CASE REPORT

MOUTH UNDER SIEGE : DRUG-INDUCED ERYTHEMA MULTIFORME IN FOCUS

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ABSTRACT

Erythema multiforme (EM) is an acute, immune-mediated mucocutaneous disorder. Various virus, bacteria, immunologic conditions are known to precipitate this disease. However, certain medications have also been identified as causative agents. The condition typically presents with distinctive target-like lesions affecting the skin and mucous membranes. In cases where the lesions are confined exclusively to the oral cavity without any cutaneous involvement, the condition is referred to as oral erythema multiforme (OEM). Drug-induced OEM is a rare but important clinical variant, often underrecognized due to its restricted presentation. Effective care and the prevention of recurrence depend on early diagnosis and timely drug removal.

The present case reports a case of oral erythema multiforme of a 31year old male patient in which drugs (Ofloxacin-Ornidazole) seems to be the precipitating factor.

KEY WORDS

Oral erythema multiforme, Target lesions, Drug-induced reactions, Intraepithelial split.

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INTRODUCTION

Erythema multiforme (EM) is a reactive mucocutaneous disorder in a disease spectrum that comprises a group of acute exanthematic reactions, which are occasionally chronic and recurrent eruptions.[1]

Bateman was the first to identify EM in 1817. Later, in 1866, Hebra described the eruption's morphologic features under the term "erythema exsudativum multiforme," stating that it was caused by internal or systemic factors rather than local ones. In 1922, Stevens and Johnson described EM as "a new eruptive fever associated with stomatitis and ophthalmia" thatprimarily affected the oral and conjunctival mucous membranes. In 1968, Kennett reported an inflammatory oral illness with lesions reminiscent of the oral lesions of EM as "EM affecting the oral cavity."[2]

Clinical manifestations of EM can range widely, from moderate (EM minor) to fulminating severe (Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]). EM is a skin and mucous membrane response pattern. A wide range of antigens including herpes and drugs has been suggested as triggering the disease.[1,3]

Oral EM is typified by recurring, chronic, or episodic intraoral bullae and erosions that interfere with swallowing, mastication, and speech over an extended period of time, leading to significant morbidity. Involvement of the lip vermilion occurs in some patients. Cutaneous involvement 25% of patients have typical symmetric target lesions that are acrally dispersed.[4]

Because the clinical presentation resembles that of other oral inflammatory and vesiculobullous illnesses, the diagnosis is frequently challenging.[5]

Here we report a case of oral erythema multiforme caused by drug therapy without skin involvement except involvement of lip vermillion, highlighting to underscore the significant association between EM and medication use.

CASE PRESENTATION

A 31-year-old male patient reported to the

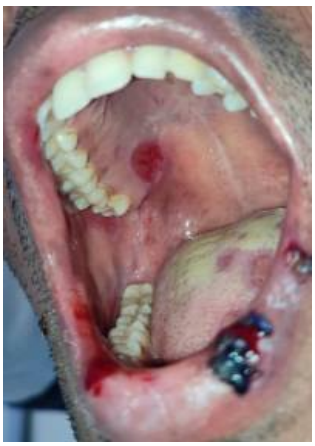

Figure 1: Ulceration with hemorrhage observed on right soft palate, right commissure of both upper and lower lip, right lower labial mucosa along with encrustation seen in lower left vermillion border.

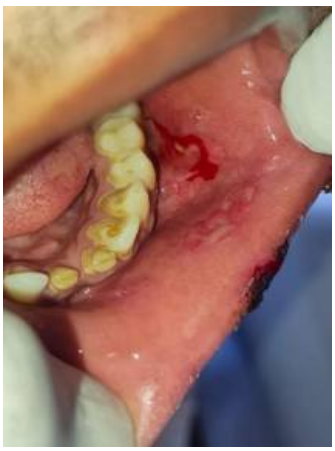

Figure 2A: Ulceration with hemorrhagic encrustations were visible in left buccal mucosa and depth of gingivobuccal sulcus.

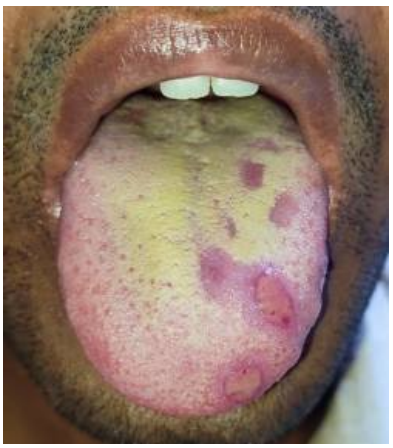

Figure 2B: Multiple small to moderate depapillated areas over the dorsal surface of the tongue probably caused by rupture of vesicles.

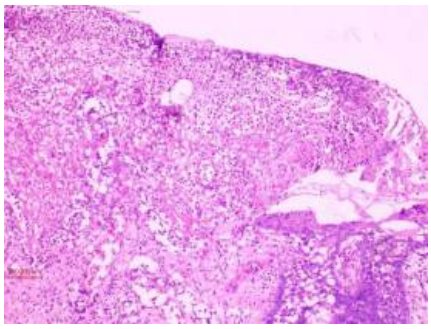

Figure 3A (10X): H&E-stained section revealed the presence of stratified squamous epithelium which is denuded at places with ulceration and connective tissue stroma revealed dense inflammatory cells chiefly perivascularly infiltration.

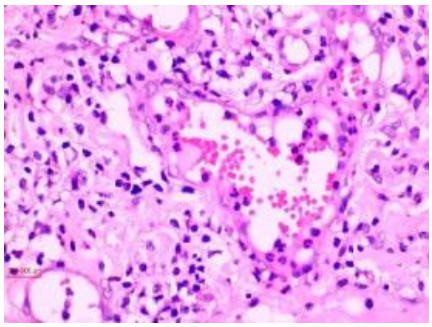

Figure 3B (40X): H&E-stained section reveals numerous inflammatory cells like lymphocytes, plasma cells, eosinophils in stoma and also engorged red blood cells in vascular space.

Department of Oral and Maxillofacial Pathology with a chief complaint of ulceration in the lower lip, palate and buccal mucosa since last 5 days. There was also history of burning sensation while taking food and difficulty in swallowing.

History revealed that the patient consulted a general physician for gastrointestinal disturbances five days back and was prescribed a five -day course of ofloxacin-ornidazole (tablet O2 twice daily). Within a day of starting the medication, he developed multiple vesicles on the lips and oral cavity, some of them later ruptured, forming ulcers.

On extra-oral examination, diffuse areas of multiple ulcerations with irregular borders and hemorrhagic encrustations [Figure 1] were observed on the mucosa and vermillion border of both the upper and lower lips. The lips displayed cracks and fissures and were dry and slightlyswollen. The ulcers were elicited pain on manipulation and even light pressure caused bleeding.

Intraoral examination revealed multiple small to large vesicles with erythematous patches and yellowish slough seen on the palate, dorsum of the tongue, buccal vestibule, labial mucosa, and on both buccal mucosae. Some of them ruptured and formed ulceration. Blood encrustations were visible in some areas. [Figure 2A and 2B]

Routine hematological investigations were advised and found within normal range.

After hematological examination, biopsy was planned and performed from early vesicular lesion. The specimen was stained with hematoxylin and Eosin for histopathological evaluation.

H&E-stained section reveals the presence of parakeratotic stratified squamous epithelium with denudation at places and irregular rete-ridges. Intraepithelial split is noted. The underlying fibrovascular connective tissue revealed dense inflammatory cells infiltrate, chiefly perivascularly. [Figure 3A,3B]

Methylprednisolone, an oral corticosteroid, was initiated at a dose of 32 mg per day. All of the mucosal lesions healed in 5-7 days. The patient was advised to take adequate water and mouthwash containing antiseptics and local anesthetics were administered.

DISCUSSION

Erythema Multiforme is a reactive mucocutaneous disorder in a disease spectrum that comprises an exanthematic, cutaneous variant with minimal oral involvement (EM minor) to a progressive, fulminating, severe variant with extensive toxic epidermal necrolysis.[1-3]

In 1817, it was first described by Bateman. Ferdinand von Hebra, who first used the term "erythema exudativum multiforme" in 1866, gave a thorough account of the distinctive morphological characteristics and etiologies of this particular eruption. Thomas then proposed a classification system for EM in 1950, breaking it down into "minor" and "major"kinds. Kennett identified an oral inflammatory disease in 1968 that resembles the common oral EM lesions but does not involve the skin.[2]

Aetiology of EM is unexplained; however, it seems to be an immunological hypersensitivity reaction when cytotoxic effector cells, or CD8+T lymphocytes, arrive in the epithelium, causing dispersed keratinocytes to undergo apoptosis and resulting in satellite cell necrosis.[1,2]

A number of agents have been known to trigger erythema multiforme.

In viruses, the most common infection causing Erythema multiforme is Herpes Simplex Virus (HSV) but other herpesviruses, adenoviruses, enteroviruses, hepatitis viruses, influenza, paravaccinia, parvovirus B19, poliomyelitis, vaccinia and variola have all been implicated.[2]

Other less frequently implicated infectious agents may include bacteria such as Mycoplasma pneumoniae, borreliosis, cat scratch disease, diphtheria, haemolytic streptococci, legionellosism etc, fungal infections such as coccidiodomycosis, dermatophytes or histoplasmosis and parasites such as Trichomonas and Toxoplasma gondii.[2,3]

Immune disorders including sarcoidosis, graft versus host disease, systemic lupus erythematosus, or BCG or hepatitis B vaccination may also precipitate EM.[1,2]

Aetiological agents have also been identified in food additives and chemicals such terpenes, nitrobenzene, benzoates, and fragrances.[3]

The medications commonly known to precipitate are Oxicam, Non-steroidal anti-inflammatory medicines, Barbiturates, Cephalosporins, Aminopenicillins, Quinolones, Chlormezanone, Anticonvulsants, Protease inhibitors, Allopurinol, Sulphonamides (e.g. co- trimoxazole), corticosteroids etc.[3]

Genetic predisposition to EM includes HLA-B15 (B62), HLA-B35, HLA-A33, HLA-DR53 and HLADQB1*0301. Patients with the uncommon HLA variant DQB1*0402 may have significant mucosal involvement.[3]

In our case the patient had taken ofloxacin-ornidazole after seeing a general practitioner for gastrointestinal issues and experienced several vesicles on his lips and oral cavities within a day of starting the drug.Although people of all ages can develop erythema multiforme, it often affects adults between the ages of 20 and 40.[1,4] It is more common in men than women, with a ratio of 1: 5.[5]

Oral erythema multiforme is distinct but the lesser-known variant among the spectrum of erythema multiforme. Early oral EM events often solely impact the mouth mucosa with later hours involving the skin.[6,7,8]

Oral lesions may be seen in 25% to 70% of cases of EM[8]. They tend to affect the non-keratinized mucosa and the anterior regions of the oral cavity. The major affected regions include the lips (36%), followed by buccal mucosa (31%), tongue (22%), and labial mucosa (19%).[7,9]

The oral symptoms range from delicate to painful deep hemorrhagic bullae and erosions as well as delicate superficial erythematous and hyperkeratotic plaques. Edema, erythema, and erythematous macules of the lips and buccal mucosa are the early symptoms of oral lesions, followed by the development of multiple vesicles and bullae, which rupture rapidly and cause the creation of pseudomembranes. Lip swelling and characteristic bloody encrustations are commonly noticed.[6-10]

These similar features were also noted in our case.

The histopathological analysis of this type of lesion is essential for the diagnosis of the lesion. Monteiro et al stated that histologically there is presence of epithelium with spongiosis, intraepithelial cleft, inflammatory cell infiltration in the connective tissue stroma along with neutrophils and plasma cells. Similar features were also noted in our case.[8,9,11]

Diagnosis of EM mainly rely's on clinic onset, positive triggering factor and clinical appearance.[12]

There is currently no specific therapy available despite advancements in diagnosis. In addition to supportive care, the causal agent or substance should be identified and removed. The mainstay of treatment for mild cases of oral EM is sympathetic measures, such as the use of topical anesthetic mouthwashes with soft diet. For patients with no serious contraindications, a brief course of systemic corticosteroids can be used to treat moderate to severe cases of oral EM. and the dosage should be gradually

reduced over two to three weeks. Drugs thatmodulate or suppress the immune system, such as dapsone, azathioprine, and levamisole, have recently shown encouraging results in slowing the progression of disease.[12,13]

In presented case, Methylprednisolone was prescribed initially at a dose of 32 mg per day. Additionally oral fluid, mouthwashes containing antiseptics and local anesthetics were prescribed as supportive measures.

CONCLUSION

One rare and less described variant of Erythema Multiformae is drug-induced oral EM. It primarily affects the oral mucosa, presenting as painful ulcers, erythematous patches, and sometimes with hemorrhagic crusting of the lips, without involving the skin or other mucosal surfaces. Early and accurate diagnosis is critical to differentiate it from other ulcerative oral conditions such as herpetic stomatitis or autoimmune diseases. With timely treatment, the prognosis is usually excellent, and avoiding the medicine that caused the problem can help prevent recurrence. Raising awareness among medical professionals is crucial for prompt diagnosis and treatment, minimizing patient discomfort, and averting critical consequences.

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