CMV-IgM seropositivity was detected in 1.85% of EM patients (one 3-year-old boy presenting with fever and no identifiable trigger; this

patient was also positive for HSV1/2-IgM and MP-IgM), compared with 10% in the HCs group. Previous reports have suggested a possible role of CMV in EM pathogenesis. Seishima *et al.* described five patients with fever, sore throat, predominantly acral target lesions, and spontaneous resolution within one week; CMV-IgM titers declined after 2-3 months, while CMV-IgG seroconversion was observed in initially seronegative patients.¹⁰ Similarly, Petrosino reported a 7-year-old boy who developed fever, sore throat, and target lesions on the ears and face, with isolated CMV-IgM positivity followed by a marked rise in CMV-IgG four weeks

Table 3 Comparison of seropositivity rates for selected microorganisms by age group.

Groups	Antibodies	< 30-year age group		≥ 30-year age group		P*
		n	%	n	%	
EM	n		25		29	
	CMV-IgM	1	4	0	0	0.463
	CMV-IgG	25	100	29	100	1
	EBV-IgM	4	16	1	3.45	0.1704
	EBV-IgG	24	96	29	100	0.463
	HSV1/2-IgM	9	36	3	10.34	0.0238†
	HSV1/2-IgG	18	72	29	100	0.0027
	MP-IgM	10	40	4	13.79	0.0284†
HCs	MP-IgG	3	12	8	27.59	0.1562†
	n		15		15	
	CMV-IgM	1	6.67	2	13.33	1
	CMV-IgG	15	100	15	100	1
	EBV-IgM	1	6.67	0	0	1
	EBV-IgG	15	100	15	100	1
	HSV1/2-IgM	2	13.33	0	0	0.4828
	HSV1/2-IgG	14	93.33	15	100	1
	MP-IgM	4	26.67	1	6.67	0.3295
	MP-IgG	3	20	0	0	0.2241

*Fisher's exact test; † Chi-square test; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HSV: Herpes simplex virus; MP: *Mycoplasma pneumoniae*.

Table 4 Seropositivity rates for selected microorganisms in the EM group according to lesion distribution.

Antibodies	Generalized (n = 48)		Localized, acral sites (n = 6)		P*
	n	%	n	%	
CMV-IgM	1	2.08	0	0	1
CMV-IgG	48	100	6	100	1
EBV-IgM	2	4.17	3	50	0.0074
EBV-IgG	47	97.92	6	100	1
HSV1/2-IgM	9	18.75	3	50	0.1156
HSV1/2-IgG	44	91.67	3	50	0.0235
MP-IgM	12	25	2	33.33	0.6433
MP-IgG	10	20.83	1	16.67	1

*Fisher's exact test; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HSV: Herpes simplex virus; MP: *Mycoplasma pneumoniae*.

later, supporting acute CMV infection as a potential trigger of EM.¹¹

EBV-IgM seropositivity was observed in 9.26% of EM patients and 3.33% of HCs. Within the EM group, positivity was higher in patients with localized and acral lesions than in those with generalized lesions (50% vs. 4.17%). Viral infections may increase susceptibility to drug-induced hypersensitivity through altered antigen

presentation, changes in drug metabolism, or immune dysregulation. Although the role of EBV in EM remains uncertain, interactions between EBV infection and medications may contribute to disease development. Chen *et al.* detected EBV-specific gene sequences in lesional skin from only 2 of 32 EM patients, suggesting that EBV is unlikely to be a major pathogenic factor.¹³ Nevertheless, Gonzalez-Delgado reported EM following amoxicillin-clavulanic acid treatment in a child with acute EBV infection,⁸ while Turnbull described persistent, treatment-refractory EM associated with EBV that improved after antiviral therapy.⁹

HSV is the most extensively documented etiological factor associated with EM. In a study of 63 histopathologically confirmed EM cases, HSV-DNA was detected in 42.9% of HSV-associated EM and 43.8% of idiopathic EM, whereas no HSV-DNA was found in drug-induced EM or Stevens-Johnson syndrome.¹⁴ Other studies have similarly demonstrated HSV-

DNA in EM lesions.^{15,16} In our study, HSV1/2-IgM positivity indicated recent or reactivated HSV infection, supporting HSV as a potential trigger. However, HSV-DNA-PCR was not performed on skin tissue; therefore, direct evidence of viral DNA in lesional skin was lacking. Serological responses generally develop within 2-3 weeks after infection, although antibodies may remain undetectable for several months; repeat testing after 6-12 weeks is recommended when HSV infection is suspected.¹⁷

Table 5 Seropositivity rates for selected microorganisms in the EM group according to fever status.

Antibodies	Fever (n = 9)		No fever (n = 45)		P*
	n	%	n	%	
CMV-IgM	1	11.11	0	0	0.1667
CMV-IgG	9	100	45	100	1
EBV-IgM	0	0	5	11.11	0.576
EBV-IgG	9	100	44	97.78	1
HSV1/2-IgM	4	44.44	8	17.78	0.098
HSV1/2-IgG	7	77.78	40	88.89	0.3298
MP-IgM	7	77.78	7	15.56	0.0005
MP-IgG	1	11.11	10	22.22	0.6667

* Fisher's exact test; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HSV: Herpes simplex virus; MP: *Mycoplasma pneumoniae*.

HSV1/2-IgM seropositivity was higher in EM patients aged <30 years than in those aged ≥30 years, with no sex-related difference. HSV1/2-IgG positivity was significantly higher in patients with generalized lesions than in those with localized and acral lesions (91.67% vs. 50%; $p < 0.05$), whereas HSV1/2-IgM positivity tended to be higher in localized and acral EM (50% vs. 18.75%), although not significantly. These findings are consistent with previous reports suggesting that classic acral target lesions are frequently associated with HSV infection, whereas generalized EM is more likely to be idiopathic.¹⁵

MP-IgM seropositivity was significantly higher in EM patients aged <30 years than in those aged ≥30 years ($P < .05$), while no such difference was observed in HCs. This finding suggests a potential role of *M. pneumoniae* in younger patients with EM. *M. pneumoniae* is a common cause of community-acquired pneumonia, particularly in children and adolescents, and may also cause extrapulmonary manifestations, including mucocutaneous disease. A pediatric study reported mucocutaneous manifestations in 22.7% of community-acquired pneumonia cases, with *M. pneumoniae*-associated oral mucositis and rash occurring in 7% of patients.¹⁸ In our EM cohort, MP-IgM seropositivity was markedly higher in patients with fever than in those without fever (77.78% vs. 15.56%; $P < .001$), suggesting an association between systemic infectious symptoms and *M. pneumoniae* infection.

Although *M. pneumoniae* may cause oral mucositis and conjunctivitis, no significant differences in MP-IgM or MP-IgG seropositivity were observed according to mucosal involvement.

This study has several limitations, including the small sample size; reliance on serological testing without PCR or culture confirmation from skin or mucosal tissue; absence of serial serological assessments during follow-up; inability to definitively establish drug-induced etiologies; and incomplete evaluation of other potential infectious agents associated with EM.

Conclusion

The precise role of microorganisms in the pathogenesis of EM remains incompletely understood. Nevertheless, among younger patients (<30 years of age), EM has been associated with infection by HSV and/or *M. pneumoniae*. Febrile cases of EM may be linked to *M. pneumoniae* infection, whereas localized and acral forms of EM may be associated with EBV infection.

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Declaration of patient consent Authors certify that they have obtained all appropriate patients' consent.

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Author's contribution

NMH, DNQ, TTH: Substantial contribution to study design, acquisition of data, manuscript writing.

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