Erythema Multiforme – A Review

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Abstract

Erythema multiforme (EM) is an acute, self-healing inflammatory mucocutaneous disorder which presents with diverse spectrum of cutaneous lesions, hence termed "multiforme". Oral lesions are quite characteristic and manifest as rapidly rupturing vesicles & bullae forming ill-defined erosions and hemorrhagic encrusted lip lesions. Wide variety of triggering factors for EM have been documented in the literature, but history of prior herpes simplex virus (HS) infection is most widely accepted. EM has been chiefly divided into two main forms- EM minor and EM major. Steven Johnson syndrome & Toxic epidermal necrolysis (Lyell's disease) are now considered as distinct clinical entities. EM has a self-limiting course and the lesions usually resolve within few weeks. This paper aims to present a recent update on Erythema Multiforme taking into account its etiopathogenesis, clinical and oral features, diagnostic aids and treatment protocols.

Keywords: Erythema multiforme; treatment; Steven Johnson syndrome, Toxic epidermal necrolysis

Introduction

It is a rare acute mucocutaneous condition caused by a hypersensitivity reaction with the appearance of cytotoxic T lymphocytes in the epithelium that induce apoptosis in keratinocytes, which leads to satellite cell necrosis.

Etiology

Immune-mediated disease (deposition of immune complexes in the superficial microvasculature of skin and mucosa).

1. **Micro-organisms**

- **Viruses:** herpes viruses (HSV, VZV, EBV), adenoviruses, enter viruses, hepatitis viruses (A, B and C), HIV, influenza
- **Bacteria:** Mycoplasma pneumonia, Chlamydia, Corynebacterium diphtheria, Hemolytic streptococci, Legionellosis
- **Fungi and parasites:** coccidioidomycosis, dermatophytes, histoplasmosis, sporotrichosis

2. **Drugs:** Allopurinol, barbiturates, cancer chemotherapeutic agents, carbamazepine, cephalosporin's, non-steroidal anti-inflammatory drugs, penicillin's, phonation, protease inhibitors.
3. **Food additives or chemicals:** benzoates, nitrobenzene, terrenes, ethanol
4. **Immune and other conditions:** graft versus host disease, immunization (BCG, hepatitis B), inflammatory bowel disease, pregnancy, sarcoidosis, systemic lupus erythematous.

Variants of Erythema Multiformae

- EMm, erythema multiforme minor.
- EMM, erythema multiforme major.
- SJS, Stevens-Johnson syndrome.
- TEN, toxic epidermal necrolysis.

Clinical Features

- Acute, self-limiting disease that may be episodic or recurrent.
- Arise in the third and fourth decades of life, it can also affect children and adolescents.
- Rarely affects individuals under the age of 3 or older than 50.
- Characterized by coetaneous disease, including the typical and/or atypical raised targets affecting less than 10% of skin surface.
- Mucosal involvement is uncommon and not severe.
- Coetaneous target lesions follow a symmetric distribution with a predilection for the extensor surfaces of the extremities.
- Involvement of the skin of the face or trunk is less.

- The Nikolsky's sign is negative.
- Lesions last for 1 to 3 weeks and heal without scarring to leave areas of hyper pigmentation and/or hypo pigmentation.
- Mucosal disease is limited to only 1 site, most commonly the mouth.
- Oral lesions manifest with edema, erythema, and erythematous maculas of the lips and buccal mucosa, followed by the development of multiple vesicles and bullae that quickly rupture and result in pseudo membrane formation.
- Lips tend to become swollen and show distinctive bloody encrustations
- Intact vesicles are rarely observed because they rapidly break down to form ill-defined ulcers.
- Mild extension of erythematous patches or superficial erosions of the oral mucosa and the lip.

Erythema multiformae major (EMM)

- EMM differs from EMm by the involvement of at least 2 different mucosal sites, which typically includes the oral mucosa.
- Oral lesions commonly appear along with skin lesions
- Coetaneous involvement of EMM is usually less than 10% of the body surface but is generally more severe than that of EMm.
- Erythema multiforme major can be preceded by erythematous maculas.
- Oral lesions usually widespread and severe.
- The vesicles tend to rupture to leave multiple areas of superficial irregular erosions that are usually covered by a yellow fibrin us pseudo membrane.
- Eventually, multiple, large, shallow, irregular, painful ulcers surrounded by an erythematous margin and covered by whitish plaques of desquamated epithelium occur.
- Affect the lingual, buccal, and/or labial mucosa, and less frequently the floor of the mouth, palate, and the gingival.
- Trismus, dysphonic, dysarthria, and/or dysphasia.
- Oral lesions of EMM usually heal without scarring.

Typical target or "iris," lesions

Individual lesions less than three cm diameter with a regular round shape, well-defined border, and at least 3 different zones, that is, 2 concentric rings around a central disk. One ring consists of palpable edema, paler than the center disk.

Raised atypical target lesions

Round, edematous, palpable lesions similar to EM but with only 2 zones and/or a poorly defined border.

Flat atypical target lesions

Round lesions characteristic of EM but with only 2 zones and/or a poorly defined border and non palpable with the exception of a potential central blister.

Severe forms of EM?

- Stevens-Johnson syndrome
- Toxic epidermal necrolysis (TEN)

1. Stevens-Johnson syndrome

- Stevens-Johnson syndrome (SJS) was first described in 1922 by A. M. Stevens and F. C. Johnson.
- Severe bullous form of erythema multiforme with widespread involvement of skin, oral cavity, eyes and genitalia.
- Abrupt fever.
- Malaise.

A. Skin lesions

Similar to erythema multiforme, although they are commonly hemorrhagic and are often vesicular or bullous.

B. Oral mucous membrane lesions

- Lesions are severe and extremely painful.
- Mucosal vesicles or bullae occur that rupture and leave surfaces covered with thick white or yellow exudates.
- Erosions of the pharynx
- Ulceration of lips with bloody crusting.

C. Eye lesions:

- Photophobia.
- Corneal ulceration.
- Panophthalmitis.
- Blindness due countercurrent bacterial infection.

D. Genital lesions

- Urethritis.
- Balanitis and/or vaginal ulcers.

Toxic epidermal necrolysis (TEN)

- The first described by the Scottish dermatologist Alan Lyell in 1956.
- It is a rare, acute, and life-threatening mucocutaneous disease that is usually drug related.
- It is considered as a confluent form of Stevens-Johnson syndrome.
- This condition is due to extensive keratinocyte cell death that results in the separation of significant areas of skin at the dermal-epidermal junction with the production of bullae followed by skin sloughing.

Clinical features of TEN

- Cutaneous lesions appear in the face, palms, and soles of the feet.
- Mucosal involvement occurs in more than 90% (mouth, genitalia, and/or ocular region)
- Erythema and erosions characterize the lesions.
- Early cutaneous lesions present as livid, erythematous maculae.
- During the course of the disease, the lesions rapidly coalesce and become tense bullae.
- With disease progressions, they form large confluent areas of epidermal detachment.

Classification system for SJS and TEN?

A classification system for SJS and TEN according to the extent of skin detachment:

- 1–10%: SJS
- 11–30%: SJS-TEN overlap disease
- >30%: TEN

Diagnosis of EM

- Erythema multiforme is diagnosed clinically.
- Laboratory tests (e.g., HSV-1 and -2, immunoglobulin M and G) may confirm a suspected history of HSV infection.
- Histological examination and immune staining often shows:

1. Moderate to dense perivascular inflammatory infiltrate (CD4+ lymphocytes and histocytes) within the papillary dermis and along the dermoepidermal junction, dermal edema.
2. Intraepithelial/subepithelial vesicles and/or bullae.
3. Hydropic degeneration of basal keratinocytes
4. Non-specific immune deposits of IgM, C3 and fibrin along basement membrane.

Direct and indirect immune fluorescence is unhelpful.

Treatment of EM

- Oral antihistamines and topical steroids.
- Prednisone at dosages of 40 to 80 mg per day for one to two weeks then tapered rapidly.
- Patients with co-existing or recent HSV infection:

A. Oral acyclovir (400 mg two times per day).
B. Valacyclovir (Valtrex; 500 to 1,000 mg per day) and famciclovir (Famvir; 125 to 250 mg per day).

Differential diagnosis of EM

Lupus erythematosus, herpetic gingivostomatitis, Behçet's disease, erosive lichen planus.

Conclusion

Erythema multiforme should be considered as a differential diagnosis in cases of acute, multiple vesiculobullous lesions. The disorder manifests a bizarre array of clinical features and poses a diagnostic dilemma. Hence, early and accurate diagnosis is mandatory to combat this disease

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