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Research Article

ERYTHEMA MULTIFORME- A SHORT REVIEW

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A R T I C L E I N F O

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A B S T R A C T

Aim and Objective: To review literature in order to determine the various clinical features, pathogenesis and management strategies for erythema multiforme.
Background: Erythema mutiforme presents as an acute, immune mediated, mucocutaneous condition,which has various sources of etiologies often compromising on the patients quality of life. An important step in the management of erythema multiforme is recognition and withdrawal or prevention of contact with the causative agent. Early diagnosis of the disease remains essential to promptly initiate appropriate management and proper follow up , thus playing a role in preventing the recurrence of these lesions This article reviews literature on the various clinical features, pathogenesis and the management strategies and treatment of erythema multiforme.

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 [1,2] 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]

It affects apparently healthy, young adults and the peak age at presentation is 20-40 years although nearly as much as 20% of the cases are children.[4] Erythema multiforme is a reactive mucocutaneous disorder that comprises variants ranging from a self limited, mild, exanthamatous, cutaneous, variant with minimal oral involvement (EM minor) to a progressive , fulminating, severe variant with mucocutaneous epithelial necrosis (Steven Johnsons Syndrome, Toxic Epidermal Necrolysis). All variants share two common features: target lesions and satellite cells, with widespread necrosis of the epithelium. These features are considered to be a sequelae of a cytotoxic immunological attack on keratinocytes expressing non self antigen. [5]

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Etiology

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. [8] 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. [9] Drug-associated EM is reported in less than 10% of cases. [2] Although numerous drug culprits have been identified, the most common disease-precipitating medications are nonsteroidal anti-inflammatory drugs, sulfonamides, antiepileptics, and antibiotics [2,6]

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. [3, 10] Recurrent 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. [3,10,11,12] Repeated *M. pneumoniae* infections, hepatitis C,vulvovaginalcandidiasis, menstruation, complex aphthosis, and a high intake of food preservative (i.e. benzoic acid)are other clinical conditions thought to be associated with recurrent EM. [3,10,12,13]

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. [16,18] 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. [17]

Pathogenesis

Genetic susceptibility can be a predisposing factor in some patients with EM. Specifically, in a study of 35 EM patients and 80 control subjects, 66% of EM patients were found to carry the HLA-DQB1*0301 allele compared with 31% of control subjects. [19]. 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, HLA-DR53 alleles. [20] 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.[14,15]

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. [8] 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. [8,20,21]

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.[21] 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.[20,22] Interestingly, EM has been reported to occur in the clinical setting of TNF-α inhibitor therapy. [23]

Clinical features

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. [24]

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. [6]

Morphological Characteristics

The earliest lesions of EM are usually round, erythematous, edematous papules surrounded by areas of blanching that may resemble insect bites or papularurticaria. 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. [24] 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.

Mucous Membrane Disease

The frequency of mucosal lesions in EM has been estimated at 25-60%. [6] 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. [3] The most common mucosa involved in EM is the oral mucosa, which can be involved in up to 70% of patients.[3] Usually, involvement of the labial mucosa, buccal mucosa, non-attached gingivae, and vermillion lip is seen Lesions initially present as erythema with some edema and progress to superficial erosions with pseudomembrane formation. [6] 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]

Diagnosis

Erythema Multiforme Is diagnosed clinically, other findings which help clinche the diagnosis are as follows.

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]

Histopathological Findings

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 secondary 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. [8,20]

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 blisters [20]**.**

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]

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)

Management of Erythema Multiforme

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. [6, 24] In cases of *M. pneumoniae* infection, appropriate antibiotic therapy should be considered if the patient is symptomatic. [8] 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. Patients with extensive mucosal involvement and debilitating pain that prevents sufficient oral intake, 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 [2]

Recurrent EM

The treatment of recurrent EM is usually prolonged and challenging. [3, 10] In patients with HSV-associated recurrent EM and idiopathic recurrent EM, the first-line treatment is antiviral prophylaxis. [8-10] Antiviral therapy can be approached as continuous oral therapy, intermittent oral therapy or topical therapy. However, continuous antiviral therapy for $\geq$ 6 months has been documented as the most effective approach. [10] 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. [8]

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