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ORAL ERYTHEMA MULTIFORME: A CASE REPORT

Dental Science

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ABSTRACT

Erythema Multiforme (EM) is an acute, self limited, immune-mediated condition, most commonly induced by herpes simplex virus (HSV) infection, or by the use of medications, such as phenytoin, sulfonamides, penicillins, and barbiturates. The disease is characterized by targetoid lesions, with concentric color variations, and often are accompanied by erosions or bullae in the genital, ocular, or oral mucosae. EM is clinically characterized by a "minor" form and a "major" form. The clinical course of the disease ranges from exanthematous variant with minimal oral involvement to a progressive, fulminating, severe variant with extensive mucocutaneous epithelial necrosis (Stevens-Johnson syndrome); and toxic epidermal necrolysis. There are no specific diagnostic tests for EM, and the diagnosis is mainly clinically supported, if necessary by biopsy. This article highlights a case report of erythema multiforme in a 26 years old female patient with extensive involvement of oral mucosa.

KEYWORDS

Blisters, Corticosteroids, Erythema multiforme, Immunologically mediated, Target lesions, Ulcers.

INTRODUCTION:

Ferdinand Von Hebra described erythema multiforme (EM) in the year 1866 as a self-limited and acute skin disease that is symmetrically scattered on the extremities with a typical recurring concentric pattern in the form of "target lesion." [1] EM 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. [2] About 50% of cases are idiopathic. Most notable causes are infectious agents and drugs (penicillin, phenytoin, cephalosporins, barbiturates etc.). Infectious causes are more common in children and are implicated more commonly in EM. Herpes simplex infection is most common cause in young adults. [3] Other triggers include benign and malignant tumours, radiotherapy (phenytoin and cranial radiation therapy - EMPACT) [4] Despite being often caused by, or at least associated with, infection or drug therapy, the pathogenic mechanism of EM remains unclear, and as a consequence there are no evidence-based, reliably effective therapies.

Erythema multiforme is associated with an acute onset and, usually, mild or no prodromal symptoms. Fever, lymphadenopathy, malaise, headache, cough, sore throat and polyarthralgia may be noticed as much as one week before the onset of surface erythema or blisters. [5] Lesions may appear as irregular red macules, papules and vesicles that collapse and gradually enlarge to form plaques on the skin. Moreover, crusting and blistering sometimes occur in the centre of the skin lesions, resulting in concentric rings resembling a "bull's eye" (target lesion). In the oral cavity, the lesions are usually erythematous macules on the lips and buccal mucosa, followed by epithelial necrosis, bullae and ulcerations with an irregular outline and a strong inflammatory halo. Bloody encrustations can also be seen on the lips.[6, 7] Oral mucosal involvement in erythema multiforme may occur independently or precede cutaneous involvement. Therefore a patient present with acute ulcerations in the oral cavity must be referred to an oral medicine specialist or an otolaryngologist for further treatment and follow up.

The present article highlights the case report of a 26 years female patient with acute ulcerations in the oral mucosa and discuss about various etiological agents, pathologic mechanism and treatment options available in erythema multiforme.

CASE REPORT

A 26-year old female patient presented to the outpatient department of our institute with complaints of painful oral ulceration. Patient also complains of multiple wounds in her mouth since 2 days. Patient gives history of burning sensation on taking hot and spicy food since 1 month. Initially the burning sensation was less intense, but gradually increased with time. There is associated history of bleeding from the gums while brushing since 15 days. The bleeding starts immediately during brushing and chewing hard food and gets stopped by itself after few seconds. There is history of increased salivation from the past 2 days. Patient gives history of generalized wounds in the oral cavity from the past 2 days, due to which there is difficulty in opening mouth, eating and speech. No other associated symptoms (fever, malaise) are present. No history of intake of any medication since past 1 month. Patient gives history of normal delivery 2 months back.

On clinical examination there were presence of multiple erythematous and denuded areas with hemorrhagic crustations in the upper and lower lip which were tender and there was sloughing of the epithelium of the lips on palpation. Presence of generalized multiple large, shallow, irregular bleeding ulcers which were surrounded by erythematous margins in relation to tongue, gingiva labial and buccal mucosa, palate, floor of the mouth bilaterally. **(Figure 1, 2, 3, 4)** Few hyperemic papules and macules were also present. Pharyngeal and laryngeal examination was normal. Lymph nodes were not palpable. Other systemic findings were normal. Provisional diagnosis of oral erythema multiforme was made. As history and clinical examination were suggestive of vesiculo bullous lesion, so differential diagnosis of Primary herpetic gingivostomatitis, Erosive lichen planus, Pemphigus vulgaris, Benign mucous membrane pemphigoid were taken into consideration. Complete haematological investigations were advised. Patient was referred to the concerned gynaecologist for consultation regarding initiation of steroid therapy.

Complete blood count- Hemoglobin -11.8 gms%, Total count: 7750, Neutrophils-57%, Lymphocytes-37%, Eosinophils-04%, Monocytes-02%, ESR-06%, Bleeding time -2 min, Clotting time -6 min 30 sec, RBC count-4.10 million/cumm, Vitamin B_{12} level-568 pg/ml, Total iron-44 mcg/dl, Folic acid-23.50 ng/ml.

Patient was advised tab Prednisolone 20 mg twice a day for 7 days, Tab Vitamin B12 once daily for 30 days, Tab vitamin C once daily for 30 days, Tantum oral rinses (Benzydamine hydrochloride) 0.15% 2-3 times daily. On subsequent follow ups, there were gradual healing of the ulcers with marked reduction in burning sensation.**(Figure 5)** After 2 weeks follow up tab prednisolone was tapered gradually till 1 month and patient was later advised kenakort ointment (triamconolone acetonide) 0.1% W/W and capsules Becosules (Vitamin B_{12}). Unfortunately the patient did not report back for further follow up.

DISCUSSION

Erythema multiforme is an acute, sometimes recurrent, mucocutaneous condition of uncertain etiopathogenesis that can follow the administration of drugs infections. Infection with HSV is the most common feature in the development of erythema multiforme minor. Herpes-associated erythema multiforme (HAEM) can be found several days or weeks following an episode of HSV. Both HSV types 1 and 2 have been shown to precipitate HAEM. [8]

and health history, clinical observations and prospective studies indicate that most cases of erythema multiforme are preceded by infection with HSV, [9] Apart from herpes simplex infection, a number of etiological agents have been proposed **(Table 1)**

Erythema multiforme appears to be the result of a cell mediated immune reaction to the precipitating agent. In HAEM it is most likely

that HSV–DNA fragments in the skin or mucosa precipitate the disease. HSV–DNA fragments and in particular DNA polymerase (PoL) have been detected in the basal and suprabasal cell layers of the epidermis in lesions as well as healed lesions for up to 3 months and the T cells accumulating in active lesions are CD4+ (Vb2+) cells which respond to HSV antigens in vitro [8]

Immunocytochemicial staining and in situ hybridisation has shown that T cells do not produce IFN-c in drug-induced lesions but rather the lesions are characterised by tumour necrosis factor alpha (TNF-a) present in keratinocytes and also produced by macrophages and monocytes. [8]

Erythema multiforme may present a wide spectrum of severity, from mild limited disease to a severe, widespread and life-threatening illness. [10] Skin lesions are usually symmetrical and consist of macules or erythematous papules, which develop into classical target or iris lesions. Occasionally bullae may be seen. Skin lesions are often accompanied by ulceration of mucous membranes, particularly the oral cavity. EMm that only affects the oral mucosa may occasionally arise. EM major (EMM) typically involves two or more mucous membranes with more variable skin involvement. Symmetrically distributed typical cutaneous target lesions and/or atypical raised target lesions are the hallmark. [11]

By definition, mucous membrane involvement is limited to only one site and usually it is the oral mucosa alone that is affected.[12] Occasionally lesions may occur orally prior to their appearance on the skin or sometimes only the oral cavity is affected. Intraoral lesions occur predominantly on the non keratinised mucosae and are most pronounced in the anterior parts of the mouth. The lips are also commonly affected and are swollen and cracked, bleeding and crusted. Typically oral lesions progress through diffuse widespread macules to blisters and ulceration although only ulceration may be seen at presentation. In these cases, diagnosis may be difficult.

There are no definitive diagnostic tests for erythema multiforme as the diagnosis is usually based on the clinical appearance of the lesion and if necessary by biopsy. The clinician should be able to differentiate EM from other vesiculo- bullous diseases, particularly pemphigus and benign mucous membrane pemphigoid.[10] Biopsy shows intraepithelial oedema and spongiosis early on, with satellite cell necrosis (individual eosinophilic necrotic keratinocytes surrounded by lymphocytes), vacuolar degeneration of the junctional zone and severe papillary oedema with sub- or intra-epithelial vesiculation, and intense lymphocytic infiltration and immune deposits of fibrin and C3 at the basement membrane zone. There may be a perivascular lymphocytic infiltrate (CD4+ more than CD8+ T lymphocytes) with a few neutrophils and occasional eosinophils, and perivascular IgM, C3 and fibrin deposits. However, pathology can be variable and immunostaining is not specific for EM. [8]

A full blood count is usually not helpful, although in severe EM, there is usually a rise in the erythrocyte sedimentation rate. The detection of intralesional HSV-DNA via polymerase chain reaction, as well as immunohistochemistry for IFN-γ and TNF-α, may be useful tests to differentiate herpes associated EM from drug-associated EM. [13]

The management of EM can be difficult. There are no available systematic reviews, and randomized controlled trials are scarce. Any precipitants should be removed or treated. Casual drugs should be stopped and relevant infections treated. Antiviral agents may be indicated in herpes associated EM, and a 5 day course of acyclovir 200 mg five times daily at the first sign of lesions, or 400 mg four times daily for 6 months, or continuous treatment using valacyclovir, 500 mg twice a day, is useful for prophylaxis.[2]

Tetracycline 250 mg four times a day for at least 1 week may be indicated in EM related to ***Mycoplasma pneumoniae.*** For symptomatic relief, mouthwashes containing local anesthetic and mild antiseptic compounds may help in relieving painful oral symptoms. Chlorhexidine mouthwashes may be indicated for better oral hygiene. Analgesics and a liquid diet may be necessary. In severe forms of EM, hospital and supportive care are often important.

Corticosteroids are the most commonly used drugs in the management of EM, however their use is controversial. Minor form of EM may readily respond to topical corticosteroids such as triamconolone acetonide (0.1%) , athough systemic corticosteroids may be required in patients with severe form of the disease (prednisolone 0.5–1.0 mg / kg / day) tapered over 7–10 days) either alone or in combination with azathioprine or other immunomodulatory drugs(cyclophosphamide, thalidomide).

CONCLUSION

EM and its related conditions Steven's Johnson syndrome are a group of immunologically mediated disorders that are precipitated by infection and drugs. Although exact etiology is not well defined and pathologic mechanisms are unclear, an important step in the management of erythema multiforme is recognition and withdrawal or prevention of contact with the causative agent. Patients should be informed about the condition and counseling should be done to prevent recurrence. Corticosteroids are the mainstay of treatment and should be tapered gradually. In rare cases, recurrence may occur during the course of steroid therapy.

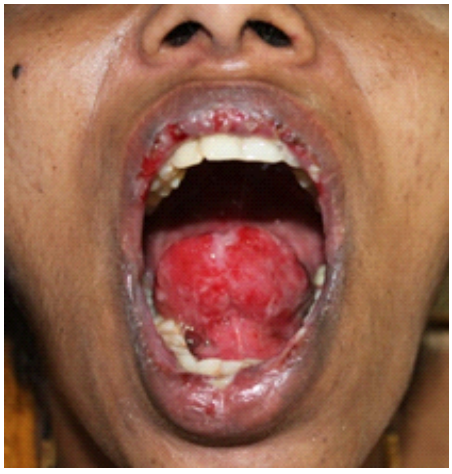

Figure-1 Extraoral radiograph showing hemmorhagic encrustations over upper and lower lip.

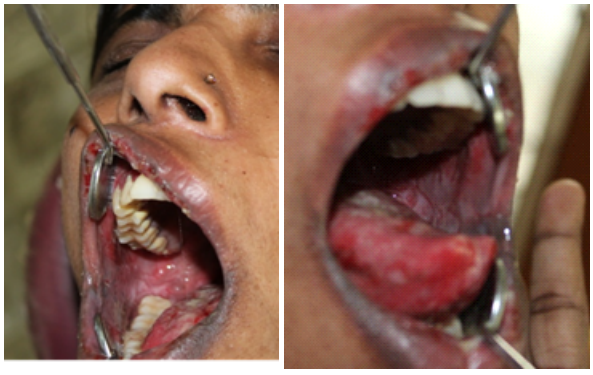

Figure- 2 Intraoral radiographs showing ulcers on the right and left buccal mucosa

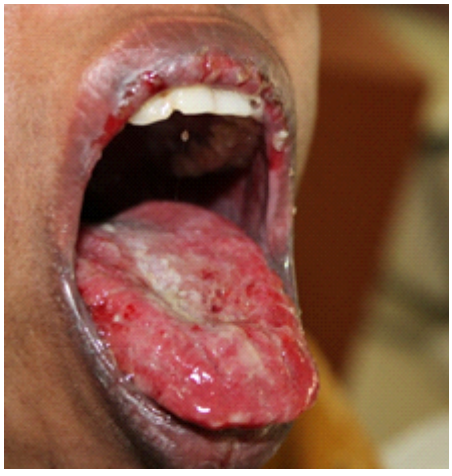

Figure 3- Showing erythema and ulcerations in the tongue

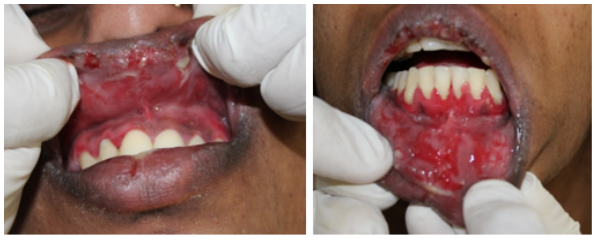

Figure 4- Showing sloughing of epithelium and ulcerations in the upper and lower labial mucosa

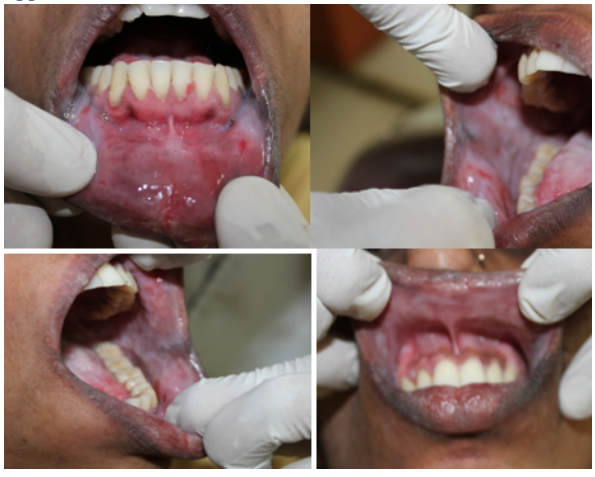

Figure 5- Showing progressive healing of the ulcers

Table 1 Possible etiological agents in Erythema multiforme

Microbial etiology	Drugs and food additives
Viruses	**Drugs**
Herpes simplex virus (HSV)	Allupurinol
Varicella zoster virus (VZV)	Barbiturates
Cytomegalo virus (CMV)	Chemotherapeutic drugs
Epstein barr virus	Cephalosporins
Enterovirus	Herbal preparations
Coxsackie B5	NSAID;s
HIV virus	Penicillin
Influenza virus	Phenytoin
	Protease inhibitors
Bacteria	
Mycobacterium tuberculosis	**Food additives**
Mycobacterium leprae	Benzoates
Mycobacterium avium complex	Nitrobenzene
Neisseria meningitides	Paraphenylene diamin
Corynebacterium diptheriae	Perfumes

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