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Case Report

Drug-induced Oral Erythema Multiforme: Report of Two Cases with Review of Literature

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Abstract

Erythema multiforme (EM) is a blistering and ulcerative mucocutaneous disease which may have oral manifestations. It appears as a diagnostic dilemma because the oral cavity presents with varied appearances (multiforme means many forms). Infections (particularly herpes simplex virus) and various drugs seem to predispose toward development of EM. These may trigger an immunologic derangement that produces the disease. Drug-induced EM is a rare entity which accounts for <10% of all cases. Health-care providers must be careful regarding such adverse effects of the drugs. Here, we report two cases of oral EM in which drugs seem to be the precipitating factor, which warrants judicious use of such drug regimens and the importance of reporting and monitoring mechanisms for effective management.

Key words: Adverse drug reactions, Erythema multiforme, Mucocutaneous disorders, Vesiculobullous lesion

INTRODUCTION

Erythema multiforme (EM) is an acute, self-limiting, hypersensitive, and mucocutaneous lesion with varied etiology. It consists of a spectrum of disorders, including Erythema multiforme minor (EMm), Erythema multiforme major (EMM), Stevens Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN).[1,2]

EM appears as a consequence of allergic host response to antigenic challenge which is triggered primarily by antigens, induced commonly by exposure to microbes or drugs. Although the exact pathogenesis is unknown, there is a tendency to consider both EMm and EMM as part of one spectrum that is most often triggered by viral infections, and SJS and TEN as a separate spectrum most often elicited by drugs. All variants of EM typically show some degree of cutaneous involvement. EMm characteristically affects single mucosa and may be associated with symmetrical target skin lesions on the extremities. EMM typically involves two or more mucous membranes with more variable skin involvement. The severe variants SJS and TEN usually involve the skin extensively.[2]

Oral EM is a distinct but less well recognized variant of EM, introduced by Kennett in 1968.[3,4] 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.[1] Drug-associated EM is relatively uncommon and reported to be <10%.[1] Although a variety of drugs has been associated with EM, antibiotics and analgesics are most commonly implicated.[2-5]

Here, we present two case reports of drug-induced oral EM associated with intake of Fluoroquinolones and Nitroimidazole groups of antibiotics. The etiology, pathogenesis, diagnostic criteria, differential diagnoses, and treatment have been discussed in detail. The purpose of the article is to enlighten and empower the health-care providers so as to enable them to identify and manage such cases of drug-induced oral EM.

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CASE REPORT

Case 1

A 62-year-old female patient from semi-urban area reported to Department of Oral Pathology with chief complaint of burning sensation and pain in mouth due to ulcers for the past 10 days. After careful and thorough history taking, it was revealed that the patient had an episode of stomach upset approximately 10–12 days ago for which she took over the counter tablet of Norfloxacin and Tinidazole combination as self-medication. Subsequently, she developed blisters on her lower lip and cheeks next day. The blisters later transformed into extensive and irregular ulcerations in the mouth. She visited the local physician who prescribed chlorhexidine gel, but symptoms did not subside. Then she was referred to higher center.

Extraoral examination revealed ulcerations of both upper and lower lips showing cracking and fissuring with blood encrustation. Intraoral examination showed extensive and irregular ulcerations covered with yellowish-white slough surrounded by erythematous border on the upper and lower labial mucosa. Similar ulcerations were also present on the buccal mucosa bilaterally near the angle of mouth. [Figure 1] There was no involvement of the masticatory mucosa. On palpation, the ulcers were tender and bleeding was elicited on slightest provocation. The sudden onset and positive drug history along with above mentioned features were suggestive of oral EM. In this case, norfloxacin and tinidazole were the causative drugs for the lesion.

Patient was advised to discontinue the medications and was treated with systemic corticosteroid (Tab Prednisone 20 mg BID), levocetrizine 5 mg OD, topical anesthetic gel for 5 days. As the lesions were regressed clinically after 5 days, systemic steroids were tapered by 10 mg/day for a week to a maintenance dose of 5 mg/day for the next 1 week. The lesions completely regressed in 15 days. [Figure 2] No recurrence was noted over a follow-up of 6 months.

Case 2

A 46-year-old male patient from rural area reported to the outpatient department with chief complaint of mouth ulcers and difficulty in eating and drinking for the past 1 week. History revealed sudden onset of ulcers on his tongue and cheek 7 days back, which increased gradually in size. The patient visited physician for which he was prescribed multivitamins and topical steroids for local application.

After thorough questioning, the patient recalled that he had taken some over the counter medications of ofloxacin and ornidazole combination for loose motion almost 7 days back. The symptoms appeared from the next day of taking medication. Intraoral examination revealed a large bullae measuring about 1. 5 × 1. 2 cm in dimension involving the ventral surface of tongue and floor of mouth, covered with pseudomembrane, surrounded by erythematous halo and irregular borders. Erythematous areas were also noted on the left buccal mucosa and posterior palatal region in respect of 25, 26, and 27. [Figure 3] Nikolsky's sign was negative. Positive association of drug history and appearance of lesion along with the clinical features were suggestive of oral EM. Ofloxacin and ornidazole were the causative drugs in this case.

Patient was treated with systemic corticosteroid (Tab Prednisone 20 mg BID for 5 days which was tapered

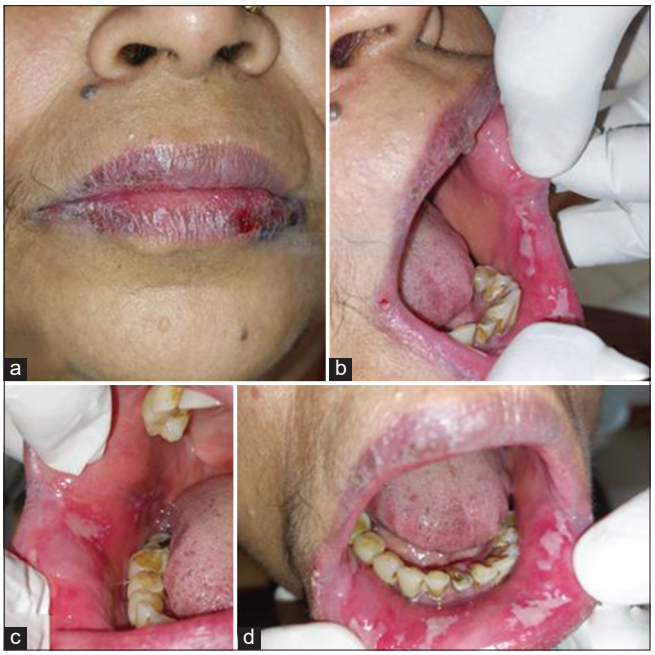

Figure 1: Composite image depicting encrustation on lips (a), irregular ulceration covered with pseudomembrane on buccal mucosa (b and c), and labial mucosa (d)

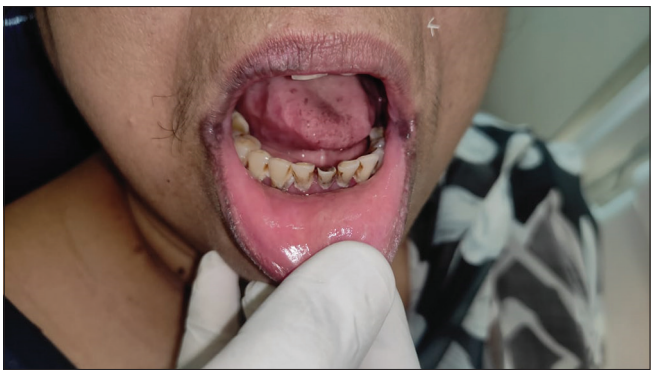

Figure 2: Photograph showing complete regression of the lesions after the treatment

gradually upto a maintenance dose of 5 mg/day), levocetrizine 5 mg OD, and topical anesthetic gel. Mouth rinse with Sucralfate suspension was advocated to promote healing of ulcer and alleviate the symptoms. Complete regression of lesion was seen after 10 days. [Figure 4] The patient is currently under review with no recurrence till date.

DISCUSSION

EM was first described by Von Hebra in 1866 as a relatively benign condition characterized by skin lesions with concentric color alterations. These lesions may have a variety of appearances including vividly erythematous discrete macules, papules, or occasionally vesicles and bullae (multiforme means many forms).[6,7] Stevens and Johnson in 1922 reported the severe form of EM with involvement of oral and conjunctival mucous membrane along with skin lesions. In 1950, Thomas suggested that EM and SJS were variants of the same pathologic process. In 1956, Lyell reported a series of patients with a life-threatening, rapidly evolving mucocutaneous reaction characterized by widespread erythema, necrosis, and bullous detachment of the epidermis resembling scalding, a condition currently known as TEN. In 1968, Kennett described an inflammatory oral disorder with lesions typical of the oral lesions of EM as "EM affecting the oral cavity"[4] [Table 1].

EM is a reactive mucocutaneous disorder. The exact pathogenesis of EM is unknown. Numerous factors such as microbial infection, drugs, food additives, malignancy, auto-immunity, radiation, immunization, and stress have been implicated to its development.[8] Herpes virus infection is considered to be involved in more than 90% of cases. Drug-associated EM is rare and reported to be <10%[1] of which most commonly implicated are antibiotics and analgesics. Very few cases of EM have been reported with the ingestion of Fluoroquinolones and Nitroimidazole groups of drugs. In our cases, manifestation of the lesion appeared after intake of these drugs. Patient was neither exposed to any kind of infection nor was allergic 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 (ofloxacin-ornidazole and norfloxacin-tinidazole) in our patients.

EM seems to result from a T-cell-mediated immune reaction to the precipitating agent, which leads to a cytotoxic immunological attack on keratinocytes that express non-self-antigens, with subsequent sub-epithelial and intraepithelial vesiculation; this leads to widespread blistering and erosions. In drug-induced EM, the reactive drug metabolites trigger the disease, and tumor necrosis factor alpha, released from keratinocytes, macrophages,

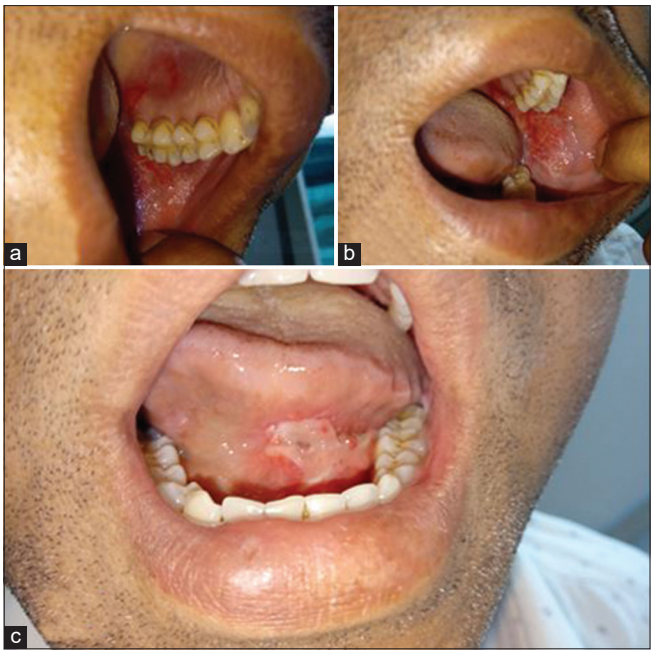

Figure 3: Composite image depicting erythematous areas in posterior palate on the left side (a), and irregular ulcerated areas in the left buccal mucosa (b), and bullae formation in floor of mouth (c)

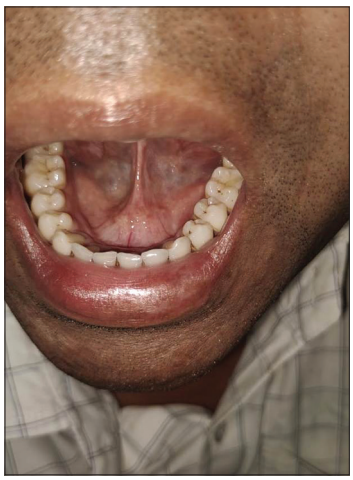

Figure 4: Photograph showing complete regression of the lesions

Table 1: Classification of the spectrum of erythema multiforme[4]

Variant	Author	Year of reporting
Erythema multiforme minor	Hebra	1866
Erythema multiforme major	Thomas	1950
Stevens Johnson syndrome	Stevens and Johnson	1922
Toxic epidermal necrolysis	Lyell	1956
Oral erythema multiforme	Kennett	1968

and monocytes, induces keratinocyte apoptosis causing the tissue damage.[2,3,8] Drug metabolism is altered and directed toward cytochrome P450 – metabolite pathway resulting in production of reactive and toxic metabolites.[1] Tissue damage is mainly due to apoptosis and not by inflammatory response. In addition to a cellular immune response, humoral immune mechanisms may be involved in the pathogenesis.[3]

The presentation of EM ranges from a self-limited, mild, and exanthematous variant with minimal oral involvement (EMM) to a progressive, fulminating, and severe variant with extensive mucocutaneous epithelial necrosis (SJS and TEN). Symmetrically distributed typical cutaneous target lesions and/or atypical raised target lesions are the hallmark.[5] Oral involvement is seen in some 70% of patients with EM.[2] Lips tend to become swollen and cracked, with bleeding and later crusting. Intraoral lesions appear typically on the non-keratinised mucosa and are most pronounced in the anterior parts of the mouth,[2] which were present in our cases too. The lips, labial mucosa, buccal mucosa, tongue, floor of mouth, and soft palate are the most common sites of involvement. Usually, the gingiva and hard palate are spared.[7]

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 non-specific.[3] Diagnosis of EM usually entails excluding other similar diseases by careful review of the clinical history and detailed clinical examination.[8] Features more suggestive of EM are the acute onset (or recurrent nature), oral lesions appearing on the lip and anteriorly in the mouth, and pleomorphic cutaneous lesions (typical and atypical target lesions).

Drug-induced oral EM needs to be primarily differentiated from fixed drug eruptions (FDE). FDE is a type of drug reaction which is characterized by recurrence of lesion at the same site on repeated exposure to the drugs. It usually occurs within 30 min to 8 h after the drug is taken.[9] The confirmatory test is an oral challenge test. The most common site of involvement is skin and glans penis.[9] Isolated involvement of oral mucosa is rare and any intraoral site including hard palate may be involved in FDE. Whereas, lining mucosa in the anterior part of the mouth is typically affected in oral EM sparing the hard palate and gingiva.[7] Furthermore, primary attacks of oral EM are confined to oral mucosa without skin involvement.[1] The patients in our cases did not give any history of similar recurrent lesions with such drugs on any previous occasion. Other differential diagnoses to be considered in the lesions confined to oral cavity are herpes infection, vesicullobullous lesions such as pemphigus, pemphigoid, and erosive LP. Herpetic lesions are usually smaller, well circumscribed, more common in lips, and keratinized mucosa especially the gingiva and hard palate; and almost always invariably preceded by prodromal symptoms. Our cases had no gingival lesion or prodromal symptoms. The lesions were large and irregular. Temporal relationship between the drug intake and onset of disease excludes the possibility of vesiculobullous lesions such as pemphigus or pemphigoid. Nickolsky's sign was also absent in our cases. Lichen planus may show similar ulcerations accompanied with Wickham's straie, which were absent in our cases.[1,3]

Drugs are double edged sword, which gives beneficial results and can also cause adverse reaction in certain conditions. Adverse drug reaction (ADR) can manifest in many forms such as erythema multiforme, fixed drug eruption, and anaphylactic reactions.[1] Very few cases have been reported as EM associated with Fluoroquinolones and Nitroimidazole groups of drugs. After extensive literature search, the list of the reported cases is summarized in Table 2. The fluoroquinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, etc.) are a family of broad spectrum, systemic antibacterial agents that have been used widely as therapy of respiratory, urinary tract, and G.I.T. infections. They are active against a wide range of aerobic Gram-positive and Gram-negative organisms.[10] On the other hand, Nitroimidazole antibiotics (Metronidazole, Ornidazole, Tinidazole, etc) have been used against anaerobic bacterial and protozoal infections.[10] In India, these drugs are among the most common drugs self-medicated by general population for any gastrointestinal infections. Furthermore, both these groups of drugs are used extensively by Dental Surgeons for management of oral and dental infections, both pre and postoperatively, due to coverage of aerobic and anaerobic micro-organisms and potency against the infective oral microflora in dental infections. Therefore, health-care providers must be cautious before prescribing such drugs and should be aware of their adverse effects.

The management of EM can be challenging. Triggering agent must be identified and withdrawn immediately. Corticosteroids are the most commonly used drugs in the management of EM.[1-3,5] Second-line therapies are generally reserved for refractory cases and include alternate immunosuppressive agents and antimicrobial medications.[11] In our cases, both patients responded very well with the systemic prednisolone therapy along with symptomatic management of erosions and ulcers. They were also sensitized and cautioned about the offending drugs.

Table 2: Case reports showing EM with Fluoroquinolones and/or Nitroimidazole group

Author	Age	Sex	Site of involvement	Diagnosis	Suspected Drug	Drug taken for	Duration of onset of symptoms after taking drug	Treatment given
Singbal and Rataboli (2005)[12]	30	Male	Skin, oral mucosa	EM, SJS	Tinidazole	Diarrhoea	02 days	Not available
Mazumdar and Shome (2012)[13]	50	Male	Lips, oral mucosa, skin	SJS	Metronidazole	Erosive LP	06 h	Systemic steroids
Deore *et al*. (2014)[14]	21	Female	Skin, conjunctiva, oral mucosa	SJS	Ciprofloxacin, Tinidazole, Diclofenac	Dental pain	03 days	Systemic steroids
Bhusan (2015)[15]	Not available	Not available	Oral, genital mucosa, skin	SJS	Tinidazole	Not available	01 h	Not available
Narasimhamurthy *et al*. (2015)[16]	39	Male	Skin	EM Skin	Ciprofloxacin, Metronidazole	Road Traffic Accident	01 day	Systemic steroids and Anti- histaminics
Chandak *et al*. (2020)[17]	27	Male	Lips	EM oral	Ofloxacin, Ornidazole	Loose motion	03 days	Topical steroids and Anti- histaminics
Aschalew *et al*. (2020)[18]	22	Female	Lips, vagina, skin	EM Oral and Skin	Ciprofloxacin	Typhoid fever	03 h	Systemic steroids and Anti- histaminics

CONCLUSION

Drug-induced oral EM is uncommon and needs to be differentiated from other oral ulcerative lesions for effective management. Detailed history taking and clinical examination are of utmost importance for early diagnosis. It is important for the health-care providers to report such cases to create awareness among general population and sensitize them regarding judicious use of drugs, as majority of them go unreported due to lack of knowledge of the patients and self-medication causing serious ADR in them. A robust ADR monitoring system with a feedback mechanism and awareness of the prescribers and patients can help prevent, identify, and manage such conditions much more effectively.

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