ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 23(4): 308-312, 2018
DOI: 10.5505/ejm.2018.70893

Erythema multiforme; sixty six case series with review of literature

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ABSTRACT

Erythema multiforme (EM) is an acute, self-limited, and sometimes recurrent skin disease considered to be a hypersensitivity reaction associated with certain medications and infections. EM has recently been recognized as a distinct disease differentiated from the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The aim of this study was to evaluate the clinical and histopathological characteristics of patients with EM.

The retrospective study included 66 patients who received outpatient or inpatient treatment at the Dermatology department due to a diagnosis of EM between 2005 and 2017. Age, gender, etiological factor, recurrence, significant histopathological findings, presence of target lesions, mucosal involvement, and treatment methods were recorded.

The 66 patients included 22 (33.3%) men and 44 (66.7%) women with a mean age of 36.7±13.9 years. The etiological factor was Herpes labialis in 36.4%, medication in 31.8%, Orf infection in 13.6%, and no etiological factor was detected in 18.2% of the patients.

Although EM is a common entity in dermatology practice, there are a limited number of studies reporting on EM. The results indicated that EM can occur secondary to Orf infection.

Key Words: Erythema multiforme, Orf, Target lesions

Introduction

Erythema multiforme (EM) is an acute, self-limited, and sometimes recurrent skin disease considered to be a hypersensitivity reaction associated with certain medications and infections (1). EM has recently been recognized as a distinct disease differentiated from the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (2). However, epidemiological data on EM are limited mainly due to the acute course of the disease and the lack of a universally accepted classification system. Nevertheless, accumulating evidence indicates that the prevalence of EM is less than 1% and the disease mostly affects women between 20 and 40 years of age (3).

The etiopathogenesis of EM remains elusive although a reaction against antigens is considered to be the primary cause of EM and a number of pathogenic microorganisms and medications have been blamed. Recurrent EM is often caused by herpes simplex virus (HSV), accounting for more than 70% of cases. Additionally, HSV-DNA has been reported in 36-81% of EM cases. Medications are a major cause of EM, with cephalosporin being the most common medication (4).

Erythema multiforme (EM) initially manifests with multiple sharply demarcated red or pink macules that may subsequently enlarge into plaques. The central parts of the plaques are relatively darker red or brown. The characteristic "target" or "iris" lesion has a regular shape and consists of three concentric zones: a central darker red area, a paler pink zone, and a peripheral red ring. The target lesions may appear within several days after the onset of the disease (1).

Although the histopathologic examination of EM may show some important signs in the perilesional tissue such as intercellular or intracellular edema, microvesicular formation, polymorphous nuclear cell infiltrate, and necrotic keratinocytes, there are no pathognomonic histopathological features of EM (3). The differential diagnosis of EM includes drug eruption, polymorphous light eruption, urticaria, viral exanthema, and urticarial vasculitis (1). Moreover, the diagnosis of EM is primarily based on patient history and clinical and imaging outcomes, mainly because laboratory tests are nonspecific (3-5). The first step in the treatment

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Received: 30.07.2018, **Accepted:** 02.09.2018

Table 1. Demographic and clinical characteristics of the patients

		n	%
Gender	Male	22	(33.3)
	Female	44	(66.7)
Age (years)*		36.7 ±13.9	29.0
Etiology	Herpes labialis	24	(36.4)
	Medication	21	(31.8)
	Orf infection	9	(13.6)
	No etiology	12	(18.2)
Recurrence	No	51	(77.3)
	Yes	15	(22.7)
Mucosal involvement	No	45	(68.2)
	Yes	21	(31.8)
Infiltration	Lymphocytic	16	(24.2)
	Mixed	27	(40.9)
	Neutrophilic	31	(47.0)
Treatment method	Systemic prednisolone+topical steroid	50	(75.8)
	Topical steroid	2	(3.0)
	Topical steroid+antihistaminic	14	(21.2)
Target lesions	No	21	(36.7)
	Yes	45	(63.3)
Duration of disease (days)*		6.7 ±4.3	6.0

*In quantitative variables, mean±SD was used instead of n and median was used instead of %

Table 2. Comparison of demographic and clinical characteristics with regards to gender

		Gender				p
		Male		Female		
		n	%	n	%	
Etiology	Herpes labialis	10	(41.7)	14	(58.3)	0.575c
	Medication	7	(33.3)	14	(66.7)	
	Orf infection	3	(33.3)	6	(66.7)	
	No etiology	2	(16.7)	10	(83.3)	
Recurrence	No	17	(33.3)	34	(66.7)	>0.999 c
	Yes	5	(33.3)	10	(66.7)	
Mucosal involvement	No	12	(26.7)	33	(73.3)	0.163 c
	Yes	3	(60.0)	2	(40.0)	
Infiltration	Lymphocytic	7	(43.8)	9	(56.3)	0.961a
	Mixed	9	(33.3)	18	(66.7)	
	Neutrophilic	10	(32.3)	21	(67.7)	
Treatment method	Systemic prednisolone+topical steroid	18	(36.0)	32	(64.0)	0.421 c
	Topical steroid	1	(50.0)	1	(500)	
	Topical steroid+antihistaminic	3	(21.4)	11	(78.6)	
Target lesions	No	4	(19.0)	17	(81.0)	0.093a
	Yes	18	(40.0)	27	(60.0)	
Age *		31,5	(25-43)	36.0	(27-45)	0.567b
Duration of disease (days)*		7	31.5	(25-43)	36.0	0.560b

[a]Chi-square test, [b]Independent Samples *t*-test, [c]Fisher's exact test. In quantitative variables, mean±SD was used instead of n and mimimum-maximum values were used instead of %

Table 3. Comparison of demographic and clinical characteristics with regards to recurrence

		Recurrence				p
		No		Yes		
		n	%	n	%	
Etiology	Herpes labialis	15	(62.5)	9	(37.5)	0.032c
	Medication	19	(90.5)	2	(9.5)	
	Orf infection	9	(100.0)	0	(0.0)	
	No etiology	8	(66.7)	4	(33.3)	
Mucosal involvement	No	36	(80.0)	9	(20.0)	0.786 c
	Yes	15	(71.5)	6	(28.5)	
Infiltration	Lymphocytic	20	(74.1)	7	(25.9)	0.262a
	Mixed	23	(74.2)	8	(25.8)	
	Neutrophilic	8	(100.0)	0	(0.0)	
Treatment method	Systemic prednisolone+topical steroid	39	(78.0)	11	(22.0)	0.576 c
	Topical steroid	1	(50.0)	1	(50.0)	
	Topical steroid+antihistaminic	11	(78.6)	3	(21.4)	
Target lesions	No	17	(81.0)	4	(19.0)	0.758 c
	Yes	34	(75.6)	11	(24.4)	
Age*		32.0	(25-45)	35,0	(31-52)	0.331b
Duration of disease (days)*		6.0	(3-10)	6	(3-7)	0.211b

[a]Chi-square test, [b]Mann-Whitney U test, [c]Fisher's exact test. In quantitative variables, median was used instead of n and percentile (25-75[th]) values were used instead of median.

of EM is the identification of the suspicious infectious agent or drug causing the development of EM. Mild cases of EM often require no treatment although oral antihistaminic agents and topical steroids can be used for relief of symptoms. In the patients accompanied by HSV, oral acyclovir has been found to provide effective outcomes while topical acyclovir provides no favorable outcome (1-6).

Literature reviews indicate that there are a limited number of large-scale studies reporting on EM. In this study, we aimed to evaluate the clinical and histopathological characteristics of patients with EM.

Materials and Methods

The retrospective study included 66 patients who received outpatient or inpatient treatment due to a diagnosis of EM at University Medical School Dermatology Department between 2005 and 2017. Age, gender, etiological factor, recurrence, significant histopathological findings, presence of target lesions, mucosal involvement, and treatment methods were recorded. Inclusion criteria included age over 18 years and a diagnosis of EM confirmed clinically and histopathologically. Patients with TEN and SJS were excluded from the study. The study was conducted in accordance with the Helsinki Declaration and was approved by the local ethics committee. (Date: 17.05.2018, Number: 97)

Statistical Analysis: Data were analyzed using SPSS 15.0 for Windows (SPSS Co., Chicago, IL, USA). Normal distribution of data was analyzed using histogram plots and the Kolmogorov-Smirnov test. Descriptive statistics were expressed as mean, standard deviation (SD), median, and 25-75[th] percentile values. Categorical variables were compared using Pearson's Chi-Square Test and Fisher's Exact Test. Variables with normal distribution (*i.e.* parametric variables) were compared using Independent Samples *t*-test and the variables with nonnormal distribution were compared using Mann-Whitney U test for more than two groups. A p value of <0.05 was considered significant.

Results

Table 1 presents the demographic and clinical characteristics of the patients. The 66 patients comprised 22 (33.3%) men and 44 (63.7%) women with a mean age of 36.7±13.9 years. The etiological factor was Herpes labialis in 36.4%, medication in 31.8%, Orf infection in 13.6%, and

no etiological factor was detected in 18.2% of the patients. Recurrence occurred in 22.7%, target lesions were present in 68.2%, and mucosal involvement was detected in 31.8% of the patients. Lymphocytic infiltration was found in 40.9%, neutrophilic infiltration in 12.1%, and mixed infiltration in 47.0% of the patients. Most common treatment method was systemic prednisolone+topical steroid therapy (75.8%), followed by topical steroid+antihistaminic therapy (21.2%), and topical steroid therapy (3.0%). Mean duration of disease was 6.7 ±4.3 days (Table 1).

No significant difference was found between the demographic and clinical characteristics of the patients with regards to gender (p>0.05) (Table 2).

Similarly, no significant difference was found between the demographic and clinical characteristics of the patients with regards to recurrence (p>0.05) (Table3). The etiologic factor in the presence of recurrence was found to be significantly higher in herpes labialis cases (n=37.5%) than in drug and orf (respectively: 9.5%, 0,0%) (p: 0.032)

Discussion

The results indicated that EM leads to high recurrence rates and Orf infection is an important agent in the etiology of EM. Previous studies reported that EM is a common disease in young individuals, particularly in their second and third decades of life (2). Similarly, the mean age in our patients was 36.7 years, which was consistent with the literature.

Literature also indicates that EM is more common in women than in men (3-5). Similarly, in our study, there was a female preponderance of 66.7%. However, Kondolot et al. reported that there was a male preponderance in their pediatric patients (7).

Herpes simplex virus (HSV) is known as the most common cause of EM. Ng et al. detected HSV-DNA in patients with HSV-related EM and patients with idiopathic EM (in almost 43% the patients in both groups) while no HSV-DNA was detected in patients with drug-induced EM (8). In our patients, HSV-DNA was detected in 36.4% of the patients, which was similar to the rate reported by Ng et al. However, in most of our patients with HSV-DNA, the diagnosis of HSV was established clinically and no serological tests were performed. Even so, we believe that HSV is an important agent in the etiology of EM, as suggested by previous studies.

Medications constitute another major cause of EM, particularly when accompanied by mucosal involvement. Most common medications associated with EM include sulfonamides, penicillin, cephalosporin, and nonsteroidal anti-inflammatory drugs (9). Shabahang et al. detected a suspicious drug in 49.2% of their EM patients (10). In our study, medications accounted for 31.8% of the etiologies detected in our patients, which was lower than the rate reported by Shabahang et al. However, this finding implicates that medications are important agents in the etiology of EM.

Orf infection has recently been implicated in the etiology of EM. Joseph et al. suggested that Orf infection can result in EM, though rarely (11). In our patients, EM resulted from Orf infection in 9 (13.6%) patients, which was higher than the rates reported in the literature. This high rate could be attributed to the widespread livestock farming in our region.

Mucosal involvement can also lead to the development of EM. Although oral mucosa is the most common mucosal site involved, other mucosal sites can also be involved such as trachea, bronchi, and gastrointestinal system. Involvement of oral mucosa can be seen in more than 50% of the patients with EM (12-14). In our study, mucosal involvement was found in 31.8% of the patients, which was consistent with the previous studies. This finding implicates that mucosal involvement should be kept in mind during the physical examination of patients with EM.

Although EM has a variable disease course, it is known as a self-limited disease that resolves within a period ranging from several days to one month. Weter et al. reported a mean duration of disease of 18.9 days (15). In our study, mean duration of disease was 6.7 days, which implicates that EM is not a chronic disease.

Topical and systemic steroids are the mainstay treatment of EM. Additionally, antimalarials, azathioprine, cyclosporine, thalidomide, dapsone, and mycophenolate mofetil are also used (1-16). Sanchis et al. reported that the use of topical and systemic corticosteroids led to complete remission in all the patients within 7-10 days (17). Similarly, we also used topical and systemic corticosteroids in most of our patients and no drug resistance was observed in any patient.

Our study was limited since it was a single-center study, serological tests for microorganisms such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and mycoplasma were not performed for

all the patients, and pediatric patients were excluded from the study.

In conclusion, although EM is a common entity in dermatology practice, there are a limited number of studies reporting on EM. The present study is the first large-scale study reporting on the patients with EM in the Van Province in Turkey and indicating that that EM can occur secondary to Orf infection. Further multicenter studies are needed to substantiate our findings.

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