A CLINICAL, ETIOLOGICAL AND THERAPEUTIC PROFILE OF ERYTHEMA MULTIFORME (EM) : A CRITICAL EVALUATION OF THE LITERATURE

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Abstract: Erythema multiforme (EM) is an acute mucocutaneous disease which involves the skin and sometimes mucosa. EM is a cutaneous, and sometimes mucocutaneous condition that is typically precipitated by viral infections, mostly herpes simplex virus (HSV), and due to the usage of specific medications.. Mechanisms describing pathogenesis of EM have been based on the investigative studies of HSV-associated EM. Such EM is thought to result from the cell-mediated immune reaction against viral antigen-positive cells that contain HSV DNA polymerasegene. This hypothesis is supported by HSV detection in paraffin-embedded biopsy specimens from the patients with EM. With topical and systemic steroids, first-line treatment of EM is generally focused on symptomatic alleviation while avoiding any known triggers, such as narcotics. Topical analgesics and antiseptics may be needed for mucosal lesions. For the recurrent EM linked to herpes simplex virus infection, prophylactic antiviral medication is necessary. Alternative immunosuppressive medicines and antibacterial drugs are included in second-line therapy, which are often saved for instances with no improvement.

INTRODUCTION

Erythema multiforme (EM) is an acute mucocutaneous disease which involves the skin and sometimes mucosa. EM is a cutaneous, and sometimes mucocutaneous condition that is typically precipitated by viral infections, mostly herpes simplex virus (HSV), and due to the usage of specific medications.[1]

The exact etio-pathogenesis of the EM is not known but it is considered as an immune-mediated disorder.[1] Although a significant proportion of EM cases remain idiopathic, it may follow the infections, (such as herpes simplex virus and Mycoplasma pneumonia); exposure to the medications (mainly such as antibiotics); vaccination and the autoimmune diseases, and drug induced have also been associated with the EM.[2]

Clinical manifestations of EM involves activation of the cytotoxic T lymphocytes in epithelium that will induce apoptosis in keratinocytes, which leads to the satellite cell necrosis.

Classically EM commences mainly with the symmetric involvement of the extremities with an appearance of "target" lesions which tend to spread centripetally on trunk.[3] Skin lesions of EM will tend to be remain fixed for at least seven days, a feature which is useful to differentiate it from the cutaneous manifestations of several immune mediated disorders for example urticaria and the allergic rashes.

In many cases, the inciting factor for the development of EM remains unknown. It will classically presents as numerous targetoid lesions with the concentric rings of distinct color variation in an acral distribution.[4,5] Target lesion appearance can be differ from patient to patient, and frequently, both the typical (lesions of three concentric rings) and also atypical (lesions with less than three concentric rings) lesions are seen. Prodromal symptoms will not accompany with the EM; nonetheless, prodromal signs have been noted when there is mucocutaneous involvement..[6–8]

According to reports, infections brought on by HSV and Mycoplasma pneumoniae are to blame for the majority of acute instances of EM. A more recent association between the EM and acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus responsible for a recent pandemic, has been described.[9,10] Recurrent cases of EM have also been likened to Mycoplasma pneumoniae infections and also HSV, as well as towards the hepatitis C infections, and the vulvovaginal candidiasis.[11] Also the other associations are menstruation, complex aphthosis, and high dietary intake of benzoic acid (a food preservative).[12] It is unknown that how many cases of EM are initially determined to be an idiopathic actually have the underlying or subclinical infection with HSV.[11-13]

Pathogenesis

Mechanisms describing pathogenesis of EM have been based on the investigative studies of HSV-associated EM. Such EM is thought to result from the cell-mediated immune reaction against viral antigen-positive cells that contain HSV DNA polymerasegene. This hypothesis is supported by HSV detection in paraffin-embedded biopsy specimens from the patients with EM.[14,15]

A few days after a recurrent HSV infection,virus is present in the blood. The virus, then phagocytosed by circulating peripheral blood mononuclear cells, such as the macrophages and CD34+ Langerhans cell progenitors, which have skin homing receptor cutaneous lymphocyte antigen. The viral DNA is then delivered to the keratinocytes from the epidermis, where it has been engulfed by the HSV molecule. Upregulation of the E-cadherin expression increases binding with the HSV-containing Langerhans cells to the endothelial cells. Additionally, the dermal inflammatory response is explained by the increase of adhesion molecules on endothelial cells.[16,17] Herpes simplex virus pol DNA is located in basal keratinocyte and also in lower spinous cell layers. HSV-specific CD4+ T helper 1 (TH1) cells are activated as a result of the expression of viral DNA fragments in the keratinocyte layer, such as the viral pol gene. Effector cytokines like interferon-c will be produced as a result of this virus-specific response (IFN-c). The release of IFN-c leads to nonspecific inflammatory amplification through the autoreactive T cells. The pathologic features seen in EM are caused by cells and cytokines.[18-20] It is unknown why a small percentage of people with recurrent HSV infection also have EM. Incomplete viral DNA fragmentation by phagocytic cells, an increase in CD34+ cells, the presence of variables that influence the development of an autoreactive response to pol protein, or a combination of these factors, have all been linked to the development of HSV-associated EM.[21] Although effector cytokine with HSV-associated EM is IFN-c, patients along with drug-induced erythema multiforme and it's are associated with the tumour necrosis factor-a (TNF-a), perfo- rin, and granzyme B, which induce epidermal destruction seen in disease.[22] EM has been stated to occur in clinical setting of TNF-a inhibitor therapy.[23]

Diagnosis for Erythema multifome

- 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, and 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 infections, autoimmune and also malignant disorders

- Special considerations in persistent EM

Serum complement

The most important data for reaching an EM diagnosis should come from the clinical presentation and patient past history. But while making a differential diagnosis, additional illnesses should be taken into account. Because some of the other diseases in the differential must be treated quickly to stop the emergence of potentially fatal consequences, an early diagnosis is crucial. Urticaria, SJS, fixed drug eruption, paraneoplastic pemphigus (PNP), bullous pemphigoid, Sweet's disease, Rowell's syndrome, and the polymorphous light eruption are all imitations of the EM (PMLE).

Treatment Strategies

Drugs	
Acyclovir	Dapsone
Azathioprine	Hydroxychloroquine
Azithromycin	Famciclovir
Cimetidine	Cyclosporine
Immunoglobulin	Thalidomide
Mycophenolate mofetil	Prednisone

With topical and systemic steroids, first-line treatment of EM is generally focused on symptomatic alleviation while avoiding any known triggers, such as narcotics. Topical analgesics and antiseptics may be needed for mucosal lesions. For the recurrent EM linked to herpes simplex virus infection, prophylactic antiviral medication is necessary.
Alternative immunosuppressive medicines and antibacterial drugs are included in second-line therapy, which are often saved for instances with no improvement. Treatment modalities are differ for acute and recurrent disease. In acute disease, treatment is rarely necessary because the lesions typically regress over a period of weeks. Instead, supportive care is given to help the symptoms get better. [24] Treatment for recurrent EM concentrates on combating the cause with systemic antiviral prophylactic medication. Treatment for refractory or resistant illness is typically more challenging and relies on systemic immunosuppression.[25]

Subtype	Treatment
Acute EM	● Avoid all inciting factors ● Mild disease ● Topical antiseptics Oral antihistamines ● HSV-induced EM ● Antiviral suppressive therapy ● Mycoplasma pneumoniae–associated EM ● Might include antibiotics
Mucous membrane EM	● Oral anesthetic solutions ● Oral antiseptic rinses ● Corticosteroid gel ● Ocular disease ● Ophthalmology consultation ● Topical ophthalmic preparations ● Severe mucosal disease ● Oral corticosteroid (prednisone, 40–60 mg/d over 2–4 weeks)
Recurrent EM	● HSV-associated recurrent EM or idiopathic recurrent EM ● A 6-month trial of continuous antiviral therapy ● Acyclovir 400 mg BD ● Valacyclovir 500 mg BD ● Famciclovir 250 mg BD Therapy-resistant recurrent EM ● Azathioprine ● Mycophenolate mofetil ● Dapsone ● Others: hydroxychloroquine, thalidomide, cimetidine, intravenous immunoglobulin, cyclosporine

4. Mucosal EM

The severity of EM with mucosal involvement determines how it should be treated in significant part. Along with oral antiseptic washes and oral anaesthetic solution, high potency topical corticosteroid gel is utilised in mild or severe illness.[26] In severe disease with extensive mucosal involvement, hospitalisation is generally recommended due to the limited oral intake. Electrolyte replenishment and intravenous fluid administration are recommended. Systemic glucocorticoid therapy is another option, with prednisone 40–60 mg/d decreased over 2-4 weeks being the most popular dose. Hospitalisation is typically advised in cases of severe illness with substantial mucosal involvement because of the poor oral intake. Electrolyte replenishment and intravenous fluid administration are advised. Additionally, systemic glucocorticoid medication is used; the most common dose is prednisone 40–60 mg/d, decreased over 2-4 weeks.[27] Ophthalmologic evaluation is required if ocular involvement is suspected in order to avoid potentially fatal future complications. To speed up recovery and relieve symptoms, ophthalmologists may give ophthalmic drugs such antibacterial eyedrops, corticosteroid eye drops, and topical ocular lubricants.[28]

5. Recurrent EM

Due to its refractory character, recurrent EM is the hardest type of EM to treat. The antiviral prophylaxis is the primary line of treatment for both HSV-associated and idiopathic EM.[21] Acyclovir 400 mg twice daily, famciclovir 250 mg or valacyclovir 500 mg twice daily twice daily are the current guidelines.[28] Both continuous and intermittent oral administration of these drugs is possible. The most successful course of treatment, according to a 1995 randomised controlled trial, was continuous oral antiviral therapy for a duration of at least six months.[29] Patients whose condition has a clear relationship with the HSV infection benefit most from antiviral medication. The purpose of treatment is to lessen relapses and to induce remission, which is challenging to sustain. Once antiviral treatment is discontinued, recurrence is common.[30]

Patients with recurrent EM have had clinical improvements after using antibiotics, particularly azithromycin and dapsone. A case series from 2017 showed that 6 out of 13 patients had a full response to dapsone.[31] More recently, a case report from 2008 featured a single patient who, after 6 months of chronic EM that was unresponsive to the medicine valacyclovir, had an excellent clinical response to the drug thalidomide. Levamisole significantly reduced the recurrence of EM in 23 individuals, according to an observational study published in 2018; this was in contrast to usual care, which included corticosteroids and antiviral medication.[32] According to a systematic evaluation of the management of EM in 2019, other immunosuppressants, such as mycophenolate mofetil, have proven less effective, with a full response observed in just 3 out of 8 patients.[33]

DISCUSSION

Clinically, erythema multiforme can be categorised into 3 types that is major, minor, and persistent variations. According to estimates, oral involvement affects 25% to 60% of EM patients.[34] Further differentiation is aided by the disease's intensity and the location of the lesions. Lesions affecting one or more mucosal membranes are indicative of EM major, which is linked to a more severe appearance.[35] No laboratory tests can aid in diagnosis of the EM. Nonetheless, serologic testing for autoantibodies like the antinuclear antibodies should be taken into consideration if autoimmune blistering illnesses are in the differential diagnosis.[36]

EM-related lesions often develop over a period of three to six days and disappear after one to three weeks. However, more serious EM instances involving the mucous membranes may not fully recover for up to six weeks.[37] These episodes could happen six times a year on average, lasting anywhere between six and ten years. Recurrent erythema multiforme, often known as recurrent EM, is a subgroup of disease that may be brought on by a herpes simplex virus infection.[38] In a few rare cases, lesions develop over an extended period of time—at least more than a year—without stopping. Persistent erythema multiforme, often known as persistent EM, is a variation that is typically linked to viral infections.[39-41]

Erythema multiforme has a self-limited clinical course, but patients with moderate symptoms may find some relief from corticosteroid treatment. Strong systemic glucocorticoids have been observed to help patients with extensive mucosal involvement and discomfort.[42] Antiviral medication has proven to be an effective prophylactic in patients with recurrent erythema multiforme.

CONCLUSION

Erythema multiforme is a mucocutaneous disorder that is immune-mediated, acute, and frequently brought on by HSV infection. The targetoid lesion is the main cutaneous symptom of this illness, and it has concentric zones of colour change. In order to distinguish an entity from clinical mimickers like urticaria, SJS, fixed drug eruption, bullous pemphigoid, PNP, Rowell's syndrome, PMLE, Sweet's syndrome and cutaneous small-vessel vasculitis, it may be helpful to consider both the clinical findings and the histopathologic characteristics. Once EM has been diagnosed, treatment should begin in accordance with the existence of mucosal disease, emergence of recurrent disease, overall

severity of disease, or a combination of these. Although symptomatic management of moderate cutaneous EM may be sufficient, treatment along with antiviral prophylaxis is necessary for HSV-associated recurrent EM and idiopathic recurrent EM. Patients who have extensive mucosal involvement that affects oral intake and causes a fluid and electrolyte imbalance may also require inpatient hospitalisation.

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