Drug Induced Oral Erythema Multiforme: A Rare Case Report

Aditi Agarwal*, Sujatha G.P., Ashok Lingappa*****

Author Affiliation:
*PG Student ,** Professor,
*** Professor and Head, Dept. of Oral Medicine and Radiology, Bapuji Dental College and Hospital, Davangere.

Reprint Request:
Aditi Agarwal, PG Student, Dept. of Oral Medicine and Radiology, Bapuji Dental College and Hospital, Davangere, Karnataka 577004
E-mail:
draditiagarwal@yahoo.co.in

Abstract

Erythema multiforme (EM) is an acute, self- limited, inûammatory disease of the skin and mucous membranes involving oral mucosa most often, although other mucosal surfaces, such as the genitalia may also be involved Oral lesions are often an important component of the clinical picture and are occasionally the only component, making it important to identify and distinguish them from other ulcerative disorders, for early management and preventing subsequent more severe form. Oral erythema multiformeis often triggered by HSV infections and rarely by adversedrug reactions.This article highlights one such case of drug induced erythema multiforme with a detailed review of literature.

Keywords: Oral Erythema Multiforme; Ulcerations; Vesiculobullous; Drug Induced.

Introduction

Erythema multiforme (EM) is an acute, self- limited, inûammatory disease of the skin and mucous membranes involving oral mucosa most often, although other mucosal surfaces, such as the genitalia may also be involved [1]. It is a clinical conundrum, the name of which means multiple forms of redness and reflects the broad morphological spectrum of the lesions. The lesion appears mostly as symmetrical papules, later developing into “target” or “iris” lesions with an erythematous periphery and a central zone of necrosis. Other characteristic features include bullae and vesicles. The lesions usually appear bilaterally on the dorsal surfaces of the hands and feet. The oral lesions appears typically as inflammation accompanied by rapidly rupturing vesicles and bullae [2]. Based on the severity and the number of mucosal sites involved, the disease has been subclassified into EM minor and major. EM minor shows ulcerations involving a single mucosal site with typical skin target lesions. EM major shows ulcerations involving more than one mucous membrane with skin target lesions. These lesions can be triggered by HSV infections or adverse drug reactions [3]. Since the oral lesions, crusted erosions on the lips or intraoral ulcerations and erosions, are often an important component of the clinical picture and are occasionally the only component, it is important to identify and distinguish them from other ulcerative disorders involving oral cavity for early management and preventing subsequent more severe form [4]. This article reports a case of drug induced oral EM.

Case Report

A 50 year old male reported the department with a complain of pain and ulcerations in oral cavity since last one week. History of present illness revealed that patient first experienced pain especially in throat and jaw region which was insidious in onset, continuous, moderate in intensity with no aggravating or reliving factors. Two days later he developed ulcerations which first started over lower lip and later involved complete oral cavity. He was also having difficulty in swallowing. There was no history of fever and

other symptoms associated with it. Patient also gave history of intake of tab ibuprofen 400 mg twice daily for two days before initiation of symptoms. Past medical history revealed he was known case of hypertension since last 8 years and was taking tab Amcard-5 (Amliodipine) once daily. He was also having psoriasis since last 11 years for which he was applying clobetasolproprinionsalicyclic acid topically and since last 6 months was taking tab Neotrexate once daily. He was also gave history of smoking since last 20 years 10-8 cigarettes per day. General physical examination revealed skin lesions(Figure 1). Extraoral examination showed bloody encrustations over lower lip (Figure 2).

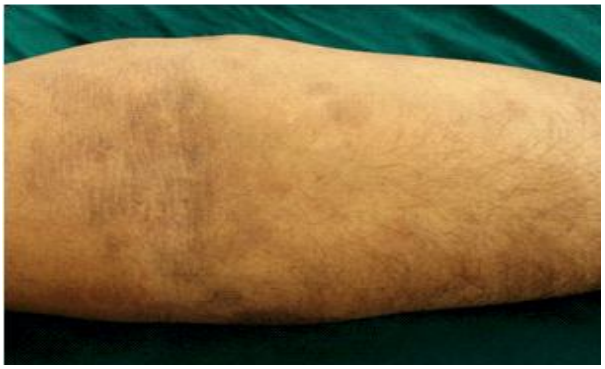

Fig. 1: Skin lesions

Fig. 2: Lower lip

Lymph node examination showed palpable right and left submandibular lymph nodes which were tender, soft in consistency, mobile.

In intraoral examination, soft tissue examination revealed multiple erosions and diffuse erythema over lower labial mucosa, left and right buccal mucosa, posterior soft palate (Figure 2). Multiple ulcerations were also present over lower labial mucosa and right buccal mucosa of size 1x2cm, having irregular shape, erythematous margins and bleeding floor. On palpation it was tender with soft base. Solitary unrupturedbulla was seen over upper labial mucosa (Figure 3).

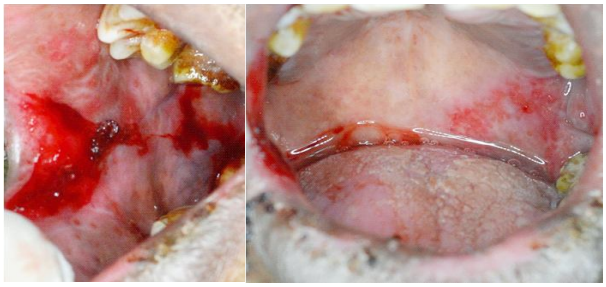

Fig. 3: Diffuse erythema and ulceration over buccal mucosa and soft palate

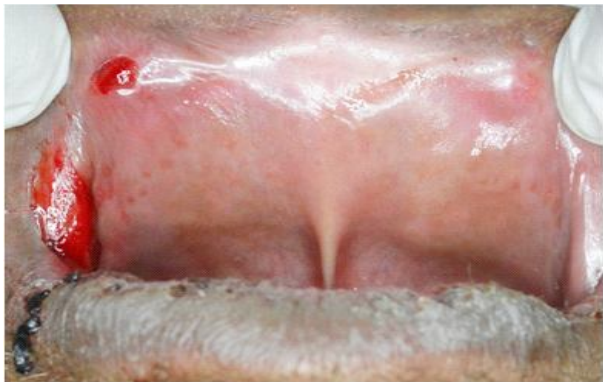

Fig. 4: bulla seen over upper labial mucosa

Hard tissue examination revealed normal compliment teeth with missing 16,15,47. Generalized attrition was present. Other findings were normal.

Provisional diagnosis of acute multiple ulcerative lesion was considered. Differential diagnosis included were oral erythema multiforme, acute herpetic stomatitis, autoimmune vesicullobullous lesions such as pemphigus vulgaris or bullous pemphigoid.

Investigations carried out was complete hemogram, RBS, and serum creatinine levels which were in normal range.

Diagnosis was made based on clinical picture. Acute onset of ulcerations with positive drug history in our case ruled out the possibility of autoimmunevesicullobullous lesions like pemphigus vulgaris or bullous pemphigoid. Absence of gingival ulceration and extensive irregular ulcerations involving the lining nonkeratinized mucosa in our patient were suggestive of erythema multiforme rather than herpetic lesionswhich are more common in the keratinized mucosa. Also ulcers seen in herpetic lesions are smaller with regular borders than ulcers associated with EM.

Based on these findings final diagnosis of erythema multiforme was given. Patient was asked to stop the use of ibuprofen and was given prednisolone 10 mg three times a day for eight days.

Patient was followed up. After 2 days of therapy, patient showed reduction in symptoms and lesion (Fig4), while after 8 days complete resolution of lesion with scarring of lower lip and pigmentation of buccal mucosa was seen (Fig 5).

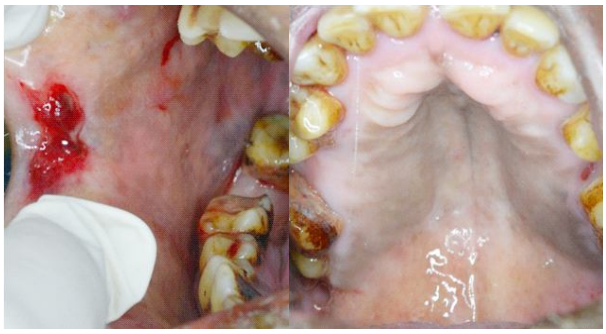

Fig. 5: After 2 days of therapy, reduction in erythema and ulceration over buccal mucosa and soft palate

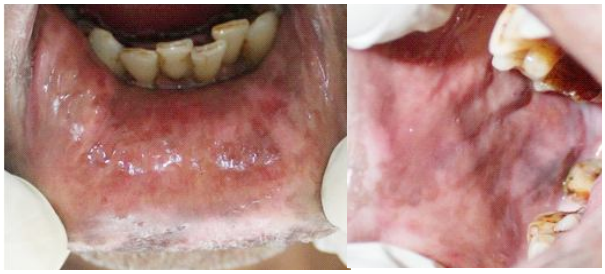

Fig. 6: Complete resolution of lesions

Discussion

Erythema multiforme (EM) is an acute inûammatory disease of the skin and mucous membranes. The disease was first recognized in 1817 by Batemanand Bulkley and in 1846, reported the first American cases as "Herpes Iris." Later in 1866, Hebrafully described the morphologic features of the eruption under the term "erythema exsudativum multiforme" and also recognized erythema multiforme to be of internalor systemic origin and not local in causation. Erythema multiforme was supposed to be essentially cutaneous inlocation with oral mucosal involvement present in about 25 per cent of the cases, but the association ofsevere vesiculobullous oral mucosal lesions with a paucityof cutaneous lesions and in some instances occurrence of severe mucous membrane with entire absence of askin eruption, produced a confusing and bizarreclinical pictures. Some investigators described theseunusual mucous membrane manifestations of erythema multiforme as new diseases [5]. In 1916, Rendu, termed a severebullous stomatitis associated with similar lesions on theconjunctival, anal, and penile mucous membranes and acutaneous vesicular eruption, "Ectodermose Erosive Pluriorificielle." Baader, in 1925, named severe erythema multiforme of the oral cavity associated with cutaneous lesions,"Dermatostomatitis." Stevens and Johnson in 1922, reported erythema multiforme with predominant involvementof the oral and conjunctival mucous membranes as "a neweruptive fever associated with stomatitis and ophthalmia." This syndrome has also been referred to in the medicalliterature as "Stevens-Johnson disease." The erythemamultiforme group may also belong the "triple syndromecomplex" of Behcet consisting of ulcerations of the oraland genital mucous membranes associated with retinitis andiridocyclitis. Later in 1968, Kenneth described oral lesions typical of EM as an inflammatory oral disorder but without any skin involvement [6] .

Etiology and Pathophysiology

EM is a hypersensitivity Reaction,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.[1]

There are various precipitating factors and Herpes simplex virus (HSV) is the most commonly identified etiology, accounting for more than 50 percent of cases. Fungal infection, Mycoplasma pneumoniae is another commonlyreported etiology, especially in children [7].

The medications most often associated with erythema multiforme are barbiturates, hydantoins, nonsteroidal anti-inflammatory drugs such as diclofenac, ibuprofen, and salicylates, penicillins, phenothiazines, and sulfonamides. In addition, there have been reports of erythema multiforme associated with vaccines (diphtheria-tetanus, hepatitis B, smallpox), other viruses (varicella zoster virus, hepatitis C, cytomagalovirus,and human immunodeficiency virus). Recurrent erythema multiforme often is secondary to HSV-1 and -2 reactivation [8].

The pathogenesis of herpes-associated erythema multiforme has been well studied and is consistent with a delayed-type hypersensitivity reaction.The disease begins with the transport of viral DNA fragments to distant skin sites by peripheral blood mononuclear cells. HSV genes within DNA fragments are expressed on keratinocytes, leading to the recruitment of HSV specific CD4+ T1 cells (helper T cells involved in cell-mediated immunity). The $CD4^+$ cellsrespond to viral antigens with

productionof interferon-γ, initiating an inflammatory cascade. In drug associated erythema multiforme lesions test positive for tumor necrosis factor α and not interferon-γ as in herpes associated erythema multiforme lesions [9].

ClinicalManifestation

Erythema multiforme usually occurs in adults 20 to 40 years of age, although it can occur in patients of all ages. The disease is more common in males than females in a ratio of 3:2. Erythema multiforme has been classified as minor, major, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis(TEN), where erythema multiforme minor is the mildest type of lesion and toxic epidermal necrolysis the most severe. In Erythema multiforme minor, major and SJS Body surface area with epidermal detachment is less than 10% while in TEN it is more than 10% [10].

General Features**-**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 1 week before the onset of surface erythema or blisters. 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) [11].

Oral features - 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. The common sites involved are lips, buccal mucosa, and tongue. Oral 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 [12].

Diagnosis

There is no specific diagnostic test for EM. Cytologic smears and virus isolation may be done to eliminate the possibility of primary herpes infection.Biopsies are advisedonly in the early vesicular lesions and not in the ulcerated ones ashistopathologic appearances are nonspecific. The histologic picture shows a perivascular lymphocytic inûltrate, non-specific immune deposits of IgM, fibrin at these sites and epithelial edema and hyperplasia [1,13].

Thus the diagnosis is made on the basis of the total clinical picture and by excluding other oral inflammatory and vesicullobullous lesions.Features more suggestive of EM are the acute onset (or recurrent nature), oral lesions typically located on the lip and anteriorly in the mouth, and pleomorphic skin lesions (typical and atypical target lesions). These findings differentiate EM from other vesicullobullous lesions like pemphigus vulgaris or bullous pemphigoid. Also oral EM lesions are larger, irregular, deeper, and often bleed. Based on these clinical appearance it is differentiated from viral lesions, which are small, round, symmetric, and shallow. In bullous lichen planus, lesions that may have similar ulcerations but presence of Wickham's striae, which is absent in EM is a differentiating feature. Anaphylactic stomatitis often shows urticarial skin reactions with other signs and symptoms of anaphylaxis which will be absent in EM [14,15].

Management

Mild cases 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, systemic and topicalantibiotics to prevent secondary infection. Moderate to severe oral EM may be treated with a short course of systemic corticosteroids in patients without signiûcant contraindications to their use. An initial dose of 30 mg/d to 50 mg/d of prednisone or methylprednisolone for several days, which is then tapered, is helpful in shortening the healing time of EM, particularly when therapy is started early in the course of the disease.Triggering agent should also be identified. If it is found to be HSV infection patients have to be put on antiviral medications while it is an adverse drug reaction, the drug is immediately stopped [16,17].

Conclusion

Oral erythema multiforme is a rare vesiculo-ulcerative disorder which is often triggered by HSV infections and rarely by adversedrug reactions. Diagnosis is based on clinical presentation with no specific diagnostic test. Thus identification of associated triggering agent is important for therecognition and management of erythema multiforme. Management depends on severity of lesions which varies from supportive care to

corticosteroid therapy.

References

1. Lynch MA, editor. Burket's oral medicine: diagnosis and treatment. Lippincott; 1977.
2. Aurelian L, Ono F, Burnett J. Herpes simplex virus (HSV)-associated erythema multiforme (HAEM): a viral disease with an autoimmune component. Dermatology online journal. 2003 Jan 1; 9(1).
3. Katz J, Liveh A, Shemer J, Danon YL, Peretz B. Herpes simplex-associated erythema multiforme (HAEM): a clinical therapeutic dilemma. Pediatric dentistry. 1999; 21: 359-62.
4. Joseph TI, Vargheese G, George D, Sathyan P. Drug induced oral erythema multiforme: A rare and less recognized variant of erythema multiforme. Journal of oral and maxillofacial pathology: JOMFP. 2012 Jan; 16(1): 145.
5. Robinson SS, Tasker S. Severe Stomatitis Due To Erythema Multiforme—Its Differentiation from Human Foot And Mouth Disease. California medicine. 1948 Aug; 69(2): 140.
6. Shah SN, Chauhan GR, Manjunatha BS, DaGruS K. Drug Induced Erythema Multiforme: Two Case Series with Review of Literature. Journal of clinical and diagnostic research: JCDR. 2014 Sep; 8(9): ZH01.
7. Patel TK, Barvaliya MJ, Sharma D, Tripathi C. A systematic review of the drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Indian population. Indian Journal of Dermatology, Venereology, and Leprology. 2013 May 1; 79(3): 389.
8. Osterne RL, Matos Brito RG, Pacheco IA, Alves AP, Sousa FB. Management of erythema multiforme associated with recurrent herpes infection: a case report. J Can Dent Assoc. 2009 Oct 1; 75(8): 597-601.
9. Lamoreux MR, Sternbach MR, Hsu WT. Erythema multiforme. Am Fam Physician. 2006 Dec 1; 74(11): 1883-8.
10. Patil B, Hegde S, Naik S, Sharma R. Oral blistering-Report of two cases of erythema multiforme& literature review. Journal of clinical and diagnostic research: JCDR. 2013 Sep; 7(9): 2080.
11. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. International journal of dermatology. 2012 Aug 1; 51(8): 889-902.
12. Kohli PS, Kaur J. Erythema multiforme-Oral variant: case report and review of literature. Indian Journal of Otolaryngology and Head & Neck Surgery. 2011 Jul 1; 63(1): 9-12.
13. Schifter M, Yeoh SC, Coleman H, Georgiou A. Oral mucosal diseases: the inflammatory dermatoses. Australian dental journal. 2010 Jun 1; 55(s1): 23-38.
14. Talacko AA, Gordon AK, Aldred MJ. The patient with recurrent oral ulceration. Australian dental journal. 2010 Jun 1; 55(s1): 14-22.
15. Arisawa EA, Almeida JD, Carvalho YR, Cabral LA. Clinicopathological analysis of oral mucous autoimmune disease: A 27-year study. Medicina oral, patologia oral y cirugiabucal. 2008 Mar 1; 13(2): E94-7.
16. Michaels B. The role of systemic corticosteroid therapy in erythema multiforme major and Stevens-Johnson syndrome: a review of past and current opinions. The Journal of clinical and aesthetic dermatology. 2009 Mar; 2(3): 51.
17. Williams RM, Cocklin RC. Erythema multiformea. Review and contrast from Stevens-Johnson syndrome/toxicepidermal necrolysis. Dent Clin North AM. 2005; 49: 67–76.