Acta Dermatovenerol Croat 2009;17(1):9-15 CLINICAL ARTICLE

Erythema Multiforme with Reference to Atypical Presentation in an HIV-Positive Patient Following Antiretroviral Therapy Discontinuation

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Received: March 31, 2008
Accepted: January 20, 2009

SUMMARY Erythema multiforme (EM) is a skin disease caused by numerous potential triggering agents. It is characterized by symmetrically distributed, round, erythematous iris lesions, with remarkable tendency of recurrence. The purpose of this randomized retrospective study was to summarize our experience concerning the etiology, clinical variants and management of EM. We present 12 EM patients, along with laboratory, clinical and histopathologic analysis, and an overview of the treatment used. According to clinical presentation and histopathologic analysis, there were six cases of EM major, five cases of EM minor and one case of Stevens-Johnson syndrome. In five patients, EM was associated with the use of certain drugs (terbinafine, azithromycin, diclofenac, piroxicam). In three patients, the disease was triggered by the herpes simplex virus infection. In four cases, the etiologic factor (involved in the occurrence) of EM remained unknown. We also present an unusual case of an HIV-positive patient with multiple acral target lesions without mucosal involvement, which developed upon antiretroviral therapy discontinuation. To our knowledge, no case of such EM occurrence has yet been reported. There are various etiologic factors and numerous clinical presentations of EM, including acral target lesions and atypical widely distributed cutaneous and mucosal lesions.

KEY WORDS: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

INTRODUCTION

Erythema multiforme (EM) represents as an array of heterogeneous skin diseases with many potential triggering agents, characterized by symmetrically distributed skin target or iris lesions (1-4). The spectrum of EM includes eruptions of typical skin lesions located primarily on extensor extremity surfaces (EM minor) to serious systemic illness with mucosal erosions accompanying skin lesions (Stevens-Johnson syndrome, SJS) or confluent areas of epidermal detachment (toxic epidermal

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necrolysis, TEN)(5-7). Originally, Ferdinand von Hebra in 1866 described "erythema multiforme exsudativum" as a self-limited cutaneous eruption lasting for several weeks, with symmetrically distributed, round, erythematous skin lesions, some of which acquired concentric changes in color, thus producing iris or target lesions or blisters (5).

EM is considered to be a distinct type of skin reaction to various causative agents such as recurrent herpes simplex virus (HSV) infection, mycoplasma or bacterial and fungal infections, malignant tumors and some autoimmune disorders (lupus erythematosus, Wegener granulomatosis, polyarteritis nodosa), occasionally medicaments, x-rays or sarcoidosis, although these agents are rarely identified. EM typically affects young healthy adults and occurs sporadically throughout the year. About one-third of cases are recurrent, more often in EM minor (1,2).

The disease may begin with prodromal symptoms, mostly associated with the upper respiratory tract, which can be seen in about one-third of cases (1). EM often starts with typical symmetrical skin lesions on the extremities, on the hands and feet at first (palms and soles included) and the extensor aspects of the arms and legs (1,2,8). It typically spreads from acral to more proximal areas and the trunk, with eruption of fresh skin lesions over 3 to 5 days. However, in SJS or TEN, the trunk may be prominently affected, and progression may occur from days to several weeks (1,2). Sometimes there are atypical skin lesions, particularly in more serious varieties (EM major), with poorly demarcated maculopapular skin lesions that may progress to confluent areas of erythema, large bullae, or epidermal sloughing (1,2). The frequency of mucosal involvement varies widely within the EM type (e.g., 25% to 70% in EM minor), usually confound to the oral region (1).

Stevens-Johnson syndrome/toxic epidermal necrolysis overlap, as a combination of these two disorders, is characterized by atypical target lesions covering 10%-30% of the body surface, including the trunk, with blisters and mucosal lesions.

While EM minor causes virtually no complications, SJS and TEN are associated with significant complications, mostly ocular and pulmonary manifestations. In cases with widespread cutaneous lesions (TEN), the prognosis is similar to the second-degree skin burns with possible complications such as sepsis or fluid and electrolyte imbalance. Death may occur in up to 18% of cases of EM with pneumonia and up to 50% of TEN cases (1).

The most common cause of EM is viral infection, caused by herpes labialis, typically following labial cold sores, supported by identification of HSV DNA in the majority of such cases, even in idiopathic ones, where a definite history of a preceding HSV infection was not identified (9-11). Recurrences of the disease are common (1,2,12). The proportion of EM cases caused by HSV varies among reports, but is likely greater than 50%. Other viruses may also be implicated, but far less often. A second well-documented triggering agent for EM is infection with *Mycoplasma pneumoniae*, especially in children and young adults after respiratory infections. It is characterized by mucosal erosions and bullous skin lesions, usually diagnosed as SJS or bullous EM (13).

Occasionally EM accompanies streptococcal infections or other bacterial infections, deep fungal infections, malignant tumors or some autoimmune disorders (lupus erythematosus, Wegener granulomatosis, and polyarteritis nodosa) (2).

SJS or TEN are often medicamentous, caused by sulfonamides, penicillins, anticonvulsants, nonsteroidal anti-inflammatory drugs, or topical sulfa drugs. In most instances, there are eruptions with extensive mucosal erosions, large bullae, confluent erythema, or epidermal detachment, mostly 2 to 3 weeks following drug administration, without recurrence unless the drug or a cross-reacting drug is readministered (1,2).

Regarding the pathogenesis of EM, current concepts classify EM as a syndrome rather than a single disorder. Clinical observations also support the concept that EM represents a mucocutaneous reaction to certain antigenic stimuli (recurrent HSV infections, mycoplasma infections, drugs), supported by histopathologic studies which indicate certain antigens as stimuli of immune responses, resulting in tissue damage (1-4). On the other hand, some authors suggest immune complex-mediated reactions.

The purpose of the study was to summarize our experience concerning the etiology and clinical variations in presentation of EM, and corresponding management.

MATERIAL AND METHODS

We present a randomized retrospective study involving patients with EM, conducted at our Department of Dermatology and Venereology. The

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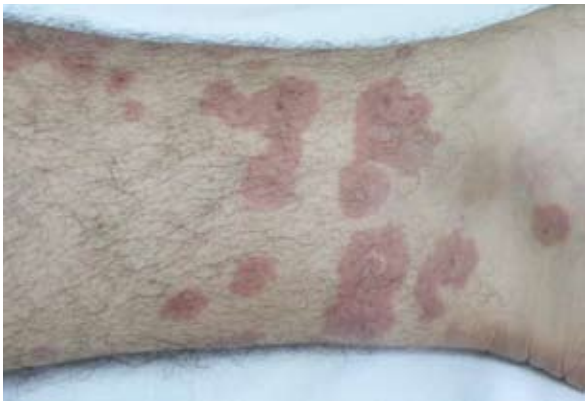

Figure 1. Lesions on the lower part of the arm

study included 12 patients with EM, along with laboratory, clinical and histopathologic analysis, followed by a treatment overview.

RESULTS

Twelve EM patients had different clinical presentation, caused by various etiologic factors (Table 1). Six female and six male patients, age range 25-70 years, were included in the study. Six cases of EM major, five cases of EM minor and one case of SJS were diagnosed according to clinical presentation and histopathologic analysis (Figs. 1-4). Patients with TEN were not reported.

Five patients had drug-induced EM. Drugs involved in the occurrence of the disease were terbinafine, an antifungal agent used in the treatment of onychomycosis, and azithromycin, a macrolide antibiotic used in the treatment of acute respiratory infections. Two patients were taking diclofenac and piroxicam, nonsteroidal anti-inflammatory drugs, prescribed for lumboischial pain.

In three patients, the disease commenced with herpes simplex infection. In four cases, the etiologic factor involved in the occurrence of EM was not found.

Topical corticosteroids and systemic antihistamines were used in the treatment of EM minor. Treatment regimens focused on systemic and topical corticosteroids and systemic antihistamines in patients with EM major and SJS. Regression followed in all of our patients. There were two cases of recurrence, with remission lasting for one year on an average.

We present a case of an HIV-positive patient with EM. The patient presented at our clinic for multiple acral target cutaneous lesions without mucosal involvement. His history indicated that skin changes appeared upon antiretroviral therapy (ART) discontinuation. History data revealed herpes labialis two weeks before the occurrence of skin lesions. Laboratory tests and histopathologic analysis confirmed EM. Topical corticosteroids and systemic antihistamines were administered, followed by regression in several days. There was no recurrence during the two-year follow up period.

DISCUSSION

Although diagnostic clinical criteria for EM generally include symmetrically distributed iris lesions, lasting for 1 to 6 weeks with corresponding histopathology, there may be heterogeneous clinical presentations of EM. In recent years, several attempts have been made in order to classify EM according to causative factors and management strategies for various clinical forms (1,2,14). One approach would be to designate EM minor for Hebra's disease and EM major for more atypical and severe illness (5,6). Another approach is clinical classification of EM, SJS, or TEN based on skin lesion types and the extent of skin surface involved (1,9). EM nosology can be difficult and confusing, since the classic variety of EM may be associated with oral erosions, while those with SJS and TEN may have confluent areas of epidermal detachment (1,2).

The minor form of EM is characterized by symmetric target lesions on the hands or rarely on the trunk, with preceding HSV infection, as supported by positive HSV markers in the skin of EM patients and amelioration after antiviral therapy (1,2). Mucosal involvement may occur, although typically only the lips are involved. EM minor has good prognosis with often rapid resolution, but recurrences are common. If other infections or drugs are responsible, the course is often fulminant but the recurrence rate is much lower.

The major form is a severe form of EM characterized by acral target lesions, occasionally with trunk involvement and blisters in the center of target lesions which involve less than 10% of the body surface area. The majority of patients have mucosal involvement (mouth, eyes and/or genital mucosa). Mycoplasma and HSV are the typical triggers and the prognosis is good with less common recurrences (1,2).

Rarely, TEN manifests with blisters and diffuse macular exanthema of the trunk, face and limbs, forming large flaccid blisters, with large shedding areas; however, no such cases were observed in our study (2). Mucosal involvement is uncommon and, when present, it is usually minimal. There is

Table 1. Patient data

Patient No.	Age	Sex	Type	Cause	Skin	Mucous membranes	Therapy	Outcome	Recurrence
1.	68	F	EM major	Drug (terbinafine) used in the treatment of onychomycosis	Acral and truncal erythematous maculae with annular and targetoid lesions	No lesions	Systemic and topical corticosteroids, antihistamines	Regression	No
2.	50	F	EM minor	Unknown	Acral target lesions	Erosions located on the lips	Topical corticosteroids, systemic antihistamines	Regression	No
3.	57	M	EM major	Respiratory infection + drug (azithromycin)	Acral and truncal erythematous maculae with annular and targetoid lesions	No lesions	Topical corticosteroids, systemic antihistamines	Regression	No
4. (Fig. 1)	50	M	EM minor	Drugs (diclofenac + piroxicam)	Acral target lesions	No lesions	Topical corticosteroids, systemic antihistamines	Regression	No
5.	80	M	EM major	Unknown	Acral and truncal erythematous maculae with annular and targetoid lesions	No lesions	Systemic and topical corticosteroids, systemic antihistamines	Regression	No
6.	71	M	EM major	Drug (cephalexin - due to crural ulcer *S. aureus* infection) + HSV infection + *Klebsiella* spp. isolated from nasal swabs	Acral and truncal erythematous maculae with annular and targetoid lesions	No lesions	Systemic and topical corticosteroids, systemic antihistamines	Regression	No
7.	60	F	EM major	Unknown	Acral and truncal erythematous maculae with annular and targetoid lesions	No lesions	Systemic and topical corticosteroids, systemic antihistamines	Regression	No
8.	67	F	EM major	Unknown	Acral and truncal erythematous maculae with annular and targetoid lesions	No lesions	Systemic and topical corticosteroids, systemic antihistamines	Regression	Yes
9.	69	F	EM minor	Urinary tract infection	Acral target lesions	No lesions	Topical corticosteroids, systemic antihistamines	Regression	Yes
10. (Fig. 2)	25	M	Stevens-Johnson syndrome	Herpes simplex infection	Acral target lesions	Erosions of oral mucous membranes	Acyclovir tbl., local corticosteroids	Regression	No
11. (Fig. 3)	63	F	Stevens-Johnson syndrome	Drug (diclofenac for lumboischial pain management)	Acral and truncal erythematous maculae with annular and targetoid lesions	Erosions of oral mucous membranes, conjunctivitis	Systemic and topical corticosteroids, systemic antihistamines	Regression	No
12. (Fig. 4)	27	M	EM minor	Discontinued antiretroviral therapy (HIV infection) + HSV infection	Acral target lesions	No lesions	Topical corticosteroids, systemic antihistamines	Regression	No

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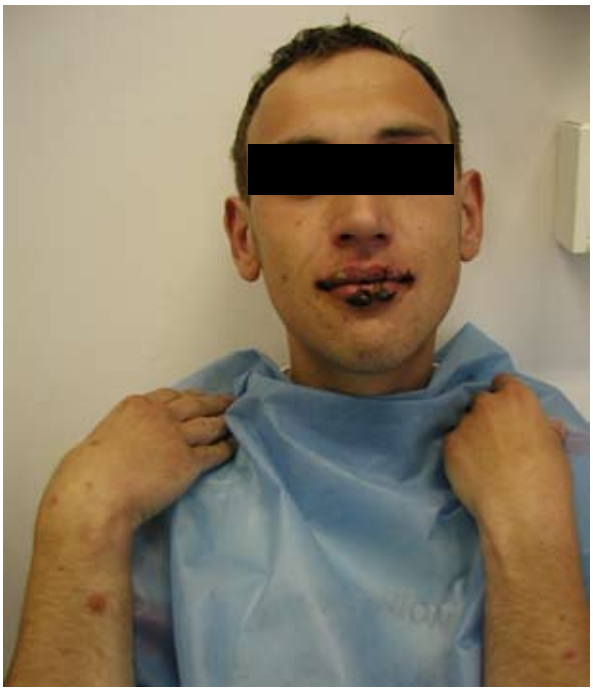

Figure 2. EM lesions on the lips

a significant mortality risk in case of inappropriate treatment. TEN begins with a prodromal phase, often related to an underlying viral or bacterial disease, with possible fever, rhinitis, conjunctivitis or dysuria, suggesting initial mucosal involvement. Relationship between TEN and SJS is one of the great controversies, but it is universally accepted that SJS is the more severe form of EM (4).

Skin lesions in SJS originate on the trunk as coalescing erythematous maculae, sometimes with target lesions and blister formation (with less than 10% of the body surface area involved); all patients have mucosal involvement. Drug reactions are the most likely trigger, but HSV or Mycoplasma infections, as seen in our patient, are rarely involved (1,2). Due to imprecise description, lesions in SJS became known as target lesions and SJS was equated with EM; however, EM major and SJS are not the same entity, yet SJS overlaps with TEN.

There is a pathogenetic hypothesis of cell-mediated immune response that leads to tissue damage, mediated by lymphocytes and monocyte-macrophages with a predominance of T cells with HLA-DR expression in the epidermis. Potential antigens of the precipitating infective agent or drug are located in the skin or mucosa (possibly in the epithelium), thereby stimulating cell-mediated immune response as a homeostatic mechanism for their elimination. If this is the case, EM would represent an appropriate immune reaction rather

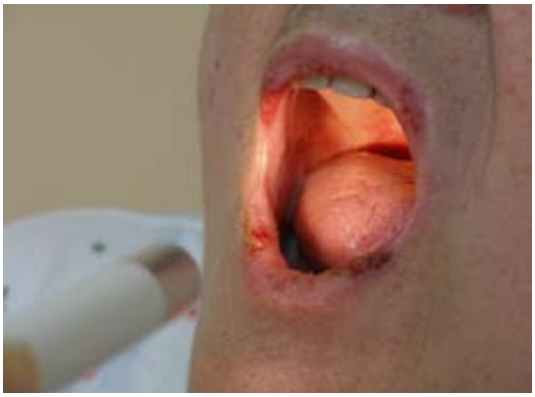

Figure 3. Erosions on oral mucous membranes

than being an ill-defined “hypersensitivity” phenomenon. However, currently there is no explanation how such antigen might localize throughout skin and mucosal sites (1,15).

Viral antigens and even DNA are found in the dermis where they trigger cell-mediated reactions, although it remains unclear how they produce such symmetric lesions and more widespread skin loss (1,2). In case of delayed appearance after streptococcal infection, type IV reaction appears to be most likely. Others have suggested that the primary damage occurs in the epidermis and that the entire process is designed to eliminate epithelial antigens.

In our study, we encountered an HIV-positive patient with EM. The patient presented at our Clinic with advanced acral target lesions without mucosal involvement, which appeared upon discontinuation of ART. According to the patient’s history, he had labial HSV infection two weeks before the appearance of skin lesions, which could be related to the appearance of EM lesions. Skin biopsy was performed and histopathologic analysis confirmed EM. Topical corticosteroids and systemic antihistamines were therapeutically administered.

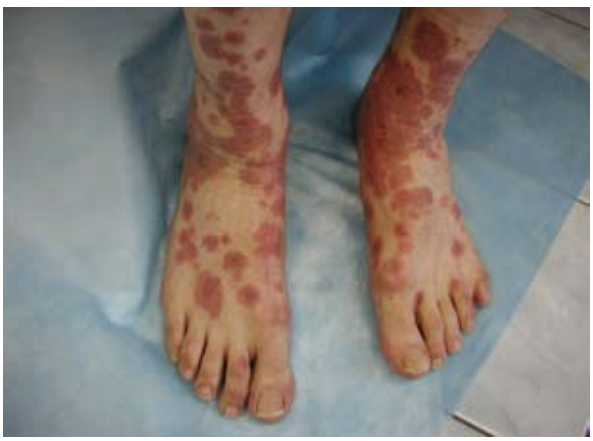

Figure 4. Acral target lesions in HIV patient

Regression occurred after several days with no recurrence during the two-year follow up period.

Generally, the occurrence of EM in patients with HIV has been reported in ART-treated patients. Although life-threatening toxicities are rare during ART, sometimes they necessitate ART discontinuation. Severe rash such as SJS or EM would indicate change in the ART regimen (16). These rashes have most frequently been reported with non-nucleotide reverse transcriptase inhibitors (NNRTIs): delavirdine (rarely), efavirenz (0.1%), and nevirapine (1%) (16). Our case indicates that even discontinuation of ART may provoke EM. However, it remains unclear whether in our HIV positive patient the trigger for EM was herpes simplex infection, cessation of ART or HIV itself.

EM management requires the subtype and presumable etiology to be determined prior to the introduction of specific therapies (1). In case of classic EM minor, especially with recurrent eruptions, reactivation of HSV is the most likely cause. In SJS, infective agents such as mycoplasma infections and drugs should be considered, whereas in TEN drugs represent the most common etiologic agents. Generally, approaches to therapy of EM include prevention of the antigenic stimulus, suppression of the host immune response and immune-mediated tissue damage by conservative supportive or symptomatic measures (1,2).

Topical therapy for EM is generally supportive and rarely dramatically effective and includes topical corticosteroids, wet soaks and ointments, perhaps with antibacterial agents. Similarly, topical corticosteroids and systemic antihistamines can be used in the treatment of patients with EM minor, and systemic and topical corticosteroids with systemic antihistamines in patients with EM major and SJS. However, topical application of corticosteroids does not influence the course of the disease significantly (14,15).

Early systemic short-term corticosteroid therapy may be indicated in severe cases (major type with mucous membrane involvement), although its value is debatable (systemic corticosteroid therapy may postpone the reparatory phase, predisposing the patient to secondary infections and potentially earlier recurrence of HSV infections) (14). Systemic steroid therapy, however, may be appropriately instituted in potentially serious cases, early in the course, especially for drug-associated SJS or TEN.

Systemic therapy of EM depends heavily on the suspected trigger and the disease severity (2). Thus, in a patient with several attacks of EM *per* year, oral acyclovir can be used as prophylaxis for recurrent HSV lesions, although there is no convincing evidence that acyclovir therapy of EM or preceding HSV lesions shortens the course of EM (1,2). Patients with recurrent EM without obvious signs of HSV usually benefit from acyclovir prophylaxis as well, suggesting subclinical HSV as a trigger (1,2).

Supportive care is the most important factor in more severe forms (burn care, including infection prophylaxis, fluid restoration and wound care). Ophthalmologist and internal medicine specialist consultation is crucial in order to achieve the best outcome.

CONCLUSION

There are various etiologic factors and numerous clinical presentations of EM, including acral target lesions and other, less typical cutaneous and mucosal presentations. Drugs, HSV and other triggers are the most common etiologic factors in the pathogenesis of diseases from the EM group. Besides HSV infection, other viral infections may also provoke EM, such as possibly in HIV patients. It remains unclear whether in our HIV positive patient the trigger for EM was herpes simplex infection, cessation of ART or HIV itself.

References

1. Clark Huff J. Erythema multiforme. In: Mitchell SWJr, Lynch PJ. Principles and Practice of Dermatology. 2nd Edition. New York: Churchill Livingstone; 1996. pp. 483-90.
2. Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC. Dermatology. 2nd Edition, Completely Revised Edition. Berlin: Springer; 2000. pp. 414-6; 579-82.
3. Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. J Am Acad Dermatol 1983;8:763-75.
4. Fitzpatrick JE, Aeling JL. Dermatology Secrets in Color. Drug Eruptions. 2nd Edition. Boston: Hanley and Belfus, Inc; 2001. pp. 93-94; 428-9.
5. von Hebra F. On Diseases of the Skin Including Exanthemata. Translated by CH Fagge Vol. 1. London: New Sydenham Society; 1866. pp. 285-9.
6. Stevens AM, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia. Am J Dis Child 1922;24:526-33.

7. Lyell A. A review of toxic epidermal necrolysis in Britain. Br J Dermatol 1967;79:662-71.
8. Howland WH, Golitz LE, Huff JC, Weston WL. Erythema multiforme: clinical, pathologic, and immunologic studies. J Am Acad Dermatol 1984;10:438-46.
9. Zaim MT, Giorno RC, Golitz LE, Kunke KS, Huff JC. An immunopathologic study of herpes-associated erythema multiforme. J Cutan Pathol 1987;14:257-62.
10. Orton PW, Huff JC, Tonnesen MG, Weston WL. Detection of herpes simplex virus antigens in skin lesions of erythema multiforme. Ann Intern Med 1984;101:48-50.
11. Brice SL, Krzemien D, Weston WL, Huff JC. Detection of HSV DNA in cutaneous lesions of erythema multiforme. J Invest Dermatol 1989;193:183-7.
12. Schofield JK, Tatnall FM, Brown J, McCloskey D, Navarrete C, Leigh IM. Recurrent erythema multiforme: tissue typing in a large series of patients. Br J Dermatol 1994;131:532-5.
13. Sontheimer RD, Garibaldi RA, Krueger GG. Stevens-Johnson syndrome with *Mycoplasma pneumoniae* infections. Arch Dermatol 1978;114:241-4.
14. Bork K, Bräuninger W. Skin Disease in Clinical Practice. Erythema Multiforme. 2nd Edition. Philadelphia: WB Saunders Company; 1998. p. 61.
15. Auquier-Dunant A, Mockanhaupt M, Naldi L, Correia O, Schroder W, Roujeu JC. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and TEN: results of an international prospective study. Arch Dermatol 2002;138:1019-24.
16. Bulat V**,** Lugović L, Šitum M. Prominent features and variations in clinical presentation of erythema multiforme. Acta Clin Croat 2007**;**46:55-62.
17. Rotunda A, Hirsch RJ, Scheinfeld N, Weinberg JM. Severe cutaneous reactions associated with the use of human immunodeficiency virus medications. Acta Derm Venerol 2003;83:1-9.

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