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Erythema Multiforme: A Recent Update

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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. Most other cases are seen after the intake of certain medications. 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. Symptomatic management along with recognition and alteration of the alleged precipitating factors is usually sufficient in the majority of cases. However, in advanced lesions, steroid therapy may be helpful. 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, Herpes virus infection, Vesiculobullous disorder, Target Lesions.

INTRODUCTION

Erythema multiforme is a rare autoimmune mucocutaneous disorder that is acute in onset, recurrent in nature and is usually self-limiting. EM primarily affects apparently healthy young adults; (20-40 years) however, the disorder may involve children in 20% cases [1,2]. Two main forms of Erythema multiforme are EM minor and EM major. In EM minor (EMm), only one mucous membrane is affected and symmetrical target cutaneous lesions on the extremities are seen. This is in contrast to EM major (EMM) which affects two or more mucosal membranes and the cutaneous lesions are quite variable [3]. Oral features are quite characteristic with the formation of blisters on the lips and oral mucosa

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which eventually break and coalesce to form erosive and ulcerative lesions, followed by greyish pseudo membrane. Gingival Desquamation, hemorrhagic crusted lip lesions, and a positive Nikolsky's sign is also seen[4].

DISCUSSION

Erythema multiforme (EM) is an acute, immunological, vesiculobullous disorder that primarily affects the skin and mucous membranes. The exact etiology is obscure, although, prior infection with herpes simplex virus (HSV) and the intake of certain drugs are the common precipitating factors.[5,6] The characteristic targetoid skin lesions show acral distribution with concentric color disparity, and are often accompanied by erosive lesions of the oral, genital, or ocular mucosa[5]. Erythema multiforme major shows one or more mucous membrane involvement, in contrast to Erythema multiforme minor which do not involve the mucosal membrane[7].

Previously EM signified a wide range of diseases and comprised of EM minor, EM major, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis. However, According to recent researches, EM major and SJS are considered as different clinical entities which present with similar mucosal lesions but distinct skin lesions[5,8,9]. EM is mostly triggered by infectious agents, such as herpes simplex virus (HSV). However, lesions of SJS and TEN are induced by the intake of certain medications.

Etiopathogenesis

The cutaneous and mucosal lesions in EM are usually due to an immunological reaction to an inciting infectious agent or drugs[10]. Majority of EM patients have a history of prior herpes simplex virus (HSV) infection. Other infectious agents include bacterial (*Mycoplasma pneumonia,* Borreliosis), viral (Adenoviruses, Enteroviruses), and fungal infections (Coccidiodomycosis, Dermatophytes) [4,10]. Drugs- Antibiotics (penicillin, cephalosporins, sulphonamides), Non Steroidal Anti-Inflammatory Drugs (NSAIDS), and Anticonvulsant drugs (Phenytoin), foodstuffs (Benzoates, Nitrobenzene), and chemicals (Perfumes) may also act as triggering factors[4,11].

Clinical features

Erythema multiforme lesions are usually acute in nature with mild or no prodromal symptoms. [12 Asymmetrical erythematous maculopapular lesions eventually break and coalesce to form plaques on the skin. Target or iris lesion ("bull's eye") is the classical cutaneous lesion of EM. These lesions manifest as central bulla or a pale clearing area encircled by concentric bands of edema and erythema.

In EM minor, the initial lesion is a papule, which might enlarge and in due course form the characteristic targetoid lesion (area of pale centre encircled by eythema). They might then progress further to form more confluent patches or annular lesions[13]. The lesions in EM minor predominantly affects the limbs, chiefly the extensor surfaces, but sometimes, they can be widespread in the body, without mucous membrane involvement.

Lesions in EM major are seen in 20% to 60% cases and affects one or more mucous membranes[13,14]. Oral mucosa is the most frequently affected site and the lesions manifest initially as edema that progresses to superficial erosions[13,15]. Anogenital, ocular, and nasal mucosa are the other affected mucosal surfaces in EM major.

Erythema multiforme in children

Oral manifestations

About 70% EM cases present with characteristic oral features[4]. The oral lesions have a predilection for the non keratinized mucosa and anterior parts of the oral cavity. The primary sites involved are the Lips (36%), buccal mucosa (31%), tongue (22%), and labial mucosa (19%) [16]. EM present with a wide array of oral manifestations ranging from shallow erythematous and hyperkeratosis plaques to tender deep-seated hemorrhagic bullous and erosive lesions. The initial oral lesions present with edematous and erythematous macular lesions of the lips and buccal mucosa. Advanced lesions manifest as multiple vesiculobullous lesions that eventually break down and forms a pseudomembrane. Swollen lips along with typical blood tinged crusted lesions are the hallmark of EM. Intact vesicles are infrequently seen and eventually rupture forming irregular ulcerative lesions. Although, targetoid lesions may appear on the lip but they are rarely seen

intraorally[17]. The oral mucosa is the most frequently affected mucous membrane. However, as the disease progress further, it may involve any mucosa, including tracheobronchial or gastrointestinal tract epithelium[18,19].

EMM presents with larger oral lesions as compared to EMm and ulcerative lesions of multiple mucous membranes may be seen in more than 50% cases[20]. Constitutional features such as trismus, dysarthria, dysphonia, and/or dysphagia may also be seen. In most cases, the oral lesions heal without scarring, however, occasionally hyperkeratotic plaques mixed with erythematous areas may also be seen[17].

Diagnosis of EM

Diffuse and extensive oral ulcerations of EM may mimic other vesiculobullous disorders (pemphigus and mucous membrane pemphigoid), viral stomatitis and Toxic epidermal necrolysis. Lesions of EM usually show the following features[17]

- The acute nature of lesions (or recurrent nature)
- Oral lesion predilection for lips and anterior oral mucosa.
- Pleomorphic presentation of cutaneous and other lesions.

Differential diagnosis

1. Primary Herpetic gingivostomatitis (HSV)- HSV presents as small, well-circumscribed lesions and lacks the typical skin rash. These lesions show culture positivity for HSV.
2. Autoimmune vesiculobullous diseases (pemphigus and pemphigoid)- They present as chronic, slowly progressive, persistent lesions. The cutaneous lesions are bullous in contrast to maculopapular lesions of EM.
3. Recurrent aphthous ulcers may mimic recurrent oral EM- aphthous ulcers present as isolated lesions, as compared to diffuse lesions of EM.
4. Severe EM cases with hemorrhagic lip lesions may mimic paraneoplastic Pemphigus. Lesions in paraneoplastic Pemphigus are usually chronic in nature, show severe ocular and cutaneous lesions and have a malignant potential[16].

Treatment

EM has a self-limiting course and the lesions usually resolve within few weeks without major complications [21,22]. Symptomatic management along with recognition and alteration of the alleged precipitating factors is usually sufficient in the majority of cases. However, Severe cases of EM may necessitate hospitalization, analgesia, antiviral therapy, and systemic therapy with corticosteroids, immunosuppressants, and/ or antiviral suppressive therapy.[13,21 Patients with recurrent EM may be treated with antiviral therapy on a daily basis[23].

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. The management protocol includes symptomatic and supportive care with elimination of precipitating factors. Severe cases may require steroid therapy.

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