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Case Report

A case of drug induced oral erythema multiforme

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ABSTRACT

Erythema multiforme (EM) is an acute, self-limited, usually mild, and often relapsing mucocutaneous syndrome. It occurs predominantly in younger age group with slight male preponderance. The classical cutaneous target lesions and mucosal bullae or erosions are clinical manifestations of EM. Drug induced oral EM a rare clinical entity which involves only the lips and oral mucosa without skin involvement. These lesions are difficult in diagnosing with other oral ulcerative lesions with similar clinical manifestations. Here we are reporting a case of phenylbutazone induced oral EM. The causality of phenylbutazone in the reaction was "probable" as per Naranjo scale and seriousness of the reaction was "prolonged hospitalization". The patient was managed by immediate withdrawal of the suspected drug along with conservative managements to prevent secondary infections. The patient was discharged successfully after 15 days of admission.

Keywords: Oral EM, Phenylbutazone, Ulceration

INTRODUCTION

Erythema multiforme (EM) is an acute, self-limited, and sometimes recurring skin condition that is considered to be a type IV hypersensitivity reaction associated with certain infections, medications, and other various triggers. The disease is usually related to an acute infection, most often a recurrent herpes simplex virus (HSV) infection. EM is defined only by its clinical characteristics: target- shaped plaques predominant on the face and extremities. The absence of specific pathology, specific cause, and biologic markers contribute to a confusing nosology. The definition of EM here is based on the classification proposed by Bastuji-Garin et al.[1] Sub-types of EM is given in Table 1.

EM is considered relatively common, but its incidence is unknown. Evaluations have been limited to cases severe enough to require hospitalization. Such cases are definitely rare, with figures in the range 1 to 6 per million per year. Minor forms of EM are certainly more frequent, but diagnosis of EM is nonetheless too often made. EM occurs in patients of all ages, but mostly in adolescents and young adults. There is a slight male preponderance (male- female sex ratio of approximately 3:2). EM is recurrent in at least 30% of patients.[2]

Table 1: Erythema multiforme sub-types.

S. no.	Types
1	Erythema multiforme minor: Skin lesions without involvement of mucous membranes.
2	Erythema multiforme major: Skin lesions with involvement of mucous membranes.
3	Herpes-associated erythema multiforme.
4	Mucosal erythema multiforme (Fuchs syndrome, ectodermosis pluriorificialis): mucous membrane lesions without cutaneous involvement.

Most cases of EM are related to infections. Herpes virus is definitely the most common cause, principally in recurrent cases. Proof of causality of herpes virus is firmly established from clinical experience, epidemiology, detection of HSV DNA in the lesions of EM, and prevention of EM by suppression of HSV recurrence.[3-5] *M. pneumoniae* is the second major cause of EM and may even be the major cause in pediatric cases.[6] In cases related to *M. pneumoniae* the clinical presentation is often less typical and more severe than in cases associated with HSV. The relationship to *M. pneumoniae* is often difficult to establish. Clinical and radiologic signs of atypical pneumonia can be mild, and *M. pneumoniae* is usually not directly detected. PCR testing of throat swabs is the most sensitive technique. Mechanism have been investigated in depth in herpes- associated EM. It is not known whether similar pathophysiologic mechanisms apply to EM due to other causes.

The skin rash arises abruptly. In most patients, all lesions appear within 3 days, but in some, several crops follow each-other during one episode of EM. Often there are a limited number of lesions, but upto hundreds may form. Most occur in a symmetric, acral distribution on the extensor surfaces of the extremities (hands and feet, elbows, and knees), face, and neck and appears less frequently on thighs, buttocks, and trunk. Lesions often first appear acrally and then spread in a centripetal manner. Mucosal lesions are present in up to 70% of patients, most often limited to the oral cavity. Predilection sites for mucosal lesions are the lips, on both cutaneous and mucosal sites; non- attached gingivae; and the ventral side of the tongue. The hard palate is usually spared, as are the attached gingivae. On the cutaneous part of the lips, identifiable target lesions may be discernible. Early lesions of EM exhibit lymphocyte accumulation at the dermal-epidermal interface, with exocytosis into the epidermis, lymphocytes attached to scattered necrotic keratinocytes (satellite cell necrosis), spongiosis, vacuolar degeneration of the basal cell layer, and focal junctional and sub-epidermal cleft formation.[2]

Fever and other constitutional symptoms are usually absent in EM minor, and the physical examination is normal. Fever higher than 38.5°C (101.3°F) is present in 32% cases of EMM.[2]

Drugs are a rare cause of EM with mucous membrane lesions. It may be argued whether these eruptions are truly EM or mere imitators, for example, annular urticaria or maculopapular eruption with some lesions resembling targets.

The etiology and pathogenesis of EM is unclear in most patients, but appears to be an immunological hypersensitivity reaction with the CD8+ T lymphocytes, in epithelium, inducing apoptosis of scattered keratinocytes and leading to satellite cell necrosis.[7] Various exogenous factors trigger an immunological reaction that appears as a sub and intra-epithelial vesiculation. A genetic predisposition to EM may be present, along with associations of recurrent EM with HLA-B15 (B62), HLA-B35, HLA-A33, HLA-DR53 and HLADQB1* 0301. HLA DQ3 has been proven to be especially associated with recurrent EM and should be a helpful marker for distinguishing HAEM (herpes-associated EM) from other diseases with EM-like lesions. Patients with severe mucosal involvement may have the rare HLA allele DQB1*0402.[8] Thus viral infections tend to trigger EM minor or major but drug ingestion tends to trigger more severe SJS or toxic epidermal necrolysis (TEN).[9] The lesions due to drug-associated EM when compared with herpes associated EM test positive for tumor necrosis factor α and not interferon-γ as the later thus suggesting a varying mechanism.[10] Here we are reporting a case of oral EM which was induced by phenylbutazone.

CASE REPORT

A 22 years old male patient came to general medicine OPD with complains of difficulty in swallowing and left knee joint pain and swelling on 08/12/2022. On examination, the patient was currently having multiple ulcers on vermilion border of upper and lower lips (Figure 1), and there was bilateral proptosis and swollen chin areas. No skin or ocular lesions were evident. Ulcers were encrusted showing varying size of 1 to 2 mm. Based on positive drug history and evidence of lesions, provisional diagnosis of drug induced EM was given. On history taking, the patient's attendant revealed that the patient had taken tablet phenylbutazone, 100 mg 2 days back for left knee joint pain. Initially patient experienced burning sensation an hour after administration of the drug. Burning sensation became severe after administration of the second dose. There was no history of fever after administration of the drug. Immediate withdrawal of the drug was done and management was done by IV antibiotics, benzocaine gel and chlorhexidine mouthwash for oral ulceration and tapering dose of tablet Prednisolone. Systemic steroid prednisolone 20 mg /d for 1 week with tapering dose of 10 mg/ d for the second week was administered. Healing of the lesions were evident on third week of follow up. The patient was discharged after 15 days of admission.

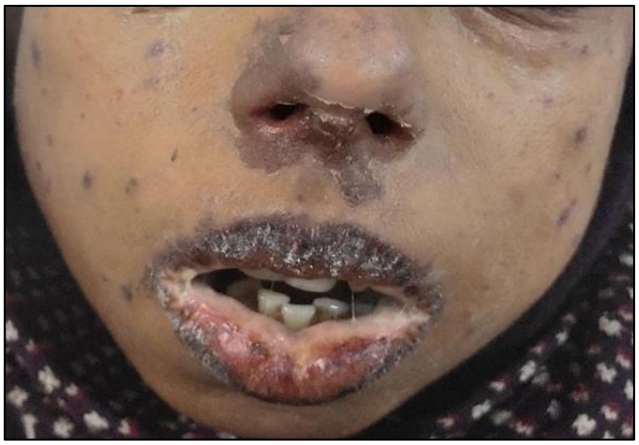

Figure 1. Ulcerative encrusted lesions on lips.

Oral lesions are seen on the lips and buccal mucosa which appear as erythematous macules, and bloody encrustations involving lips. Isolated oral lesions are rare entity which makes diagnosis in question. This rare variant has been considered as oral EM.[11]

DISCUSSION

Drugs are double edged sword, which gives beneficial results and can also cause adverse reaction in certain conditions. Adverse drug reaction can manifest as many forms like EM, fixed drug eruption and anaphylactic reactions. EM was first reported in literature by Bateman and Bulkey in 1846 followed by Hebra in 1866 who described as erythema exudative multiforme.[12] In 1922 Stevens and Johnsons reported severe form of EM with involvement of oral and conjunctival mucous membrane along with skin lesions.[13] In 1968, Kenneth described an inflammatory oral disorder which resembled to that of EM without any skin involvement.[14] Most common drugs which induce reactions are non-steroidal anti-inflammatory drugs and antibiotics. Very few cases of EM have been reported with the ingestion of paracetamol and diclofenac sodium. Database showed 2.06% of cases of EM were due to diclofenac sodium and 6.17% of cases were due to ingestion of paracetamol.[15] In our case the patient had no history of any kind of infection or allergy to any food additives. Hence with this temporal occurrence of drug intake and appearance of the lesion, it was considered that etiological agent was drug in the case, most probably phenylbutazone. The probability of adverse drug reaction was 6 according to Naranjo scale.[16] The causality of phenylbutazone in the reaction was "probable" as per Naranjo scale and seriousness of the reaction was "prolonged hospitalization".

Drug induced EM express tumor necrosis factor alpha instead of interferon-gamma. Drug metabolism is altered and directed towards cytochrome p450-metabolite pathway resulting in production of reactive and toxic metabolites. Tissue damage is mainly due to apoptosis and not by inflammatory response. Oral EM is a distinct but less well recognized variant of EM. Very few cases have been reported in the literature with this form.[17] It has been reported that primary attacks of oral EM are confined to oral mucosa without skin involvement. Subsequent attacks can produce more severe form of EM involving the skin.[18] Oral mucosa is the commonest site with labial mucosa, buccal mucosa and lips involving in 70% of cases. In considering differential diagnosis, most common is aphthous ulcer which occurs commonly on the lining mucosa. They are round or oval ulcers with yellowish gray membrane surrounded by erythematous halo. Herpes simplex infections are seen more on attached mucosa like gingiva, palate and lips with regular margins and small in size.[17] In our case there were no such lesion seen on the attached mucosa. Recurrent herpes labialis can affect lips, but onset is viral and our patient does not have any prodromal symptoms with clinical features not correlate to that of viral infection. Lesions like pemphigus are seen on gingiva resembling desquamative gingivitis. An important clinical sign noted in pemphigus is nikolsky sign which was negative in our patient.[17] Fixed drug eruption occurs due to hypersensitivity reaction to drugs characterized by skin lesions that recur at same anatomical location upon repeated exposures to drug.[19] Diagnosis of EM mainly rely on clinical onset, positive triggering factor and clinical appearance. Histopathology of EM will be nonspecific and biopsy can be obtained only in vesicular stage of lesion.

The aims of treatment are to reduce the duration of fever, eruption, and hospitalization. Treatment of EM is based on identification and removal of triggering factors. These lesions usually respond to corticosteroid. Topical steroids can be started in case of minor lesion and systemic steroids for severe conditions for a period of 1 week with tapering dose. In our patient offending drug was discontinued and was prescribed systemic steroid for a week and later tapered. Lesion healed completely in 15 days without any scar formation.

CONCLUSION

Drug induced oral EM is considered to be a rare and less described variant of EM. HSV infections mostly responsible for triggering EM rather than the systemic administration of drugs which in turn result in adverse reactions. Even though it has been observed that the primary attack of drug induced EM is confined to the oral mucosa the subsequent attack can produce more severe forms of EM (EM minor, EM major) involving their skin. It is important for oral pathologists and general dentists to have a clear knowledge about the differential diagnosis related to EM in order to differentiate from other vesiculobullous lesions from drug induced EM thus helping in prompt management and proper follow-up.

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