CASE REPORT

DRUG INDUCED ORAL ERYTHEMA MULTIFORME: A CASE REPORT

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ABSTRACT

Oral erythema multiforme presents with oral and lip ulcerations typical of erythema multiforme but without skin target lesion. The primary attack is confined to oral mucosa but subsequent attacks can produce more severe forms of erythema multiforme involving skin. It is important to distinguish it from other oral ulcerative disorders for early diagnosis and treatment. Here we report a case of oral erythema multiforme induced by drug with literature review.

Key words: Oral erythema multiforme, drug reactions, lips.

J Odontol Res 2013;1(2):72-5

INTRODUCTION

Oral Erythema Multiforme (EM) is considered as a third category of EM other than EM minor and major. Oral erythema multiforme characterized by oral mucosal ulcerations & lip lesions typical of EM without any skin lesions. Kenneth described oral lesions of EM without any skin involvement in 1968[1]. EM minor shows ulcerations involving single mucosal site with typical skin target lesions. EM major shows ulcerations involving more than one mucous membrane with skin target lesions. A wide range of antigens including herpes and drugs has been suggested as triggering the disease. Ferdinant Von Hebra first described EM in 1866[2]. Thomas coined the term erythema multiforme minor and major in 1950[3]. Here we report a case of drug induced oral erythema multiforme highlighting its importance of early diagnosis and treatment, as oral lesions precedes skin lesion of erythema multiforme.

CASE REPORT

A 60 year old male reported to the out patient department with a chief complaint of redness and ulceration of both lips since 1 week. Patient gave history of extraction of his left upper back tooth and was prescibed Mefenamic acid [Meftal forte]. He felt burning sensation on intake of food and noticed ulcers on left buccal mucosa and the lips 3 days after taking medication.

On intraoral examination patient had multiple ulcerations of the labial mucosa and irregular ulcerations and blood encrustations of both the lips. Skin lesions were absent. Multiple ulcerations of labial mucosa and blood encrustations seen on the vermilion zone of the lip (figure 1). Provisional diagnosis of drug induced oral erythema multiforme was made. Patient was asked to stop all the medicines and given Prednisolone 5mg twice daily for 10day, Levocetrizine once daily for 10 day and Pantoprazole 40mg once daily for 10 days. Patient was asked to come for review after 10 days. On review patient showed symptomatic progress (figure 2). Prednisolone dose tapered and stopped.

DISCUSSION

Erythema multiforme(EM) is a rare, acute inflammatory disorder that affects skin, or mucous membrane or both. It present with a wide spectrum of severity. Erythema multiforme minor represents a localised eruption of the skin with mild or no mucosal involvement. Erythema multiforme major and Steven Johnson are more severe mucosal and skin diseases and are potentiallly life threatening disorders.EM occurs chiefly in young adults and peak age of presentation is 20-40 years. Peak incidence seen in second to fourth decades of life and males are more commonly affected than females[4]. The incidence of oral lesions in EM varies considerably from 25-70%. It is usually triggered by herpes simplex infections, but rarely by drug intake. The antigens are primarily microbial agents (Herpes simplex virus, mycoplasma, pneumonia and histoplasmosis), gastrointestinal conditions like Crohn's disease and ulcerative colitis, other conditions like radiotherapy and recent vaccination or drugs[5]. The most common drugs that trigger EM lesions are long acting sulfa drugs especially sulphonamides, co-trimoxazole, phenytoin, carbamazepine and nonsteroidal antiinflammatory drugs such as diclofenac, ibuprofen, and salicylates. About 5% of EM are attributed to drug intake. The positive drug history associated with onset of oral ulcerations ruled out other oral ulcerative and autoimmune vesiculobullous disease in our case. Literature review of drug induced erythema multiforme is given in Table 1.

In drug-induced erythema multiforme, the reactive metabolites of the initiating drug induce the disease[6]. Drug-induced erythema multiforme usually develops 1 to 3 weeks after exposure but may occur within hours or days which is the time it takes for an immune response to appear. Second reccurence occurs significantly shorter than that of the first episode and is indicative of a secondary immune response. Immunocytochemicial staining and in situ hybridisation has shown that the lesions are characterised by tumour necrosis factor alpha (TNF- α) present in keratinocytes. Much of the tissue damage in drug-induced lesions appears to be due to apoptosis and due to the paucity of the inflammatory reaction. Locally produced TNF-α has been shown to mediate keratinocyte apoptosis and it is possible that this mechanism plays an important role in drug induced erythema multiforme[6]. EM results from a T-cell-mediated immune reaction to the precipitating agent. It leads to cytotoxic immunological attack on keratinocytes that express non-self antigens, resulting in sub-epithelial and intra-epithelial vesiculation. Drugs or other antigens like herpes virus form circulating immune complexes that filter into the basement membrane in skin and mucosa. These components bind complement and initiates a vasculitis with thrombosis and ischemic necrosis of the overlying epithelium. This leads to wide spread blistering and erosions[5].

Intraoral lesions seen typically on the non-keratinised mucosa and most pronounced in the anterior parts of the mouth. The oral mucosal ulcerations are usually irregular and large with necrotic tissue tags. Lip ulcerations are blood encrusted. The clinical presentation of the oral lesions is typically with swollen lips, labial erosions and blood stained serosanguinous exudate.

Table 1- Cases reported with drug induced erythema multiforme[1,7,8]

AUTHOR	YEAR	DRUG
Taylor S. W et al	1989	Methotrexate
Dubey N. K et al	1995	Paracetamol
Rzany B et al	1996	Allopurinol - 18 cases Aminopencillin – 7 cases Carbamezepine – 13 cases Co – trimoxazole – 22 cases Dexamethasone – 8 cases Paracetamol – 11 cases Phenytoin – 11 cases
Amichai. B et al	1998	Methotrexate
Chen W.C et al	2002	Pyrazolone
Worhl .S et al	2005	Phenytoin
Dilhuydy M . S etal	2007	Sorafenib
Joseph T. I et al	2012	Diclofenac

Oral lesions progress through diffuse widespread macules to blisters and ulceration. Oral involvement is seen in about 70% of the cases with erythema multiforme[6]. Literature review showing oral lesion in erythema multiforme given in table 2.

Table 2 - Oral lesions in erythema multiforme [2,6,7]

AUTHOR	YEAR	NUMBER OF CASES	ORAL LESIONS
Huff and Weston	1989	22 cases	22.7%
Schofield et al	1993	65 cases	69%
Farthing et al	1995	82 cases	70%
Lamireau T et al	2000	42 cases	78.5%
Wetter and Davis	2010	48 cases	62.5%

When only oral mucosa is involved the differential diagnosis to be considered include herpes, autoimmune vesiculobullous lesions such as pemphius vulgaris or bullous pemphigoid and other patterns of drug reactions. Herpetic lesions more common on keratinized mucosa. In our case patient positive drug history, clinical appearance and distribution of lesion ruled out possibility of autoimmune vesiculobullous disease. Other clinical patterns of adverse reaction to drug like lichenoid drug reaction, pemphigoid like drug reactions can be differentiated based on clinical pattern. Anaphylactic stomatitis which often shows urticarial skin reactions signs symptoms of anaphylaxis. In fixed drug eruption, lesion is confined to localized area of oral mucosa.

Histopathologically subepithelial or intraepithelial vesiculation may be seen with necrotic basal keratinocytes. Satellite cell necrosis ie, individual eosinophilic necrotic keratinocyte surrounded by lymphocytes may be seen. Sometimes oedema results in pooling of oesinophilic coagulum within the epithelium described as keratin mucopolysaccharide dystrophy[5]. There is intense lymphocytic infiltration and vacuolar degeneration of basement membrane zone. A mixed inflammatory infiltrate is present in connective tissue consisting of lymphocytes, neutrophils and often eosinophils arranged in a perivascular orientation. Immunofluorescence reveals that deep perivasculitis is positive for antibodies of Ig M and C3[3,4,9]. Histopathological examination of the ulcerative lesion in erythema multiforme is non specific and non diagnostic[1]. Hence biopsy was not undertaken in the present case. Biopsies are advised only in early vesicular lesions of erythema multiforme.In the present case diagnosis was made based on clinical appearance and positive drug history.

Fukiwake et al in 2007 demonstrated anti - keratinocyte cell surface antibodies in the serum of a paient with oral erythema multiforme by indirect immunofluorescence. It revealed that the autoantibodies are bound to the plasma membrane of epidermal keratinocytes. Indirect immunofluorescence shows anti-desmoplakin monoclonal antibody which react with keratinocyte cell surface [DP I& II] of esophageal mucosa. On immunoblotting patient's serum showed autoantibodies reactive were DP I and II which exist in the cytoplasmic attachment plaque

Fig1: Irregular ulcerations with blood encrustations

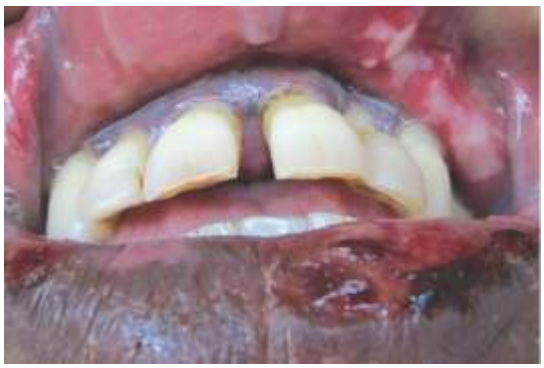

Fig 2: 10 days post treatment,
the oral and lip ulcerations shows healing

of desmosomes [10].

Managed by identification of triggering agent. If it is found to be HSV infection patients have to be put on antiviral medications. If the triggering agent is an adverse drug reaction, the drug is immediately stopped. Usually lesions of oral EM can be treated palliatively with analgesics for oral pain, viscous lidocaine rinses, soothening mouth rinses, bland soft diet, avoidance of acidic and spicy food, oral antihistamines, systemic and topical antibiotics to prevent secondary infection. Oral antacids may be helpful for discrete oral ulcers. Lesions of EM usually respond to topical steroids, for more severe cases systemic corticosteroids are recommended[4].

CONCLUSION

Oral EM is a rare and less described variant of EM. Even though primary attacks of oral EM are confined to the oral mucosa the subsequent attacks can produce more severe forms of EM (EM minor and major) involving the skin. Hence, it is important to distinguish oral EM for their early diagnosis, proper management.

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