

Erythema Multiforme Etiopathogenesis and Treatment A Review Article.

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ABSTRACT

Background: Erythema multiforme is an acute inflammatory hypersensitivity reaction triggered by different infections and drugs characterised clinically by typical target or iris lesions. It is clinically classified into EM minor, EM major depending on the severity and serious complications like Steven Johnsons syndrome and Toxic Epidermal Necrolysis may be seen. Treatment involves identifying the triggering factor followed by corticosteroid and antihistamines in mild cases and antiviral therapy like prescribing acyclovir in herpes associated erythema multiforme.

Keywords: Corticosteroids, erythema multiforme, hypersensitivity reaction, iris or target lesions.

INTRODUCTION

Erythema multiforme described by Hebra in the year 1866 is an acute self-limiting disease characterized by target or iris lesions of the skin and mucous membrane.^[1,2] The peak age of presentation of erythema multiforme is usually around 20-40 years affecting around 20 % children of the population, initially erythema multiforme was recognised as a clinical spectrum of disease citing erythema multiforme minor as the most mild and TEN ie toxic epidermal necrolysis the most severe variant of erythema multiforme as the most severe.^[3]

Basically, erythema multiforme is described as a reactive mucocutaneous disorder which comprises of variants ranging from a self-limited, mild, exanthematous, cutaneous variant with minimal oral involvement (EM minor) to a more progressive, fulminating, severe variant with extensive mucocutaneous epithelial necrosis which is known as Stevens-Johnson syndrome: SJS; and toxic epidermal necrolysis: TEN sharing two common features ie typical or less typical cutaneous target lesions and more severe

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widespread epithelial necrosis which are considered to be sequelae of a cytotoxic

immunologic attack on keratinocytes expressing non- self-antigens.^[4,5]

Etiology and Pathogenesis

The pathogenesis of erythema multiforme is basically a immunologically mediated process considered to be a hypersensitivity reaction to certain infections and medications. The commonest infections implicated are fungal infections , Herpes simplex virus 1 and 2 (where it is the most commonly identified etiology), Mycoplasma pneumonia. The commonest implicated medications are Hydantions, Phenothiazines, Non-steroidal anti-inflammatory drugs, Barbiturates, Sulfonamides and Penicillins.^[4] Alongwith this various vaccines(hepatitis B,^[6] smallpox,^[7] diphtheria-tetanus),^[8] viruses (cytomegalovirus,^[9,10] hepatitis C,^[11] human immunodeficiency virus and varicella zoster virus) and newer medicines (bupropion [Wellbutrin],^[12-14] candesartan cilexetil [Atacand],^[15] adalimumab [Humira],^[16] ciprofloxacin [Cipro],^[17] rofecoxib [Vioxx; withdrawn from the United States market] and metformin [Glucophage] have been implicated in the pathogenesis of erythema multiforme.^[18,19]

The HSV infection may remain clinically silent where recurrent erythema multiforme is secondary to HSV-1 and HSV-2 reactivation.^[20] A study was conducted on 63 patients suffering from erythema multiforme where HSV-DNA was detected by polymerase chain reaction in skin biopsy specimens in 60 percent of patients with clinically diagnosed recurrent herpes associated erythema multiforme

and in 50 percent of patients suffering from recurrent idiopathic erythema multiforme which has been defined as erythema multiforme with no apparent clinical history of HSV infection or drug ingestion.^[10] The pathogenesis related to herpes-associated erythema multiforme has been well studied and documented as a delayed-type hypersensitivity reaction.^[21,22]

Clinical Presentation

Erythema multiforme is basically a self limited eruption disorder having or no prodromal symptom at all or mild symptoms like itching and burning at the site of eruption.^[23,24] The lesions begin acutely where numerous red or pink macules are sharply demarcated which later become papular.^[23,25]

These papules enlarge gradually into plaques whereas the central portion of the papules or plaques gradually become dark red, brown, dusky or purpuric with crusting and blistering occurring in the center of these lesions. The target or iris lesions are characteristic of erythema multiforme having a regular round shape with three concentric zones: the first zone consists of a central dusky or darker red zone, the second on a pale pink and the third a edematous zone with a peripheral ring. Some target lesions only exhibit two zones which are having dusky or darker red center and a pink or light red border.^[5,23]

Clinical Classification

Erythema multiforme is classified clinically according to the following criteria^[26]

1. EM Minor: showing raised oedematous papules of typical targets which are acrally distributed.
2. EM Major: showing raised oedematous papules of typical targets which are acrally distributed with one or more mucous membrane involvement.
3. SJS: presence of widespread blisters predominantly seen on the chest with erythematous or purpuric macules with one or more erosions of mucous membrane.

Oral Manifestations

70% of patients suffering from EM show oral involvement where initially bullae or vesicles occur which rupture leaving behind a thick white or yellow exudates. Ulceration of lips are seen with bloody encrustations which are painful. Some of these lesions may get mistaken for acute necrotizing ulcerative gingivostomatitis. This type of mucosal involvement is more severe in Steven Johnson syndrome than in erythema multiforme major. Sometimes there is presence of extensive hemorrhagic slough which extends into the whole of respiratory tract, oral cavity, esophagus and larynx. Pharyngeal erosions is also a commonly seen presenting feature.^[4,5]

Diagnosis

The diagnosis of erythema multiforme is often done clinically. However in SJS/TEN there is an elevation in blood sedimentation rate. Alongwith this findings fluid and electrolyte imbalances, elevated liver transaminase, leukocytosis, hyponatremia, hypoproteinuria, anemia and microalbuminuria may also be observed. During the acute phase of TEN, a transient decrease in CD4 + T lymphocytes may also be seen. Intraepithelial oedema and spongiosis with satellite cell necrosis ie individual eosinophilic necrotic keratinocytes surrounded by lymphocytes maybe seen on immunostaining and histological examination alongwith severe papillary oedema with sub epithelial or intra-epithelial vesiculation and degeneration of basement membrane zone. Deposits of IgM, C3 and fibrin deposits and intense lymphocytic infiltration can be seen at basement membrane zone. All the above signs are variable hence immunostaining cannot be deemed specific for diagnosis of erythema multiforme.^[27-29]

Differential Diagnosis of Erythema Multiforme^[22,30]

Stevens-Johnsons syndrome
 Urticaria
 Vasculitis
 Lupus erythematosus
 Drug eruption
 Toxic epidermal necrolysis
 Polymorphic light eruption
 Autoimmune bullous diseases
 Figurate erythema
 Pityriasis rosea
 Other different hypersensitivity reactions
 Urticarial vasculitis
 Viral exanthems

Management

The etiology has to be possibly determined whenever managing a case of erythema multiforme so as to treat the suspected infectious disease or discontinue the causal drug.^[4] Generally, no treatment is indicated for milder cases of erythema multiforme.^[24] Topical corticosteroids and oral antihistamines can be prescribed to provide symptomatic relief.^[25] Oral acyclovir (Zovirax) is prescribed in patients with coexisting or recent HSV infection to lessen the duration and number of cutaneous lesions.^[30,31] Herpes associated erythema multiforme is not prevented by application of topical acyclovir to preceding HSV lesions.^[20]

The use of corticosteroids like prednisone is controversial because as such no controlled studies of prednisone's effectiveness has been carried out, also the use of prednisone in herpes associated erythema multiforme may further lower the patients HSV resistance and in turn leads to recurrent HSV followed by recurrent erythema multiforme and

some studies have shown prednisone to be effective in dosage of 40 to 80 mg per day for one to two weeks and then has to be tapered rapidly.^[20,24,32] Recurrent erythema multiforme may also be treated by oral acyclovir (400 mg two times per day) even if HSV is not found to be an obvious precipitating factor and the role of oral acyclovir has been shown to be effective in the suppression of recurrent erythema multiforme in a double blind placebo controlled trial.^[24,33]

In patients showing no response to acyclovir, famciclovir (Famvir; 125 to 250 mg per day) and valacyclovir (Valtrex; 500 to 1000 mg per day) may be prescribed.^[3,34] Drugs other than antivirals and steroids have also been used eg dapsone (100 to 150 mg) has been prescribed which has caused partial or complete suppression of erythema multiforme,^[35] antimalarial drugs like hydroxychloroquine (Plaquenil) and mepacrine (Atabrine; not available in the United States market) has also been tried.^[24] Treatment with azathioprine (Imuran; 100 to 150 mg per day) has been successful in patients who are unresponsive to other drug treatment.^[35] Some patients suffering from recurrent erythema multiforme have been treated with cyclosporine (Sandimmune) and some two suffering from persistent erythema multiforme have been treated with thalidomide (Thalomid).^[36,37] To conclude, careful clinical assessment of the patient suffering from erythema multiforme has to be done and the necessary treatment protocol has to be followed for rapid recovery and to prevent further complications.

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