



# Current Perspectives on Erythema Multiforme

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## Abstract

Recognition and timely adequate treatment of erythema multiforme remain a major challenge. In this review, current diagnostic guidelines, potential pitfalls, and modern/novel treatment options are summarized with the aim to help clinicians with diagnostic and therapeutic decision-making. The diagnosis of erythema multiforme, that has an acute, self-limiting course, is based on its typical clinical picture of targetoid erythematous lesions with predominant acral localization as well as histological findings. Clinically, erythema multiforme can be differentiated into isolated cutaneous and combined mucocutaneous forms. Atypical erythema multiforme manifestations include lichenoid or granulomatous lesions as well as lesional infiltrates of T cell lymphoma and histiocytes. Herpes simplex virus infection being the most common cause, other infectious agents like—especially in children—*Mycoplasma pneumoniae*, *hepatitis C virus*, *Coxsackie virus*, and *Epstein Barr virus* may also trigger erythema multiforme. The second most frequently identified cause of erythema multiforme is drugs. In different studies, e.g., allopurinol, phenobarbital, phenytoin, valproic acid, antibacterial sulfonamides, penicillins, erythromycin, nitrofurantoin, tetracyclines, chlormezanone, acetylsalicylic acid, statins, as well as different TNF- $\alpha$  inhibitors such as adalimumab, infliximab, and etanercept were reported as possible implicated drugs. Recently, cases of erythema multiforme associated with vaccination, immunotherapy for melanoma, and even with topical drugs like imiquimod have been described. In patients with recurrent herpes simplex virus-associated erythema multiforme, the topical prophylactic treatment with acyclovir does not seem to prevent further episodes of erythema multiforme. In case of resistance to one virostatic drug, the switch to an alternative drug, and in patients non-responsive to virostatic agents, the use of dapsone as well as new treatment options, e.g., JAK-inhibitors or apremilast, might be considered.

**Keywords** Erythema multiforme · Herpes simplex virus · Acyclovir · *Mycoplasma pneumoniae* · Hepatitis C virus · Coxsackie virus · Epstein Barr virus · Drug reaction

## Introduction

Erythema multiforme (EM) is an acute, self-limiting disease that is typically associated with hypersensitivity reactions to viruses, primarily of the herpes simplex virus type, as well as drugs. It is characterized by targetoid erythematous lesions with predominant acral localization and can be subdivided into isolated

cutaneous and combined mucocutaneous forms. EM is considered a separate disorder from Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [1]. Depending on the time course, acute, recurrent, and chronic persistent manifestations are distinguished. Isolated mucosal (ocular and enoral) EM, also known as Fuchs syndrome, may be recurring. The Fuchs syndrome is not only associated with herpes virus but also with *Mycoplasma pneumoniae* infection [2, 3].

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## Definition

For the purpose of a consensus classification, Bastuji-Garin et al. [1] defined EM as a separate disease among other bullous skin diseases with erythema multiforme-like lesions such as SJS, SJS/TEN, and TEN. By definition, in EM, the detachment of the skin affects less than 10% body surface area (BSA) and localized typical and/or raised atypical targets are

present. Typical targets are defined as lesions less than 3 cm in diameter and characterized by three different concentric zones. Unlike typical targets, raised atypical targets normally contain only two zones. In typical and raised atypical targets, the center zone might show bullae formation as a sign of epidermal involvement [1]. Clinically, EM patterns can be classified into EM with and EM without mucosal involvement (Fig. 1). In a study published in 2010, 63% of all patients investigated had EM with mucosal involvement [4]. In an international prospective study, two or more mucosal sites were involved in 40 out of 88 patients [5]. EM has been further subdivided into EM minus (involvement of  $\leq 1$  mucosal site) and EM majus (involvement of  $\geq 2$  mucosal sites) by some authors. *Herpes simplex virus* (HSV) infection is the most commonly identified cause of EM. Assier et al. identified HSV infection in 17 of 28 patients with severe EM [6]. In

recurrent EM, 23% of patients were found to have associated HSV infection [4].

## Pathogenesis of EM

### HSV Infection

In order to corroborate the importance of HSV infection in EM, lesional skin biopsies of patients with HSV-associated EM and idiopathic EM were analyzed for HSV DNA by using nested PCR. Interestingly, in HSV-associated EM, HSV DNA could be detected in 42.9% of patients. However, in idiopathic EM, 43.8% of patients also had detectable HSV DNA, whereas HSV DNA was not detected in drug-induced EM [7]. Furthermore, Aurelian et al. found that T cells isolated from target lesions proliferated in response to HSV stimulation. The increased IFN- $\gamma$  expression shown upon HSV stimulation [8] indicates EM to be a viral disease with an auto-immune component. However, as sera of 54 patients with EM did not show reactivity in immunoblots on HACaT and HEK293 cells, Komorowski et al. concluded that autoimmunity mediated by humoral factors is unlikely [9]. During the phase of acute HSV-associated EM, CD34+ cells were increased in the patients' blood. When stimulated with cytokines and HSV, these cells differentiated into CD1a+/CD14- Langerhans cell precursors and upregulated E-cadherin expression, implicating CD34+ cells in the pathogenesis of HSV-induced EM. It was speculated by the authors that HSV DNA fragments might be transported to EM lesional skin by these cells [10]. In the Caucasian population, a genetic linkage to HLA-DQw3 was shown, especially in HSV-associated EM [11]. In addition to recurrent HSV infection, an association of recurrent EM with other infections like *Mycoplasma pneumoniae*, *hepatitis C virus* (HCV), or *Coxsackie* infection [12] was identified.

In the pediatric population, the role of HSV as causative agent of EM is discussed controversially [13]. Although seven out of 30 patients with EM had a history of HSV infection, no evidence for HSV involvement could be documented during the acute phase of EM. In 50% of the children investigated, no identifiable cause could be found. Half of these patients had mucosal involvement and recurrent EM. The most commonly identified cause in this population was *Mycoplasma pneumoniae* infection [14]. In this context, a new entity of EM named MIRM (*Mycoplasma* induced rash and mucositis) recently suggested by Canavan et al. [15] is proposed by the authors. Though recurrent EM is rare in the pediatric age group, transient NK cell deficiency leading to recurrent HSV-associated EM in an adolescent was described [16].

Besides acute and recurrent forms, persistent EM is a rare variant that is associated with *Epstein Barr virus* (EBV) infection, inflammatory bowel disease, and underlying malignancy. This form of EM is a difficult-to-treat entity [17, 18].

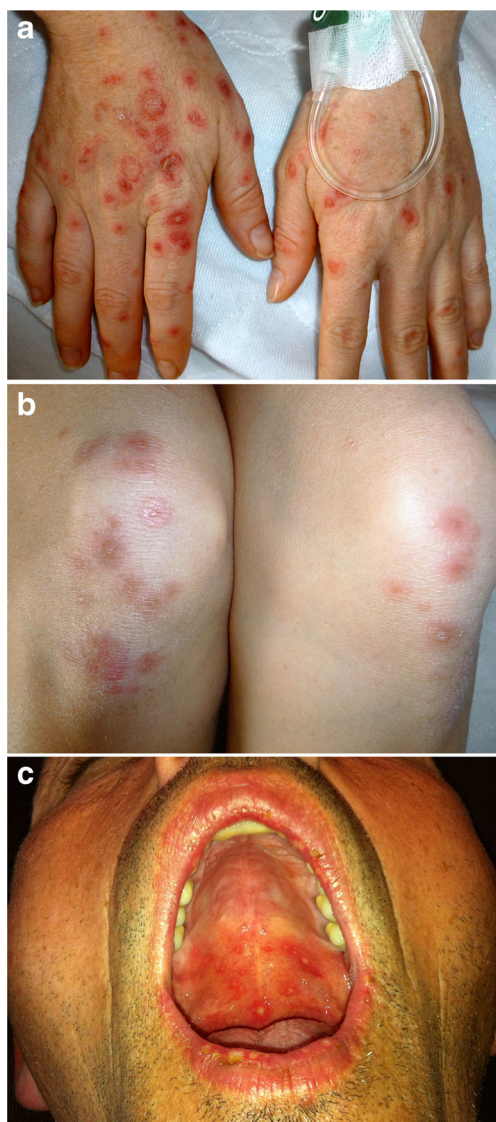


**Fig. 1** Clinical presentation of EM. **a** Target lesions on dorsal hands. **b** Target lesions on knees. **c** Mucosal involvement of lips and palate

## Drug-Induced EM

Apart from viral infection, drugs are the second most frequently identified cause of EM. In the SCAR study, a large prospective case-control study in France, Germany, Italy, and Portugal from 1989 to 1995, a total of 88 cases of EM were identified, of which 26 had a recurrent course [5]. Forty-six patients were identified to have HSV involvement, 18 cases were drug-associated, and in five cases, an association with drugs was highly suspected. The implicated drugs were oxycams, allopurinol, phenobarbital, phenytoin, anti-bacterial sulfonamides, and chlormezanone. Another study included patients treated at a group health cooperative (GHC) of Puget Sound, Seattle, USA, between 1972 and 1986 [19]. Among the identified drugs causing EM were allopurinol/diphenhydramine, amoxicillin, ampicillin, erythromycin, diphtheria-tetanus-pertussis vaccination, nitrofurantoin, tetracyclines, and valproic acid. In a Pakistani collective of 61 patients, a drug association of EM was identified in 49.2% and an association with HSV in 16.4% of cases [20]. The responsible drugs were sulfonamides, penicillin, salicylic acid, aspirin, amoxicillin, and barbiturates.

Additionally, in infants, different vaccinations have to be considered as a cause of EM [21, 22]. Newer drugs have also been described to cause EM in several case reports. However, as mostly single cases are reported, the relevance of the association is currently unclear. Since in psoriasis different TNF- $\alpha$  inhibitors such as adalimumab, infliximab, and etanercept, were reported to induce recurrent EM, a class effect of TNF- $\alpha$  inhibitors was assumed by the authors [23]. The anaplastic lymphoma kinase/ret proto-oncogene inhibitor alectinib was identified to induce EM in a patient with non-small cell lung cancer [24]. Furthermore, difficult-to-treat EM was observed in a melanoma patient treated with nivolumab and vemurafenib [25]. This suggests that the programmed-death 1 inhibitor nivolumab might trigger EM via T cell activation. Simvastatin and pravastatin were shown to cause photo-distributed EM upon repeated sun exposure in two cases [26].

Topically applied drugs, for example, imiquimod 5% cream, are also known to induce EM-like reactions [27]. Imiquimod is a Toll-like receptor (TLR)-agonist that can activate the immune system, and drug-induced TLR activation should therefore be considered a relevant mechanism in EM. The disinfectant polyhexamethylenebiguanide hydrochloride was reported to induce recurrent EM upon occupational and environmental exposure in physicians [28].

Hypersensitivity to endogenous and exogenous sexual hormones may manifest as EM as well. Though EM has a slight male preponderance, recurrent autoimmune progesterone dermatitis may present as EM, typically during the peak of progesterone in the menstrual cycle [29, 30]. Also, recurrent EM lesions were reported in autoimmune estrogen dermatitis that completely resolved after ovariectomy [31].

As an incidental cause of EM, a taurine-containing energy drink was described in a 19-year-old patient [32].

## Other Causes and Atypical Presentations of EM

There are case reports or small series on an association of EM with different conditions in the literature. At present, it remains unclear if these associations exist or if they are just a coincidence.

In 1963, the association of EM-typical target lesions with discoid lupus erythematosus and positive antinuclear antibody (ANA)-titer as well as anti-SjT antibodies was considered a new entity by Rowell [33]. However, in the context with Rowell's syndrome, the combination of other cutaneous lupus forms like annular and Chilblain-like lesions with EM was also described in numerous case reports [34–38]. In view of the lack of consistent diagnostic features, Zeitouni proposed major and minor diagnostic criteria for Rowell's syndrome [39]. According to this classification, major criteria are lupus erythematosus (non-specified), EM-like target lesions, and an increased ANA-titer with speckled pattern. Minor criteria include positive anti-La (SSB) or anti-Ro (SSA) antibodies, like in Chilblain, and reactive rheumatoid factor.

Fraser-Andrews reported two patients with recurrent EM on sun-exposed as well as non-exposed skin after multiple episodes of polymorphic light eruption. As prophylactic treatment of polymorphic light eruption could prevent development of EM, the authors concluded that UV-induced polymorphic light eruption and recurrent EM were linked [40]. Allergic contact dermatitis due to different chemical compounds, as well as plant allergens with initial vesicular skin eruption was reported to progress into EM [41]. Treatment of atypical pneumonia with cefuroxime and ibuprofen lead to pustular EM in a single patient [42].

Finally, post-EM eruptions have to be considered as well. An association of EM with HIV being described in single cases, in a patient with HIV generalized lichen planus developed on the formerly affected sites after complete resolution of EM [43]. Furthermore, EM-like lesions were seen in multifocal fixed toxic drug eruption in a patient using an unidentified over-the-counter medication [44]. A case of palmar granuloma annulare resembling EM could only be diagnosed by histopathologic examination [45].

EM-like lesions can be associated with lesional skin infiltration of adult T cell lymphoma [46]. Kikuchi-Fujimoto disease or histiocytic necrotizing lymphadenitis may induce EM-like lesions in both the presence and absence of systemic lupus erythematosus [47, 48]. Another case of "histiocytic" EM was described in a 10-year-old boy with recurrent EM where CD68+ T cell skin infiltrates resembling cutaneous Kikuchi's disease were found [49].

## Epidemiology

Calculation of EM incidence is hampered by the presumed high degree of unreported cases due to missed diagnoses and different etiology. As part of the German population-based registry for severe skin reactions, all cases of EM, SJS, and TEN in former Western Germany and West-Berlin from 1990 to 1992 were analyzed [50]. In this retrospective case-control study, the authors identified 63 EM cases, 139 SJS cases, 95 SJS/TEN overlap cases, 48 cases of TEN with macular lesions, and eight cases of TEN on large erythema. Furthermore, they were able to show a slight rise of EM and SJS cases during the study years, whereas the incidence of SJS/TEN overlap and TEN did not increase. In 1990 15, in 1991 16, and in 1992 32 cases of EM were reported, corresponding to an incidence of EM of 0.31 per million inhabitants in 1990, 0.24 in 1991, and 0.48 in 1992. For all mentioned disease groups, the reported calculated incidence for the less severe forms was between 0.83 and 0.89 per million inhabitants and year, for the more severe forms between 1.17 and 1.89 [50]. In a Seattle-based study including children, the incidence of severe EM, SJS, and TEN in hospitalized patients was 7.4 per million person-years in a collective of 3.8 million person-years observed [19]. Out of the 61 cases with severe drug reaction, 17 patients were diagnosed with EM, corresponding to 28% of patients, resulting in an incidence of 2.07 per million person-years. Differences in incidences between the German and the Seattle study might be due to under-/over-reporting, different genetic background, or different drug use. Therefore, further in-depth standardized international observational studies are strongly advised to learn more about epidemiology as well as pathogenesis of EM.

## Dermatopathology

Histological features of EM depend on the time point of biopsy during the disease course and the localization of skin biopsy [51, 52] in atypical and typical target lesions [53, 54]. Orfanos et al. described two types of bulla formation in conventional and electron-microscopy studies. Erythematous papular lesions consisted mainly of edema in the papillary layer with minimal or inexistent epidermal involvement. In contrast, classical target lesions revealed massive keratinocyte necrosis, resulting in dermal interface bullae formation (Fig. 2). The authors stated that the basement membrane zone was constantly in contact with the dermal layer [54]. In another study, histological findings were divided into a predominantly inflammatory pattern and a predominantly necrotic pattern [55]. As for the predominantly inflammatory pattern, papillary edema with dermal inflammatory infiltrates consisting of lymphocytes and histiocytes near the dermoepidermal junction were identified. Exocytosis was typically seen in these lesions with two

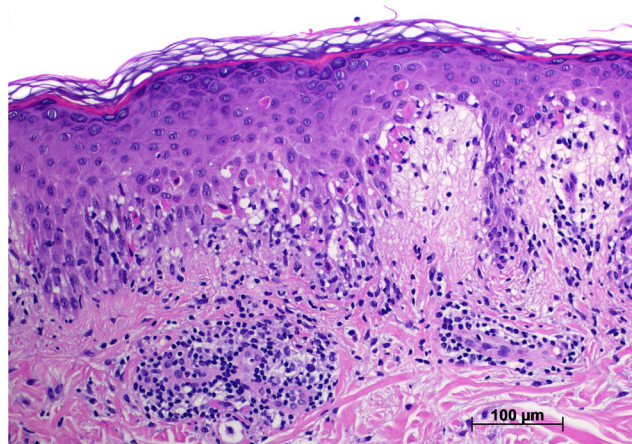


**Fig. 2** Histopathological findings in early EM. Spongiosis (intercellular edema), necrotic keratinocytes, and inflammatory infiltrate including lymphocytes in the dermoepidermal junction with focal epidermotropism and perivascular accentuation H&E, original magnification  $\times 20$

types of necrosis in the basal zone of the epidermis. One typical feature was satellite necrosis (necrotic keratinocytes surrounded by lymphocytes); the other feature was continuous necrosis predominantly in keratinocytes of the basal epidermal layers. In the predominantly necrotic pattern, widespread epidermal necrosis with detachment of the dermoepidermal zone was found; however, in these lesions, infiltration of lymphocytes and histiocytes was sparse. In both histological patterns, no signs of vasculitis were described. In the case of a predominantly inflammatory pattern, neutrophilic infiltration was seen in only one and eosinophilic infiltration in two patients. In a clinicopathological correlation, the same authors found a predominantly inflammatory pattern in 12 of 18, and a predominantly necrotic pattern in 6 of 18 patients investigated [55]. Interestingly, in HSV-related EM, the predominantly inflammatory pattern was typically seen, whereas in sulfonamide-related EM, the predominantly necrotic pattern was identified.

## Diagnostic Workup and Differential Diagnosis

The diagnosis of EM is based on the clinical appearance. Histopathological analysis including direct immunofluorescence is performed to confirm the diagnosis as well as to differentiate between EM and autoimmune mucocutaneous diseases, in particular pemphigus vulgaris (Fig. 3) and paraneoplastic pemphigus (Fig. 4), mucosal bullous pemphigoid (Fig. 5), and linear IgA dermatosis. In addition, primary herpetic infection (Fig. 6), other viral diseases such as hand-foot-mouth disease (Fig. 7), erosive lichen planus (Fig. 8), fixed drug eruption, lupus erythematosus, urticaria, cutaneous vasculitis, and some neutrophilic dermatoses have to be considered in the differential diagnosis of EM.



**Fig. 3** Mucosal involvement in pemphigus vulgaris

In addition, swabs to exclude infectious vesicle formation and autoimmune and virology workup, as well as diagnostic imaging in case of respiratory symptoms are recommended.

## Treatment

Treatment of EM depends on the severity of the disease manifestation, the underlying or coexisting causes, as well as on its acute, chronic or persistent course. In cases with a high suspicion of drug-induced EM, the first measure is to stop the drug with consecutive avoidance of re-exposure to the same drug or exposure to drugs with a potential for cross-reactivity due to similar chemical structures. In acute EM, systemic steroids are regularly given, although controlled studies are missing.

In cases of acute or recurrent HSV-associated EM, the use of antiviral therapy should be considered. Tatnall et al. performed a 6-month double-blind placebo-controlled study in 20 patients with recurrent EM, whereof 15 had a proven HSV association, with acyclovir 400 mg twice daily [56]. The study showed significant superiority of acyclovir compared to placebo treatment with regard to prevention of further EM episodes. Furthermore, after discontinuation of acyclovir, a fraction of patients remained in clinical remission, whereas all patients treated with placebo showed recurrence. A smaller study [57] treated four patients with oral acyclovir in a



**Fig. 5** Oral lesions in mucosal bullous pemphigoid

maintenance dose for up to 26 months. During the study, there was only one recurrence, and no significant side-effects of acyclovir were noticed. However, prophylactic topical treatment with acyclovir in patients with recurrent HSV-associated EM did not prevent further episodes of EM [58]. A small case series of three patients showed effectiveness of long-term therapy with valacyclovir in combination with immunoglobulin substitution in a patient with concomitant IgG1-subclass deficiency, and immunostimulation with Echinacea in the other two patients [59]. In another case series, three patients with recurrent HSV-associated EM pretreated with different medications, including valacyclovir, without sufficient response, were treated with famciclovir [60]. As famciclovir resulted in clinical response in all patients, the authors concluded that in the case of valacyclovir-resistant EM episodes, famciclovir should be considered as alternative treatment. A HCV-negative patient with recurrent HSV-related EM, where valacyclovir, colchicine, and hydroxychloroquine treatment was ineffective, only responded to interferon alpha administration [61]. Therefore, a major challenge is the treatment of patients with HSV-associated EM resistant to antiviral therapy. In a recent trial, six out of 13 patients without response to acyclovir, famciclovir, or valacyclovir showed complete response to dapsone treatment, whereas another five patients showed a partial response [62]. In another patient, disease control could be achieved by continuous acyclovir and



**Fig. 4** Lip involvement in paraneoplastic pemphigus



**Fig. 6** Primary herpetic infection

**Fig. 7** Hand-foot-mouth disease

azathioprine treatment [63]. Also, intermittent treatment with oral cyclosporine was shown to be effective in a patient with recurrent HSV-associated EM [64]. In a patient with HSV-associated EM, where tapering of valacyclovir and prednisone resulted in recurrence, adalimumab was successfully introduced as monotherapy [65]. Thalidomide with its known TNF- $\alpha$  modulating mode of action was effective in a 15-year-old patient with persistent EM [66]. Although concomitantly treated with several antiviral and immunosuppressive therapies such as valacyclovir, cyclosporine, azathioprine, dapsone, mycophenolate mofetil, and methotrexate, a patient with idiopathic EM, but no signs of HSV infection, showed recurring lesions upon tapering of prednisone below 20 mg/day. The histopathologic findings of skin biopsies were compatible with EM, and HSV was neither detected within lesions nor serologically. By performing whole exome sequencing, a heterozygous missense mutation in the TRPS-1 gene could be identified, that leads to an activation of Janus-kinase signal

transducer and activator of transcription (JAK). Oral treatment with the JAK-inhibitor tofacitinib resulted in remission [67]. Another new successful approach was reported by Chen et al., using the phosphodiesterase (PDE)-4 inhibitor apremilast in three patients with oral EM [68].

## Conclusions

Due to its typical clinical and histological features, its frequent association with HSV, and its potentially recurrent course, EM represents a distinct entity that is difficult to subsume under the classical bullous drug-induced exanthems like SJS and TEN.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Informed Consent** When necessary, informed consent has been collected from patients.

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**Fig. 8** Erosive lichen planus of penis

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