Erythema Multiforme

Introduction and Epidemiology

Erythema Multiforme (EM) is an acute, immune-mediated condition, most commonly induced by herpes simplex virus (HSV) infection, or by the use of medications, such as phenytoin, sulfonamides, penicillins, and barbiturates. The disease is characterized by targetoid lesions, with concentric color variations, and often are accompanied by erosions or bullae in the genital, ocular, or oral mucosae. EM with mucosal involvement is known as Erythema Multiforme Major, and without mucosal disease it is referred to as Erythema Multiforme Minor. It occurs predominantly in young adults, is slightly more common in females, and the incidence is somewhere between 0.01% and 1% of the population.

Etiology

Numerous factors have been linked to EM, including infections and medication use, but also radiation, menstruation, autoimmune diseases, and malignancies. Regarding infections, HSV type 1 is most commonly associated with EM, however, HSV type 2 and Mycoplasma pneumonia are both important causes of the condition as well.

In EM occurs frequently over multiple years, it is called recurrent erythema multiforme. HSV infection is the most common cause of recurrent EM, however, for many cases the cause is unclear. Other conditions that are associated with recurrent EM include M. pneumonia infections, candidiasis, hepatitis, menstruation, and high intake of food preservatives (ie benzoic acid).

There is also a rare variant of EM referred to as persistent erythema multiforme, which is characterized by a continuous, uninterrupted state of both typical and atypical lesions with widespread involvement. The cutaneous lesions in this variant are often bullous or papulonecrotic. This variant is associated with viral infections, as well as inflammatory bowel disease and malignancies.

Pathogenesis

The main mechanisms describing the pathogenesis of EM have been based on investigations with HSV-associated EM, which is thought to be a cell-mediated immunity against viral antigens in lesions. It is thought that the initial step is the phagocytosis of the virus by Langerhans cells, which transport the engulfed HSC DNA to the epidermis. The viral DNA is then transferred to epidermal keratinocytes, and expression of the HSV genes, including the viral pol gene, leads to recruitment of CD4+ Th1 cells. These cells release IFN-gamma, resulting in an inflammatory amplification through autoreactive T cells and lysis of the infected keratinocytes. Though the reason of why in some patients HSV infection will lead to EM is
unknown, factors that have been implicated include and increased number of CD 34+ cells, incomplete fragmentation of the viral DNA, and an autoreactive response to the pol protein.

Notable, there is a possible genetic predisposition in some of the patients with EM, specifically, a link between EM and HLA-DQB1*0301 has been reported.

**Clinical Presentation**

Prodromal symptoms of malaise, fever, and myalgias, are not typical, except in cases with mucosal involvement. If these symptoms present, they tend to present a week or more before the onset of EM.

Target lesions are the hallmark of the disease, but may not always be present. The first lesions that present tend to present as round, erythematous, edematous papules with a surrounding blanched area. These papules may enlarge, and develop concentric rings of color. The typical targetoid lesions will have a dark central area or blister, a red inflammatory zone surrounded by pale edema, and a peripheral erythematous halo. Atypical lesions present as round, raised, edematous lesions with only two zones of color and a border that is more poorly defined. The lesions tend to present symmetrically on the acral extemeties, more commonly on extensor surfaces. The trunk is less often involved, and it is not unusual to have palmoplantar involvement.

![Image depicting the typical targetoid lesions.](http://dermatlas.med.jhmi.edu/derm/indexDisplay.cfm?ImageID=-1662301621)
Lesions in the mucosa occur in around 25-60% of cases, most commonly in the oral mucosa. The lesions often initially present as erythema and edema, and will progress to erosions with pseudomembrane formation. If the mucosa is involved, it most commonly occurs simultaneously with skin lesions.

Erosions of the buccal and labial mucosa in a woman with recurrent erythema multiforme.

**Course of Illness**

EM is generally regarded as a self-limiting skin disease. The lesions will appear over 3-5 days, and resolve over 1-2 weeks. Itching and burning skin, swelling of the hands and feet, mucosal erosions leading to pain, and decreased fluid intake are all leading causes of morbidity in EM. Rarely, ocular involvement can lead to conjunctival scarring, visual impairment, or keratitis. Pneumonia is a rare, serious complication that may result from esophagitis and upper airway erosions.

**Histology**

A biopsy is a useful clinical tool to help make the diagnosis of EM. Pathological findings typically include liquefactive degeneration of basal epidermal cells, necrotic keratinocytes, and lymphocyte exocytosis. Around the dermoepidermal junction, a dense lymphohistiocytic infiltrate can be noted, as well as around blood vessels.
Clinical Evaluation

The crucial clues to the diagnosis rest on history and clinical findings, notably the lesions on the skin. Relevant questions in the history should be focused on any signs of HSV, M. pneumoniae, or other infections, and the use of any new medications. Laboratory findings are not diagnostic, but can be helpful in making the diagnosis. These include an increased erythrocyte sedimentation rate, as well as an increase in white blood cells and liver enzymes.

Since the most common cause of EM is HSV infection, any patient presenting with EM should be evaluated for this underlying infection. If lesions remain that raise concern for active HSV infection, sampling of the lesions with Tzanck smear or PCR studies can confirm or rule out viral presence.

If the patient has respiratory symptoms, serologic tests for M. pneumoniae can be used to aid in confirming this bacteria as the source for EM. Evaluation for this should include a Chest X-Ray, PCR testing of throat swabs, and serologic tests for M. Pneumoniae.

Severe cases of EM with mucosal involvement may lead to decreased fluid intake, and should lead to inpatient hospitalization for monitoring of fluids and electrolytes and pain management.

Treatment

The clinical course of EM is most often self-limited, and will resolve within weeks without significant sequelae. The treatment of EM is highly dependent on what caused the reaction. If EM is drug-induced, the first step should be to discontinue the offending medication.

In HSV-induced EM, the EM typically occurs eight day following the HSC infection, at which point treatment for the infection is no longer indicated, and treatment will not alter the clinical course. Topical corticosteroids and oral antihistamines can be given to patients with itching and burning of cutaneous lesions. If the patient presents with oral lesions which are painful, a high potency topical corticosteroid gel, oral antiseptic washes, and oral anesthetic solutions can be given. If the mucosal involvement is painful enough to prevent sufficient oral intake, systemic glucocorticoids (ie prednisone) may be given. It is imperative that any patients with ocular involvement receive ophthalmology consultation.

The treatment of patients with recurrent EM is challenging. In HSV-induced recurrent EM, antiviral prophylaxis is considered first-line therapy. The preferred approach is continuous antiviral therapy, with one of the following antiviral drugs:

- Acyclovir-400mg BID
- Valacyclovir-500 mg BID
• Famiclovir-250 mg BID

If the EM is resistant to antiviral therapy, second-line systemic therapies include azathioprine, dapsone, cyclosporine, or mycophenolate mofetil, though most of these treatments have yet to be validated in a controlled trial.

Differential

Steven-Johnson syndrome-This syndrome also presents with mucosal erosions and target lesions on the skin. However, in SJS, the lesions tend to be macular, whereas in EM the lesions are papular. The lesions in SJS also tend to present on the trunk and will spread distally. Furthermore, the most common cause of SJS is drug related.

Urticaria-This presents with edematous, erythematous plaques that lack the central zone typically seen in EM. The individual lesions in urticarial tend to last no more than 24 hours.

Bullous Pemphigoid- This will present with pruritic, urticarial plaques and tense bullae. Target lesions will not be seen. On histopathological slides, eosinophilic spongiosis or subepidermal bullae with numerous eosinophils will be seen.

Paraneoplastic Pemphigus- This will present with polymorphous, progressive skin lesions, and skin biopsy with immunofluorescence microscopy can help differentiation will show cell-surface IgG deposition or combined cell surface and basement membrane zone of IgG and C3 deposition, which can be used to differentiate from EM.

Fixed Drug Eruption- This is characterized by a single or multiply erythematous plaques with or without the central necrosis. Less frequently there will be mucosal involvement.

Sweet’s Syndrome (Acute Febrile Neutrophilic Dermatosis)- This is characterized by edematous, erythematous plaques. However, on histological slides there will be a predominant neutrophilic infiltrate without evidence of leukocytoclastic vasculitis.
References


