Review

Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist

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Abstract

Erythema multiforme (EM) is an uncommon, immune-mediated disorder that presents with cutaneous or mucosal lesions or both. In herpes simplex virus (HSV)—associated EM, the findings are thought to result from cell-mediated immune reaction against viral antigen-positive cells that contain the HSV DNA polymerase gene (pol). The target lesion, with concentric zones of color change, represents the characteristic cutaneous finding seen in this disorder. Although EM can be induced by various factors, HSV infection continues to be the most common inciting factor. Histopathologic testing and other laboratory investigations may be used to confirm the diagnosis of EM and to differentiate it from other clinical imitators. Imitators of EM include urticaria, Stevens-Johnson syndrome, fixed drug eruption, bullous pemphigoid, paraneoplastic pemphigus, Sweet's syndrome, Rowell's syndrome, polymorphus light eruption, and cutaneous small-vessel vasculitis. Because disease severity and mucosal involvement differ among patients, treatment should be tailored to each patient, with careful consideration of treatment risk vs benefit. Mild cutaneous involvement of EM can be managed primarily with a goal of achieving symptomatic improvement; however, patients with HSV-associated recurrent EM and idiopathic recurrent EM require treatment with antiviral prophylaxis. Inpatient hospitalization may be required for patients with severe mucosal involvement that causes poor oral intake and subsequent fluid and electrolyte imbalance. With this review, we strive to provide guidance to the practicing dermatologist in the evaluation and treatment of a patient with EM.

Introduction

Erythema multiforme (EM) is an acute, immune-mediated, mucocutaneous condition that is most commonly caused by herpes simplex virus (HSV) infection and the use of certain medications.1–3 It is characterized by acrally distributed, distinct targetoid lesions with concentric color variation, sometimes accompanied by oral, genital, or ocular mucosal erosions or a combination of these.1 Erythema multiforme with mucosal involvement is called erythema multiforme major; in the absence of mucosal disease, EM is called erythema multiforme minor. Although EM is usually self-limiting, frequent episodes over the course of years can lead to recurrent disease in a subset of patients.3

Until recently, EM was considered to represent a spectrum of disorders, including EM major, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis. However, a consensus clinical classification provided evidence that suggests that EM major and SJS are separate, distinct disorders which manifest with similar mucosal erosions but different cutaneous lesions.1,4–5

In this review, we discuss the epidemiology, pathogenesis, clinical features, evaluation, diagnosis, treatment, and prognosis of EM.

Epidemiologic factors

The exact incidence of EM is unknown; however, it is postulated to be far less than 1% but possibly greater than 0.01%.6 It occurs predominantly in young adults, with a slight female preponderance and without racial predilection.2–6,7

Etiologic characteristics

The medical literature has linked numerous factors to the development of EM. These include infections, medication use, malignancy, autoimmune disease, radiation, immunization, and menstruation.6 Of these factors, infection represents approximately 90% of cases, and the most common infectious agent is HSV.2,6–7 Although HSV type 1 is the most commonly associated cause, HSV type 2 can also
induce EM. Another well-recognized infectious agent that has a documented, clear association with EM is *Mycoplasma pneumoniae*. This bacterium appears to have particular importance in the development of EM in children. Drug-associated EM is reported in less than 10% of cases. Although numerous drug culprits have been identified, the most common disease-precipitating medications are nonsteroidal anti-inflammatory drugs, sulfonamides, antiepileptics, and antibiotics (Table 1).

### Recurrent EM

The frequent occurrence of EM over a period of years is known as recurrent erythema multiforme. In patients whose condition fits into this subgroup, research studies have shown an average of six EM episodes per year and mean disease durations of 6–10 years.

Recurrence of EM has been linked to multiple factors. Previous studies have reported that an estimated 61–100% of recurrent EM cases are caused by HSV infection. A series of 48 patients at Mayo Clinic showed HSV infection to be the most common cause of recurrent EM, although only 25% of cases in the series demonstrated a clear association with it. Repeated

### Persistent EM

A rare variant of EM characterized by the continuous occurrence of typical and atypical lesions without interruption is referred to as persistent erythema multiforme. Lesions of this entity typically are papulonecrotic or bullous and have widespread involvement. Mucosal involvement is not required for the diagnosis of persistent EM.

Cases of persistent EM are rare in the medical literature. Associations with viral infections have been reported, such as HSV, Epstein–Barr virus, hepatitis C virus, influenza virus, and cytomegalovirus. In addition, associations with inflammatory bowel disease and various neoplasms have been reported (Table 1).

### Pathogenesis

Genetic susceptibility can be a predisposing factor in some patients with EM. Specifically, in a study of 35 EM

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<th>Table 1 Causes of erythema multiforme (EM)</th>
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<td>Isolated</td>
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<td>Drugs</td>
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<td>Recurrent (&gt;6 episodes of EM per year)</td>
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<tr>
<td>Persistent (continuous episodes of EM)</td>
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</table>

### Figure 1

Clinical features of recalcitrant recurrent erythema multiforme. (Data from Wetter and Davis)
patients and 80 control subjects, 66% of EM patients were found to carry the HLA-DQB1*0301 allele compared with 31% of control subjects. This association was stronger in patients with HSV-associated EM. Among patients with recurrent EM, reports exist of increased disease susceptibility in association with the HLA-B35, HLA-B62, and HLA-DR5 alleles. Erythema multiforme

Mechanisms describing the pathogenesis of EM have been based on investigative studies of HSV-associated EM. Such EM is thought to result from cell-mediated immune reaction against viral antigen-positive cells that contain the HSV DNA polymerase gene (pol). This hypothesis is supported by HSV detection in paraffin-embedded biopsy specimens from patients with EM.

A few days after a recurrent HSV infection, the virus is present in the blood. The virus is then phagocytosed by circulating peripheral blood mononuclear cells, such as macrophages and CD34+ Langerhans cell progenitors, which have skin homing receptor cutaneous lymphocyte antigen. Then, the engulfed HSV DNA is transported to the epidermis, where the fragmented viral DNA is transferred to the keratinocytes. Upregulation of E-cadherin expression increases the binding of HSV-containing Langerhans cells to endothelial cells. In addition, adhesion molecule upregulation on endothelial cells accounts for the dermal inflammatory response.

Herpes simplex virus pol DNA is located in the basal keratinocyte and lower spinous cell layers. Expression of viral DNA fragments, including the viral pol gene, in the keratinocyte layer leads to activation of HSV-specific CD4+ T helper 1 (Th1) cells. This virus-specific response also produces effector cytokines, such as interferon-γ (IFN-γ). The release of IFN-γ leads to a nonspecific inflammatory amplification through autoreactive T cells. These cells and cytokines are responsible for the pathologic findings seen in EM.

The reason why only a small proportion of patients with recurrent HSV infection have EM is unknown. Factors that have been implicated in the development of HSV-associated EM include incomplete fragmentation of viral DNA by phagocytic cells, an increased number of CD34+ cells, and the presence of factors that affect the development of an autoreactive response to pol protein, or a combination of these factors.

Although the effector cytokine in HSV-associated EM is IFN-γ, cases of drug-induced erythema multiforme are associated with tumor necrosis factor-α (TNF-α), perforin, and granzyme B, which cause the epidermal destruction seen in the disease. Interestingly, EM has been reported to occur in the clinical setting of TNF-α inhibitor therapy.

Clinical presentation

Prodromal symptoms
In most cases of EM, prodromal symptoms of malaise, fever, and myalgias are not prominent. However, in cases of EM accompanied by mucosal involvement, prodromal symptoms are common. Usually, it is unclear whether these symptoms are part of EM or part of the infectious illness that may have led to the EM. In general, prodromal symptoms present a week or more before the onset of EM.

Cutaneous features
The clinical manifestation of EM may vary from one patient to another. In addition, a patient may have various skin lesions that change and evolve in appearance during the course of the illness. These clinical challenges sometimes make a simple morphologic description of EM difficult.

Morphologic characteristics
The earliest lesions of EM are usually round, erythematous, edematous papules surrounded by areas of blanching that may resemble insect bites or papular urticaria. These papules may enlarge and develop concentric alterations in morphologic features and color, resulting in the well-known targetoid lesions of EM. The morphologic features of a targetoid lesion include a central portion of epidermal necrosis that can appear as a dusky area or blister. Immediately outside the central portion is a dark red, inflammatory zone surrounded by a lighter edematous ring with an erythematous zone on the extreme periphery.

Lesions may evolve during the course of EM, leading to alterations in the concentric morphologic characteristics and thereby producing geographic, polycyclic, and annular configurations. Patients with EM can also present with atypical lesions. However, unlike the typical targetoid signs, these areas manifest as round, edematous, palpable lesions with only two zones or a poorly-defined border or both. Figures 2–4 depict typical and atypical targetoid lesions of EM.

Lesion distribution
In classic EM, the lesions are most commonly distributed symmetrically on the acral extremities and show a predilection for the extensor surfaces. Although lesions ultimately may spread in a centripetal fashion, the trunk is usually far less affected than the extremities. In many cases, it is not unusual to have palmoplantar involvement.

The preferential appearance of EM lesions in areas of physical trauma and sunburn suggests an isomorphic phenomenon and a photo accentuation, respectively. Finally,
grouping of lesions around the elbows and knees and edema of the nail folds are other features that may be seen in EM.  

**Mucous membrane disease**

The frequency of mucosal lesions in EM has been estimated at 25–60%.  Mucosal involvement usually occurs simultaneously with skin involvement, although it can precede or follow the onset of skin lesions by several days. Rarely, patients may present with mucosal lesions in the absence of cutaneous involvement.  

The most common mucosa involved in EM is the oral mucosa, which can be involved in up to 70% of patients.  Usually, involvement of the labial mucosa, buccal mucosa, non-attached gingivae, and vermilion lip is seen.  Lesions initially present as erythema with some edema and progress to superficial erosions with pseudomembrane formation.

Although lesions most frequently affect the oral mucosa, involvement of the ocular, genital, upper respiratory, or pharyngeal mucosa can also occur. In a study of 65 patients...
with recurrent EM, 69% had oral disease, 25% had genital lesions, and 17% had ocular involvement.10

Course of illness

Classic EM is a self-limiting skin disease. However, some patients have frequent episodes over years (recurrent EM) and, rarely, others may have continuous uninterrupted disease (persistent EM). The lesions of EM typically appear over 3–5 days and resolve over 1–2 weeks.6,24 The period from disease onset to resolution is <4 weeks. However, in severe cases of EM with mucosal involvement, resolution may require up to six weeks.6,24

Itching and burning skin, swelling of hands and feet, pain caused by mucosal erosions, and poor oral and fluid intake are important causes of morbidity in EM.6 Although the skin lesions do not lead to scarring, a resultant post-inflammatory hyperpigmentation may persist for months after disease resolution.24

Patients with ocular mucosa involvement may have keratitis, conjunctival scarring, uveitis, or permanent visual impairment.24 Esophagitis with esophageal strictures and upper airway erosions leading to pneumonia are rare, serious complications.6,24

Laboratory findings

No available diagnostic laboratory tests assist in making a diagnosis of EM.2,8 Laboratory abnormalities, such as increased erythrocyte sedimentation rate, white blood cell count, and liver enzyme levels, can be seen in cases of severe disease.6,8,24 A serum antinuclear antibody (ANA) test may be helpful in cases in which cutaneous lupus erythematosus (Rowell’s syndrome) is a consideration.8,24

Histopathologic features

Histopathologic testing of EM lesions can be useful in differentiating EM from other diseases that may have a similar clinical presentation. On such testing, mucous membrane EM and cutaneous EM have similar pathologic features. Pathologic findings include liquefactive degeneration of the basal epidermal cells, necrotic keratinocytes, and exocytosis of lymphocytes. In some cases, subepidermal clefts and vesiculation may develop secondarily to extensive basal cell vacuolar degeneration. Mild to moderate lymphohistiocytic infiltrate in a lichenoid pattern may obscure the dermo–epidermal junction. A dermal infiltrate typically shows lymphohistiocytic infiltrate surrounding the superficial and mid-dermal vessels.8,10

Erythema multiforme can be divided into epidermal, dermal, and mixed subtypes according to the predominance of various histologic features.25 The histopathologic subtype may be influenced by biopsy site and the evolutionary stage of the lesion. Dermal changes, such as papillary dermal edema, vascular dilation, and perivascular mononuclear cell infiltrates, are more prominent in the earliest papules and in biopsies from peripheral portions of lesions. Epidermal changes, such as necrosis, are seen more prominently in lesions undergoing evolution and develop most fully in the dusky central portion of targetoid lesions and blisters20 (Fig. 6).

The purpose of direct immunofluorescence (DIF) in EM is to obtain findings of other diseases that are considered in the differential diagnosis because findings on DIF in EM are usually nonspecific. Possible findings include granular deposition of C3 and immunoglobulin M (IgM) at the dermo–epidermal junction and the superficial blood vessels. In addition, homogeneous C3 and IgM staining of focal epidermal cells can be seen in regions of epidermal necrosis.20

Malignancy in EM

Although malignancy-associated EM is rare, it has been described in patients with underlying hematologic cancers, such as leukemias and lymphomas.26 In patients with persistent EM or with EM unresponsive to therapy, solid organ cancers, such as gastric adenocarcinoma,16 renal cell carcinoma,27 and extrahepatic cholangiocarcinoma,28 have been reported. Therefore, it may be prudent to perform a thorough clinical evaluation and selected laboratory testing to rule out underlying infectious, inflammatory, autoimmune, or malignant disorders in patients with idiopathic recurrent erythema or persistent EM.
Evaluation of EM

No specific objective markers or criteria are required for a diagnosis of EM. The important clues to diagnosis continue to be the clinical history and clinical findings. Pertinent components of the history include: (i) an acute, self-limiting or episodic course; (ii) signs and symptoms of associated infections, such as HSV or M. pneumoniae infection and (iii) a history of the use of new medications. Clinical clues to diagnosis include the presence of targetoid lesions, raised atypical papules or mucosal involvement, or a combination of these. Laboratory studies and skin biopsies are not required in all cases of EM. However, laboratory evaluation and histopathology may assist in confirming the diagnosis, determining the inciting factor and ruling out other diseases in the differential diagnosis.

Although histopathologic changes are not always diagnostic of EM, they can be helpful in excluding other disorders. Similarly, although no specific DIF findings of EM exist, performing a DIF study of perilesional skin can rule out autoimmune bullous disease if it is considered in the differential diagnosis. Indirect immunofluorescence (iDIF) testing can also be useful in making a diagnosis of autoimmune bullous disease.

Evaluation of EM should include testing for the common inciting factors. Because the most common cause of EM is HSV infection, every patient with EM should be evaluated for this underlying infection. This evaluation should include a thorough clinical history and examination. Skin and mucosal lesions suspicious for HSV infection should be sampled to confirm the presence of the virus through Tzanck smear, PCR studies, or viral culture.

Recurrent HSV infections have been implicated in recurrent EM. Patients with idiopathic EM may have subclinical HSV infection. In these cases, HSV DNA may be detected through PCR of skin biopsy specimens. Serologic evaluation for HSV will help to exclude HSV-associated EM when tests for IgM and IgG antibodies are negative; however, antibody titers are not useful for detecting episodes of recurrent disease.

As the second most common infectious cause of EM, M. pneumoniae infection should be considered in patients with respiratory symptoms. Evaluation for this infection should include a chest radiograph, PCR testing of throat swabs, and serologic tests for M. pneumoniae. Usually, a diagnosis is confirmed through the presence of IgM antibodies or a greater than two-fold increase in IgG antibodies.

Low serum complement levels have been reported to accompany persistent EM. Therefore, serum complement levels should be checked. Although malignancy-associated EM is rare, malignancy most commonly occurs in persistent or idiopathic recurrent EM. Of note, selected studies should be performed to rule out an underlying malignancy. The decision to test can be based on a thorough review of systems in patients with persistent or recurrent EM.

Finally, severe cases of mucosal EM with associated poor oral intake may warrant inpatient hospitalization for pain management and close monitoring of fluids and electrolytes. In these patients, erythrocyte sedimentation rate, white blood cell count, and liver function enzymes should be checked because they may be increased in severe cases of EM.

Differential diagnosis

The clinical presentation and patient history should provide the most pertinent information in making a diagnosis of EM. However, other conditions should be considered in the differential diagnosis. A prompt diagnosis is important because some of the other diseases considered in the differential must be managed urgently to prevent the development of life-threatening complications. Imitators of EM include urticaria, SJS, fixed drug eruption, bullous pemphigoid, paraneoplastic pemphigus (PNP), Sweet's syndrome, Rowell’s syndrome, and polymorphous light eruption (PMLE) (Table 2). Urticaria is a common skin lesion characterized by a wheal-and-flare reaction that is typically pruritic. Unlike EM, in which the lesion is fixed and all lesions appear within the first 72 hours of disease, each urticarial lesion is transient, lasting <24 hours, and new lesions can appear daily. The lesions are circumscribed, edematous, and erythematous in appearance and have a central zone of erythema or normal skin, unlike the dusky necrotic or bullous center seen in EM. Patients with urticaria may have coexisting mucosal edema commonly referred to as angioedema. Histologically, urticaria shows superficial dermal edema with mild perivascular and interstitial inflammation consisting of lymphocytes, eosinophils, mast cells and, occasionally, neutrophils. However, unlike EM, epidermal changes are notably absent.

Stevens-Johnson syndrome and EM are two distinct disorders which show similar mucosal erosions but different patterns of cutaneous disease. The former is characterized by widespread erythematous or purpuric macules or atypical targetoid lesions that, unlike those in EM, are macular rather than papular. In addition, SJS typically is more prominent on the trunk and spreads distally, whereas EM classically shows an acral predominance. Medications are the most frequent cause of SJS, and the urgent withdrawal of suspected causative drugs is imperative. Because histopathologic findings cannot reliably distinguish severe EM from SJS, clinical features should...
be used to make this distinction. Stevens–Johnson syndrome may show more extensive epidermal necrosis with fewer inflammatory cells than EM. In addition, constitutional symptoms often accompany SJS; thus prompt recognition is essential because of the possibility of life-threatening complications and the risk for progression to toxic epidermal necrolysis.

Fixed drug eruption shares many of the clinical and pathologic features of EM. Similarly to EM, the histopathology of fixed drug eruption shows an interface reaction pattern. However, it can be distinguished from EM by the deeper extension of the infiltrate, the presence of a few neutrophils and more prominent melanin incontinence. Although the clinical lesions of dusky erythematous plaque with or without central bullae or necrosis are similar in fixed drug eruption and EM, usually fixed drug eruption involves fewer lesions. In addition, lesion development in fixed drug eruption is typically preceded by medication history.

Clinical history
- Acute, episodic, self-limiting
- Symptoms of HSV, *Mycoplasma pneumoniae* and other infections
- Thorough medication history

Clinical examination
- Acral extremities
- Typical targets
- Raised atypical targets
- Mucosal involvement

Skin biopsy
- Hematoxylin and eosin stain
- Direct immunofluorescence (perilesional normal skin when concern for immunobullous disease)
- Tzanck smear and/or skin, oral or genital swab sent for HSV PCR

Laboratory studies
- Testing for ESR, white blood cell count, liver function enzymes, electrolytes
- When respiratory symptoms, then *M. pneumoniae* serologic testing, chest radiograph, throat swab PCR for *M. pneumoniae*
- Indirect immunofluorescence to rule out autoimmune blistering disorder

Special considerations in recurrent idiopathic EM
- Molecular ISH/PCR for HSV on skin biopsy specimen
- Serologic HSV testing
- Selected laboratory tests to rule out underlying infectious, inflammatory, autoimmune or malignant disorders

Special considerations in persistent EM
- Serum complement

Figure 7 Evaluation of erythema multiforme (EM). ESR, erythrocyte sedimentation rate; HSV, herpes simplex virus; ISH, in situ hybridization; PCR, polymerase chain reaction.
<table>
<thead>
<tr>
<th>Differential diagnosis of EM</th>
<th>Features that distinguish from EM</th>
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| **Urticaria**               | Transient plaques with central zone of normal skin or erythema  
                              | May have associated mucosal edema  
                              | Pathologic  
                              | Prominent papillary edema with mild perivascular and interstitial infiltrate containing eosinophils, lymphocytes, mast cells and, occasionally, neutrophils  
                              | Laboratory  
                              | None |
| **Stevens–Johnson syndrome**| Macular atypical targetoid lesions, widespread dusky erythema with blisters  
                              | Usually begins on trunk and spreads distally  
                              | Painful, tender skin  
                              | Severe mucosal involvement (mucosal erosions present in at least one site in >90% of patients)*  
                              | Presence of constitutional symptoms  
                              | Pathologic  
                              | Extensive epidermal necrosis with paucity of inflammatory cells  
                              | Laboratory  
                              | None |
| **Fixed drug eruption**     | Dusky plaques with/without central necrosis  
                              | Fewer clinical lesions  
                              | Typically with medication history  
                              | Less frequent mucosal involvement  
                              | Pathologic  
                              | Similar to EM, but fixed drug eruption may have deeper extension of infiltrate, few neutrophils and prominent melanin incontinence  
                              | Laboratory  
                              | None |
| **Bullous pemphigoid**      | Pruritic urticarial plaques, tense bullae  
                              | May have mucosal involvement  
                              | Pathologic  
                              | Eosinophilic spongiosis or subepidermal bullae with numerous eosinophils  
                              | Direct immunofluorescence findings of linear C3 and IgG basement membrane zone deposition  
                              | Laboratory  
                              | Presence of BP180 and BP230 autoantibodies  
                              | Indirect immunofluorescence showing anti-basement membrane IgG antibodies  
                              | Evidence of epidermal pattern on salt-split skin immunofluorescence |

*Table 2 (Continued)*

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<tr>
<th>Differential diagnosis of EM</th>
<th>Features that distinguish from EM</th>
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| **Paraneoplastic pemphigus**| Clinical  
                              | Polymorphous, progressive skin lesions  
                              | Severe mucosal involvement  
                              | Presence of underlying malignancy  
                              | Pathologic  
                              | Vacular or lichenoid interface dermatitis with suprabasilar acantholysis  
                              | Direct immunofluorescence findings of cell-surface IgG deposition or combined cell surface and basement membrane zone of IgG and C3 deposition  
                              | Laboratory  
                              | Autoantibodies against desmoglein 1 and desmoglein 3  
                              | Demonstration of antiplakin antibodies through indirect immunofluorescence against rat bladder or immunoblotting against epidermal cell extracts |
| **Sweet’s syndrome**        | Clinical  
                              | Edematous, erythematous plaques  
                              | Pyrexia  
                              | No mucosal involvement  
                              | Pathologic  
                              | Dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis  
                              | Laboratory  
                              | Peripheral leukocytosis with neutrophilia |
| **Rowell’s syndrome**       | Clinical  
                              | Large target-like lesions, annular plaques  
                              | Chilblains  
                              | Pathologic  
                              | Interface dermatitis  
                              | Direct immunofluorescence may show continuous granular deposition of multiple immunoglobulin conjugates and complement components  
                              | Laboratory  
                              | Antinuclear antibodies (speckled pattern)  
                              | Anti-Ro or anti-La antibody and positive for rheumatoid factor |
| **Polymorphous light eruption**| Clinical  
                              | Photodistributed erythematous papules, plaques  
                              | Pathologic  
                              | Although similar histologic findings, epidermal change and interface reaction pattern are more frequent in EM  
                              | Laboratory  
                              | Absence of HSV infection |

Table 2 (Continued)

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<tr>
<th>Differential diagnosis of EM</th>
<th>Features that distinguish from EM</th>
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<tr>
<td>Cutaneous small-vessel vasculitis (CSVV)</td>
<td>Clinical: Typical palpable purpura, lesions that resolve with bruise-like discoloration. Pathologic: Leukocytoclastic vasculitis. Laboratory: Studies elucidating particular etiologic factors of CSVV (i.e., infection, drug use, autoimmune connective tissue disease, and malignancy).</td>
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HSV, herpes simplex virus; IgG, immunoglobulin G.
"Data from Bastuji-Garin et al."

Bullous pemphigoid is a chronic, autoimmune blistering disease notable for the occurrence of urticarial, erythematous plaques and tense bullae that may have associated mucosal involvement. Unlike in EM, histopathologic testing shows eosinophilic spongiosis or subepidermal bulla with numerous eosinophils, and DIF is positive for IgG and C3 linear basement membrane zone deposition. Further investigations should reveal the presence of BP180 and BP230 antibodies, which are absent in EM. Finally, in bullous pemphigoid, DIF on human skin or monkey esophagus shows the presence of anti-basement membrane IgG antibodies, and immunofluorescence on salt-split skin typically shows an epidermal pattern.

Paraneoplastic pemphigus is characterized by severe and intractable oral mucositis with a polymorphous blistering eruption associated with an overt or occult malignancy, particularly lymphoma and Castleman’s disease. Erythema multiforme has an acute self-limiting, episodic course; by comparison, PNP is insidious in onset and chronic in course. Although interface dermatitis changes are seen in both EM and PNP, histopathologic testing for PNP also shows acantholysis, which is not seen in EM. Direct immunofluorescence of cell surface IgG deposition is seen in PNP and is absent in EM. Finally, desmoglein 1 and desmoglein 3 antibodies and antiplakin antibodies can be demonstrated in patients with PNP but will be absent in EM.

Sweet’s syndrome is an acute neutrophilic dermatosis that may be associated with infection of the upper respiratory tract or gastrointestinal tract. In addition, it may present as a cutaneous paraneoplastic syndrome with associated undiagnosed or relapsing hematologic malignancy or solid tumor. The clinical features of the syndrome are similar to those in EM and include edematous, erythematous plaques, although patients with Sweet’s syndrome tend to appear more ill. On histopathologic testing, patients with Sweet’s syndrome show a dense neutrophilic infiltrate with pronounced dermal edema, which is not seen in EM.

Rowell’s syndrome is a rare clinical disorder characterized by the presence of lupus erythematosus lesions and EM-like lesions. Unlike in classic EM, patients with Rowell’s syndrome have lupus erythematosus-type lesions (discoid, subacute cutaneous, or acute cutaneous lupus erythematosus) and may also have chilblains. A DIF study may show continuous granular deposition of multiple immunoglobulin conjugates and complement components in Rowell’s syndrome that will not be seen in classic EM. Antinuclear antibodies show a speckled pattern, and further investigations may show a positive rheumatoid factor and the presence of anti-Ro and anti-La antibodies.

Polymorphous light eruption may mimic the recurrent lesions of EM with the development of recurrent papulovesicles and plaques. Histopathologic findings in PMLE may be similar to those in EM, yet primary histopathologic testing in PMLE shows dermal edema with superficial and deep perivascular infiltrate consisting mainly of lymphocytes. The interface reaction pattern demonstrated in EM is rarely seen in PMLE. Unlike most cases of recurrent EM, PMLE is not associated with a preceding HSV infection but, instead, with prior ultraviolet radiation exposure.

Cutaneous small-vessel vasculitis (particularly urticarial vasculitis and childhood Henoch–Schönlein purpura) also may present with urticarial or targetoid lesions that may mimic EM lesions. Routine histopathologic evaluation showing classic changes of leukocytoclastic vasculitis, as well as DIF microscopy, can readily distinguish this entity from EM.

For patients with frequently recurring oral EM, other conditions for consideration in the differential diagnosis include pemphigus vulgaris, mucous membrane pemphigoid, oral lichen planus, and complex aphthosis. Biopsy specimens sent for DIF microscopy and serum studies sent for iDIF and enzyme-linked immunosorbent assay (e.g., BP180 and BP230, desmoglein 1 and desmoglein 3) can help to distinguish among these conditions.

Treatment of EM

An important element in EM treatment is the discontinuation of all inciting factors. In cases of drug-induced EM, this entails stopping the administration of offending medication. In addition, disease management depends on other factors, such as the presence of mucosal disease, the development of recurrent disease and overall disease severity (Table 3).
Acute EM

Acute EM is most commonly preceded by HSV infection. The average interval from infection to disease onset is eight days. Several studies have indicated that administering anti-HSV drugs for the treatment of full-blown post-herpetic EM does not alter the clinical course of this self-limiting disorder. In cases of M. pneumoniae infection, appropriate antibiotic therapy should be considered if the patient is symptomatic. Otherwise, mild cutaneous involvement of EM can be managed primarily with the goal of achieving symptomatic improvement. This management usually includes the use of topical corticosteroids and oral antihistamines for reports of pruritus or burning, or both.

Mucosal EM

Mucosal involvement in EM may vary in severity. Patients with minimal involvement, such as painful erosions, can be treated with high-potency topical corticosteroid gel, oral antiseptic washes, and oral anesthetic solutions. Unfortunately, some patients have extensive mucosal involvement and debilitating pain that prevents sufficient oral intake. These patients may require systemic glucocorticoids (such as prednisone [40–60 mg/d with dosage tapered over 2–4 weeks]) to decrease severity and disease duration, although there are no controlled studies to support this recommendation. Ophthalmology consultation is imperative for patients with ocular involvement in order to evaluate and manage involvement and to prevent long-term sequelae. Ophthalmic preparations should be used at the discretion of the ophthalmologist.

Recurrent EM

The treatment of recurrent EM is usually prolonged and challenging. In patients with HSV-associated recurrent EM and idiopathic recurrent EM, the first-line treatment is antiviral prophylaxis. Antiviral therapy can be approached as continuous oral therapy, or topical therapy. However, continuous antiviral therapy for 26 months has been documented as the most effective approach. The best antiviral treatment response is seen in patients in whom the association between HSV infection and occurrence of EM is clear. Treatment recommendations include acyclovir (400 mg twice daily), valacyclovir (500 mg twice daily), and famciclovir (250 mg twice daily). The treatment goal is to reduce the frequency of EM occurrences and to induce remission. In non-responsive EM, the medication dose may be doubled or another antiviral drug may be substituted.

Unfortunately, remission is difficult to maintain despite treatment. For instance, in a study of complete and partial remission induced in patients receiving a six-month continuous antiviral therapy for HSV-induced EM, only four of 15 patients maintained remission on the discontinuation of therapy. In general, patients who respond to continuous antiviral therapy should be treated for 1–2 years before therapy is discontinued. When EM recurs after the discontinuation of therapy, medication should be restarted at the lowest effective dose and therapy cessation can be reattempted in 6–12 months.

Recurrent EM that is resistant to prophylactic antiviral therapy may require treatment with other systemic agents. Treatments that have been used include azathioprine, dapsone, mycophenolate mofetil, immunoglobulin, hydroxychloroquine, thalidomide, and cyclosporine.

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**Table 3 Approaches to treatment of erythema multiforme (EM)**

<table>
<thead>
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<th>Subtype</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Acute EM</td>
<td>Avoid all inciting factors, such as medication use. Mild disease. Oral antihistamines. HSV-induced EM. Antiviral suppressive therapy (treatment after appearance of HSV-induced EM does not affect clinical course). Mycoplasma pneumoniae–associated EM.</td>
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HSV, herpes simplex virus.

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**Notes:**

1. Sokumbi and Wetter 2012
3. © 2012 The International Society of Dermatology
Unfortunately, most of these treatments have not been validated in controlled trials, are inconsistently effective, and have associated adverse effects.

In a small series of 65 patients with recurrent EM, azathioprine was used successfully at a dose of 100–150 mg daily in 11 patients with severe EM that had been unresponsive to other therapy. Most of these patients did not have associated HSV infection and did have disease recurrence on therapy discontinuation. This result conflicts with the findings of another study, which reported that two of five patients achieved complete or partial response with azathioprine. Thiopurine methyltransferase levels should be checked because myelosuppression occurs more frequently in patients with depressed thiopurine methyltransferase activity.

Dapsone has been reported to be effective in treatment of recurrent EM. In a series of 10 patients treated with dapsone (<200 mg/d), 50% of the patients achieved either complete or partial remission. Similarly, eight of nine patients treated with dapsone (100–150 mg/d) achieved either complete or partial remission. This drug necessitates close monitoring because its adverse effects include hemolytic anemia, methemoglobinemia, and agranulocytosis. Hemolytic anemia is more pronounced in patients with a deficiency of glucose-6-phosphate dehydrogenase.

Mycophenolate mofetil is another treatment option that may have some efficacy in recurrent EM. In the series of 48 patients with recurrent EM treated at Mayo Clinic, six of the eight patients treated with mycophenolate mofetil (≤2 g/d) achieved complete or partial remission. Other therapies with some documented benefit in recurrent EM include antimalarial therapy and immunoglobulin. Two of four patients with EM treated with antimalarial therapy noted a clinical response on treatment completion. Immunoglobulin treatment (750 mg) was given intramuscularly to 13 patients, 11 of whom reported disease suppression with treatment. However, in another series in which immunoglobulin was given intravenously, only one of three patients noted treatment response. Regardless of the systemic therapy chosen, the risks and benefits of the therapy should be carefully considered.

### Table 4

<table>
<thead>
<tr>
<th>Generic drug</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Aciclovir, Zovirax</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Imuran</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Zithromax</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>N/A</td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>Ciclosporin, Gengraf, Neoral</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Aczone</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>Farmir</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Plaquenil</td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>Immune Globulin</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>CellCept</td>
</tr>
<tr>
<td>Prednisone</td>
<td>N/A</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Thalomid</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>Valaciclovir, Valtrex</td>
</tr>
</tbody>
</table>

N/A, not applicable.

(Tables 4). Unfortunately, most of these treatments have not been validated in controlled trials, are inconsistently effective, and have associated adverse effects.

### Conclusions

Erythema multiforme is an acute, immune-mediated mucocutaneous condition commonly caused by HSV infection and the use of certain medications. The targetoid lesion, with concentric zones of color change, represents the primary cutaneous finding characteristic of this disorder. Both clinical findings and histopathologic features may assist in differentiating this entity from clinical mimickers, such as urticaria, SJS, fixed drug eruption, bullous pemphigoid, PNP, Sweet’s syndrome, Rowell’s syndrome, PMLE, and cutaneous small-vessel vasculitis. After a diagnosis of EM has been made, treatments should be initiated according to the presence of mucosal disease, development of recurrent disease, overall disease severity, or a combination of these. Although symptomatic treatment may be sufficient in managing mild cutaneous EM, HSV-associated recurrent EM and idiopathic recurrent EM require treatment with antiviral prophylaxis. Therapy-resistant cases of recurrent EM may require immunosuppressive medication, such as azathioprine and mycophenolate mofetil. In addition, inpatient hospitalization may be required for patients with severe mucosal involvement that causes poor oral intake and subsequent fluid and electrolyte imbalance.

### Questions (see answers on page 902)

1. The most common cause of erythema multiforme is?
   a. Inflammatory bowel disease.
   b. *Mycoplasma pneumoniae* infection.
   c. Herpes simplex virus infection.
   d. Lupus erythematosus.
   e. Medication use.

2. An 8-year-old boy presents with targetoid lesions on his hands and face. He has recently received a 5-day course of azithromycin for treatment of a febrile illness with upper respiratory symptoms. He has no prior history of herpes simplex virus infection. What is the most likely inciting agent of his condition?
   a. Epstein–Barr virus.
   b. *Mycoplasma pneumoniae* infection.
   c. Azithromycin therapy.
   d. Parvovirus B19 infection.
   e. Adenovirus infection.
3. Which of the following might predict a protracted course in a patient with recurrent erythema multiforme?
   a. Family history of erythema multiforme.
   b. Absence of mucous membrane involvement.
   c. Presence of prodromal symptoms.
   d. Inability to identify a specific cause.
   e. History of herpes labialis infection.

4. Which of the following cytokines has been implicated in the etiology of herpes simplex virus–associated erythema multiforme?
   a. Tumor necrosis factor-α.
   b. Interferon-γ.
   c. Interleukin 1.
   d. Transforming growth factor-β.
   e. Interferon-β.

5. Which of the following locations is the most common mucosal site affected in erythema multiforme?
   a. Genital.
   b. Ocular.
   c. Pharyngeal.
   d. Esophageal.
   e. Oral.

6. Which of the following factors favors a diagnosis of erythema multiforme vs. Stevens–Johnson syndrome?
   a. Presence of severe oral mucosa involvement.
   b. Presence of widespread dusky erythema.
   c. Truncal distribution.
   d. Presence of raised atypical targetoid lesions.
   e. Recent medication exposure.

7. What is the first-line treatment of idiopathic recurrent erythema multiforme?
   a. Continuous antiviral therapy.
   b. Oral corticosteroids.
   c. Azathioprine.
   d. Hydroxychloroquine.
   e. Mycophenolate mofetil.

8. The main purpose of obtaining a biopsy for direct immunofluorescence in cases of suspected erythema multiforme is to?
   a. Rule out other diseases with a similar clinical presentation.
   b. Demonstrate findings of a lichenoid tissue reaction pattern.
   c. Highlight stains of the superficial dermal vessels.
   d. Confirm the presence of cytid bodies.
   e. Highlight complement deposition at the dermo–epidermal junction.

9. Initiation of oral corticosteroid therapy for management of erythema multiforme should be considered only for patients who have?
   a. Recurrent episodes of cutaneous involvement occurring six times yearly.
   b. Episodes of erythema multiforme preceded by herpes labialis infection.
   c. Recurrent erythema multiforme that has failed continuous (at least six-month) antiviral therapy.
   d. Acrally distributed, targetoid lesions after a recent course of sulfamethoxazole/trimethoprim therapy.
   e. Extensive mucosal involvement and severe pain.

10. A 27-year-old man with a history of herpes labialis infection presents with a four-week history of pruritic, non-tender skin lesions located on the arms, face, and chest. He notes that each individual lesion resolves within one day. He has no history of photosensitivity and denies the presence of associated fevers. What is the most likely diagnosis?
    a. Erythema multiforme.
    b. Sweet’s syndrome.
    c. Urticaria.
    d. Rowell’s syndrome.
    e. Urticarial vasculitis.

References


**Answer key**

1. c.  
2. b.  
3. d.  
4. b.  
5. e.  
6. d.  
7. a.  
8. a.  
9. e.  
10. c.