Oral Blistering - Report of Two Cases of Erythema Multiforme & Literature Review

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ABSTRACT
Erythema multiforme and related disorders comprise a group of mucocutaneous disorders that often compromise the quality of life. The clinical classification of these disorders is variable, thus making definitive diagnosis difficult. Early recognition and prompt management will benefit the patients. This article highlights two such cases of erythema multiforme with detailed literature review on etiopathogenesis, clinical features, and treatment.

CASE REPORT
Case report 1 - A 30-year-old male patient reported to dental OPD with the complaint of extensive ulcerations in mouth and pain and inability to eat for past 1 week. He gave history of fever and cold two weeks back for which he took Cephalosporin, Paracetamol and Diclofenac injection. Subsequently he developed blisters which later transformed into extensive, irregular ulcerations in the mouth. Patient visited a dentist for the treatment of ulcers and was put on Novaclox 500mg, Metrogyl 400mg and Diclofenol for 5 days and topical application of Chlorhexidine gel, but pain did not alleviate and he was referred to our institution.

After extra-oral examination, both upper and lower lips showed ulcerations, showing cracking and fissuring with blood encrustation. Intra-oral examination showed extensive, irregular ulcerations with sloughing and erythematous borders on buccal mucosa, extending from retrocommissure to retromolar region and extending till the vestibule. The sudden onset, positive drug history, with above mentioned features lead to diagnosis of oral erythema multiforme. In this case cephalosporin, diclofenac were the causative drugs for the lesion.

Patient was advised to discontinue the medications prescribed earlier and was treated with systemic corticosteroid (Tab Prednisone 20 mg BID for 3 days followed by tapering dose of 5 mg for 10 days), Cap Erythromycin estolate 500 mg BID for 5 days, Tab Metronidazole 400 mg TID for 5 days and topical anaesthetic to aid in oral fluid intake. Healing was noticed on the third day and lesions were completely regressed in 10 days.

Case report 2 - A 22-year-old male patient reported to the dental OPD with complaint of ulcers in mouth since 3 days. Patient gave history of having food at a restaurant 3 days back, following which fluid filled blisters started appearing on the buccal mucosa, which increased in number and size. Patient visited physician for the same complaint and topical steroid application was advised.

After extra-oral examination, multiple target lesions were seen on the dorsum of hands, palms and sole. Multiple coalescing bullae with cracking and encrustations were seen on upper and lower lip. Intra-orally, multiple bullae were noticed measuring about 0.5-0.8 cm in diameter, involving labial mucosa and buccal mucosa. Slight sloughing was seen on right buccal mucosa and labial mucosa in the area of ruptured bullae, and the intact bullae coalescing to form large irregular boundaries. Nikolsky's sign was negative. Positive association between the food additive and incidence of lesion and clinical appearance of the lesions lead to diagnosis of erythema multiforme major.

An incision biopsy was performed and direct immunofluorescence test showed no immune deposits with IgG, IgA, IgM, and C3. Patient was treated with systemic corticosteroids (Tab Prednisone 20 mg BID with tapering dose of 5 mg for 3 days), Tab Roxithromycin 150 mg BID for 2 days, Tab Acyclovir 400 mg TID for 4 days. Complete regression of lesion was seen after 10 days.
Erythema multiforme is a type of reactive mucocutaneous disorder. The reaction pattern appears as a result of allergic host response to antigenic challenge [1]. The oral lesions are accompanied by rapidly rupturing vesicles and bullae leading to diffuse sloughing and ulceration of the whole surface of the skin and mucous membrane. [2,3]. Erythema multiforme can be induced by adverse drug reaction with a frequency of more than 1% [3].

Erythema Multiforme is caused by various insults often from an infectious agents, drugs and food additive [3,4,5]. [Table/Fig- 7 and 8]. In our case 1, the patient had a history of taking multidrugs and case 2 showed lesions due to food additives. Other triggers include benign and malignant tumours, radiotherapy (phenytoin and cranial radiation therapy - EMPACT) [4]. Over 50% of patients have unknown aetiology with stress or emotional factor as the second largest category [2].

The exact pathogenesis is unknown. It has been suggested that EM results from T-cell-mediated immune reaction to the precipitating agent, which lead to a cytotoxic immunological attack on keratinocytes that express non-self antigens, with subsequent to subepithelial and intra-epithelial vesiculation; that leads to widespread blistering and erosions [4].

**DISCUSSION**

A better understanding of the molecular and immunologic events underlying HSV-associated EM (HAEM) and their main differences with respect to drug induced EM has been provided by recent studies [4]. It is suggested that disease development begins with HSV infection of epithelial skin cells, and subsequently circulating...
mononuclear CD4+ cells (Langerhans cell precursors). This transports the HSV-DNA fragments to distant skin sites, where an immune mediated epidermal damage occurs due to production of interferon-γ (IFN-γ) [5,6,7]. Conversely, in drug-induced EM, the reactive drug metabolites persuade the disease, and tumour necrosis factor alpha (TNF-α) induces keratinocyte apoptosis which is released from keratinocytes, macrophages, and monocytes causing the tissue damage [4,6,7]. A subset of EM patients have been reported to have autoantibodies against desmoplakins I and II and antiepidermal autoantibodies. In addition to a cellular immune response, humoral immune mechanisms may be involved in the pathogenesis of EM-like disease [5,8].

The presentation of EM ranges from self limited, mild form (EM minor) to progressive, and aggressive form like EM major. Steven Johnson syndrome and TEN [1-10] [Table/Fig-9]. Kenneth in 1968 described an inflammatory oral disorder with oral lesions typical of EM. It has been suggested as a third category of EM by many investigators, known as oral EM that are characterized by typical lesions of EM but no target skin lesions [7,9]. Oral EM is chronically recurrent condition, with frequency of episodes varying from every 3 weeks to once yearly. Episodes may be cyclic with duration varying from 10 days to 6 weeks [11]. Our case 1 show lesions limited to oral mucosa and lips, no recurrence was seen on regular follow up for 3 months.

Differential diagnosis are to be considered in the lesion confined to oral cavity are herpes, vesiculolobules lesions like pemphigus vulgaris, bullous pemphigoid. Herpetic lesions are usually smaller and well circumscribed, more common in keratinized mucosa especially in gingiva. Our cases did not have any gingival ulceration. Extensive irregular ulcerations in the lining non keratinized mucosa were seen in our case 1 and case 2 showed mild ulcerations with intact bullae, which were typical of EM and were not feature of herpes infections. Temporal relationship between the drug intake and onset of disease excludes the possibility of any infectious etiology [8,11].

There is no specific diagnostic test for EM. Biopsies are advised only in the early vesicular lesions and not in the ulcerated ones as histopathologic appearances are nonspecific [8]. Immunostaining shows intense lymphocytic infiltration at the basement membrane zone and perivascularly, non-specific immune deposits of IgG, C3, and fibrin at these sites [4,9]. Our case 2, showed non specific deposits of IgG, IgM, C3.

Cutaneous patch test may aid in identification of causative agents. To differentiate herpes-associated EMminor/EMmajor from drug-associated EMminor/EMmajor and SJS, the detection of intralesional HSV-DNA via polymerase chain reaction, as well as immunohistochemistry for IFN-γ and TNFα, may be useful tests. A rising antibody titre between the acute and convalescent phases of EM major/ SJS may confirm M.pneumonia infection [5,9].

In summary management of EM includes supportive care, specific treatment of precipitating causes, and immunosuppressive therapy [5,9,11].

CONCLUSION

Erythema multiforme presents as a reactive ulcerative lesion which has various sources of etiologies and it mimicks other ulcerative lesions. An important step in the management of erythema multiforme is recognition and withdrawal or prevention of contact with the causative agent. As there remains no specific diagnostic test, early diagnosis of disease remains essential to promptly initiate...
appropriate management and proper follow up. By delivering apt information and educating the patient, oral physicians can play a role in preventing the recurrence of these lesions.

REFERENCES