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Research Paper

Idiopathic Recurrent Erythema Multiforme

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ABSTRACT:
Erythema multiforme (EM) is an immune-mediated condition that classically presents with discrete targetoid lesions and can involve both mucosal and cutaneous sites. The exact etiopathogenesis of erythema multiforme is not known; but appears to be an immunological hypersensitivity reaction most commonly induced by Herpes Simplex Virus (HSV) infection, use of certain medication, immunization, menstruation, pregnancy, autoimmune diseases, radiation and food or chemical additives. It occurs predominantly in the age group of 20-40 years affecting teenagers and young adult, but it can precipitate as late as 50 years of age in apparently healthy individuals. Treatment of EM depends on many factors namely: the etiology, the involved mucosal sites, the chronicity (acute vs. recurring) of the disease. If the etiology or causal medication/infection is identified, then the medication is discontinued and/or the infection is treated prior to initiating symptomatic treatment. Treatment for acute EM is focused on relieving symptoms with topical steroids or antihistamines. Treatment for recurrent EM is most successful when tailored to individual patients. First line treatment for recurrent EM includes both systemic and topical therapies. Systemic therapies include corticosteroid therapy and antiviral prophylaxis. Topical therapies include high-potency corticosteroids, and antiseptic or anaesthetic solutions for mucosal involvement. Second-line therapies for patients who do not respond to antiviral medications include immunosuppressive agents, antibiotics, anthelmintics, and antimalarials.
The current study presents a case of Idiopathic Recurrent Erythema Multiforme with oral and lip lesions and skin manifestations.

KEYWORDS: *Erythema multiforme, medication, Herpes Simplex Virus*

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I. INTRODUCTION

Erythema multiforme was first recognised by Bateman and Bulkley in the year of 1817. Later, in 1860, the term "erythema exsudativum multiforme" was described by Ferdinand von Hebra [1] along with its cause which was due to internal or systemic origin and not for any local etiology. Erythema multiforme (EM) is a self-limiting, acute, mucocutaneous disease of the skin and mucous membrane caused by a hypersensitivity reaction; with symmetric scattering of lesions on the extremities and having a typical recurring, concentric pattern in the form of target lesions. [1,2]

The exact pathogenic mechanism of EM remains unclear; it can be triggered by a range of factors; can occur due to certain drug intake or different infections, particularly herpes simplex virus (HSV)infection,[3] stress, pregnancy, menstruation, immunization, autoimmune diseases, radiation and food or chemical additives.[4] On systemic administration of drug severe reactions are manifested which presents like EM, and Steven Johnson syndrome. These reactions can also be characterized as either anaphylactic stomatitis, fixed drug eruptions, drug induced lichenoid reactions or pemphigoid–like drug reactions. [5] It is manifested as skin eruption, with or without oral or other mucous membrane lesions. [5,6]

Based on the severity and number of mucosal sites involved, EM has been classified into EM minor, EM major, Stevens- Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). EM minor is the mildest form of the disease and TEN is the most severe.[7,8] EM rarely affects the oral cavity alone, thus making it a rare entity.[7] Clinical manifestations of EM involve activation of cytotoxic T lymphocytes in the epithelium that induce apoptosis in keratinocytes, which leads to satellite cell necrosis.[9]

The annual incidence of erythema multiforme is less than 2%. [4] It is more common in adults younger than 40 years, but it can occur in individuals above 50 years.[5,6]

II. CLINICAL MANIFESTATIONS

EM begins with an acute onset that usually has mild or no prodromal symptoms.[10] The classic lesion of erythema multiforme is called as the target or iris lesion. Lesions usually erupt over a 72-hour period. These lesions can cause burning or pruritus. [10,11] It is a round lesion of three concentric segments: a dark center, surrounded by a lighter pink ring, both of which are surrounded by a red ring. Crusting and blistering sometimes occur in the center of the skin lesions, resulting in concentric rings resembling a "bull's eye" (target lesion).[11] The Oral lesions are usually erythematous macules on the lips and buccal mucosa, followed by epithelial necrosis, bullae and ulcerations with an irregular outline and an inflammatory halo. Bloody encrustations can also be seen on the lips.[12,13,] The most common mucous membranes that are involved are the lips, tongue, and the buccal mucosa.

III. CASE REPORT

A 45-year-old female patient reported to the Department of dentistry with the complaint of swelling, burning and itching sensation of the lips [Fig-1a] which later manifested as painful ulcerations with bleeding [Fig - 1b]. The burning and itching sensation were severe in intensity and aggravated on consuming food; for which the patient had taken paracetamol, cetirizine and multi-vitamin supplements.

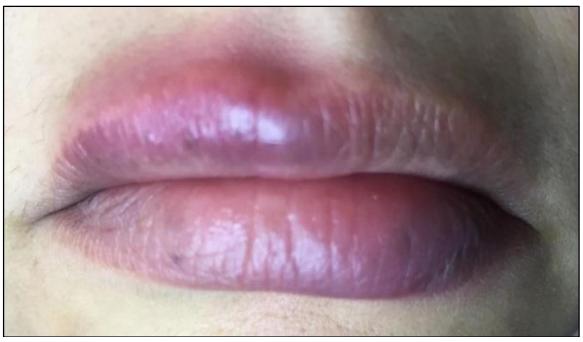

Fig -1a: Swelling of the Lips

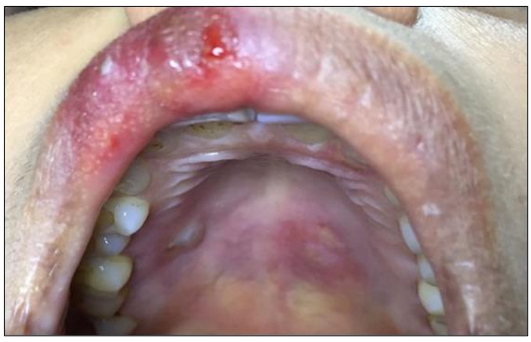

Fig-1b: Ulcerations and bleeding of the lip

The patient gave a history of a migraine and polyarthralgia 3 days prior to the onset of the lesion for which she took a single dose of tablet Etoricoxib MR. The same night she developed swelling and pruritis around her lips, followed by blister formation, which later ulcerated and bleed. She consulted a physician regarding the same; and was given anti-allergic medication. But later she developed more ulcerations in her mouth with severe burning sensation and inability to eat and associated pain.

History revealed that the patient had similar bouts of ulceration on the lips twice in the past 4 months. She correlated history of taking the same drug on having the first attack, but no drug was taken at the time of the second attack. She related these attacks to have occurred 7 to 10 days prior to her menstrual cycle which caused increased levels of stress and anxiety. The ulcers had almost a very similar pattern of presentation with pruritis around the lips, oedema, pain, ulceration and bleeding. The first and second episodes were relatively mild and involved only the upper lip and healed in 15 to 20 days; with oral acyclovir 400mgs twice a day, paracetamol 650mg and topical application of acyclovir. The patient's medical history revealed that she was having hypothyroidism and migraine and was on medication for the same. On Extraoral examination, bilateral submandibular lymph nodes were palpable and tender. Intraoral examination revealed oedematous lips with bloody encrustations and irregular shaped superficial ulcerations with fresh bleeding spots on the upper and lower lips [Fig - 2a, 2b], ulcerations were also seen on the left buccal mucosa [Fig - 2c], upper labial mucosa and on the hard palate bilaterally [Fig - 2d]. There were two well defined flat, concentric rings measuring less than 3cms in size on the anterior surface of the right hand. The dermal lesion appeared oval with three concentric segments: a dark purplish center with a small blister, surrounded by a lighter pink ring, both of which were surrounded by a red ring; the patient also had pruritis and was oedematous [Fig - 3]. The patient did not have any genital or ocular lesions.

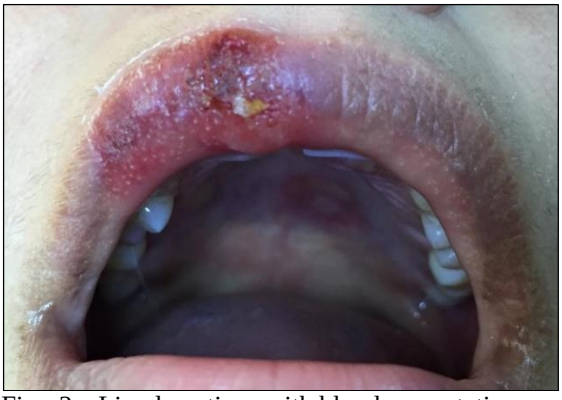

Fig - 2a: Lip ulcerations with blood encrustations

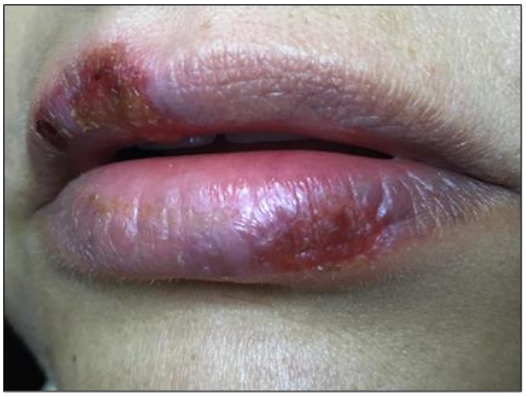

Fig - 2b: Lip ulcerations with blood encrustations

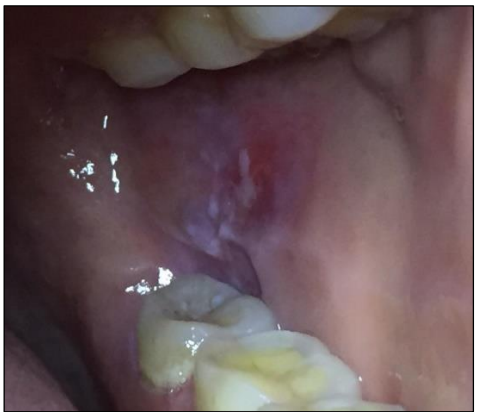

Fig – 2c: Ulceration on Left buccal mucosa

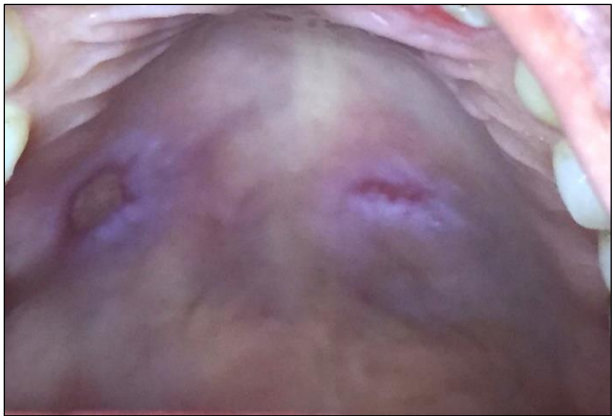

Fig – 2d: Ulceration on hard palate bilaterally

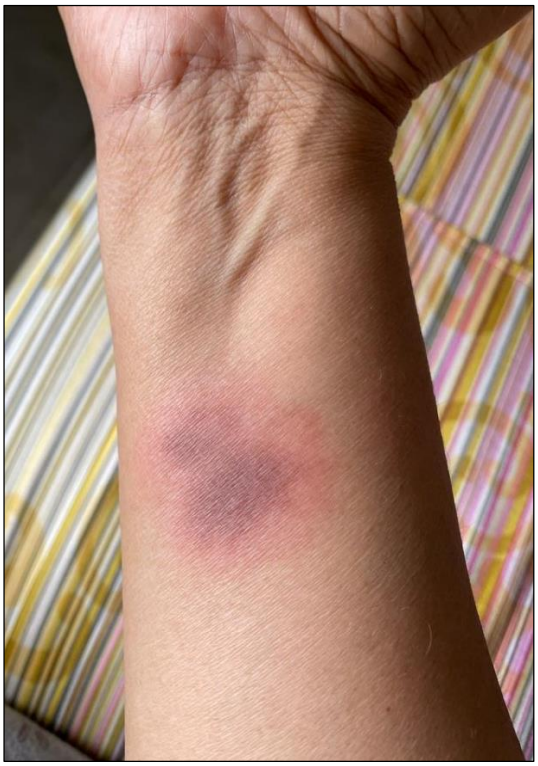

Fig – 3: Target lesion on the right hand

Clinically, a differential diagnosis of drug induced Erythema multiforme minor was made; the patient was advised about the offending drug and advised to discontinue it.

Laboratory investigations were carried out; the results were inconclusive as the patient was negative for Human Immunodeficiency Virus (HIV) and Herpes Simplex Virus (HSV), IgM and IgG were Non-Reactive. The Erythrocyte Sedimentation Rate- 30mm/hr, White Blood Cell -6,500/mcl, Haemoglobin - 8.8Gms%, Haematocrit (P.C.V)- 29.6%, Urea - 27 mg/dl, Fasting Blood Sugar-70 mg/dl, T.S.H-3.42microIU/ml, C-Reactive protein-1.40/L and Serum Creatinine-0.91mg/dl were recorded.

Although recurrent erythema multiforme has been associated with a variety of medical conditions, this case had a number of triggering factors (e.g., HSV, drug, menstruation, stress) with no definite identified cause. Therefore, considering the recurrent history, prodromal symptoms, haemorrhagic crustations involving the lip, the lesions on the buccal mucosa and palate and the dermal lesion; the final diagnosis of Idiopathic Recurrent Erythema multiforme was made.

First line of treatment for recurrent EM includes both systemic and topical therapies. Systemic therapies include corticosteroid therapy and antiviral prophylaxis. Topical therapies include high-potency corticosteroids, and antiseptic or anaesthetic solutions for mucosal and dermal involvement.

The patient was advised to stop all medications except her routine medication. She was then started on systemic corticosteroid Tab. Prednisolone (immunomodulatory agent) an intermediate acting corticosteroid 60 mg at two divided doses and gradually tapered for every week till a maintenance dose of 5mg, Tab Pantoprazole 40mg (PPI inhibitor was added to nullify the gastritis effect of steroid), Tab. Cetirizine 10 mg (an anti-histamine to reduce the hypersensitivity reaction), Tab Famciclovir 500 mg (Antiviral) twice a day for seven days, an antioxidant capsule was given once a day along with Methyl cobalamin injection (the dose being 1 ampoule (0.5 mg of Meco 1500mcg Injection) given 3 times a week intramuscularly). Magic Mouthwash containing Diphenhydramine, Maalox and Lidocaine was advised thrice daily before and after food. Topical triamcinolone acetonide 0.1% t.i.d was given for application on the lips. The patient was advised to have a bland diet and frequent hydration.

The patient was evaluated after two weeks and showed decrease in the severity and distribution of the labial haemorrhagic crustings and intraoral lesions [Fig - 4] and by six weeks follow up there was complete resolution of the oral lesions [Fig - 5]. The patient was educated regarding the recurrent nature of the disease and was advised to consult an oral physician at the earliest when the first prodromal symptoms appear.

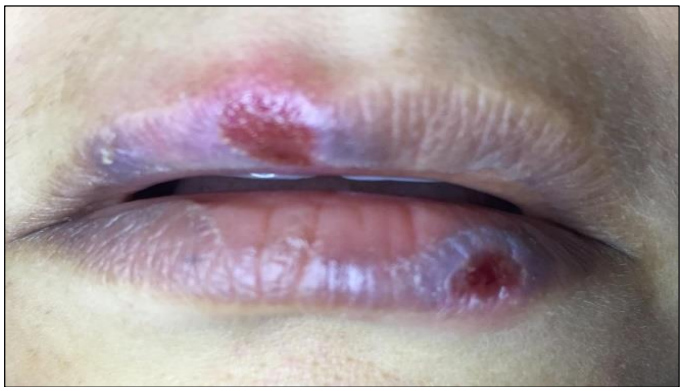

Fig- 4: Two week follow up showing marked improvement of the ulcerations.

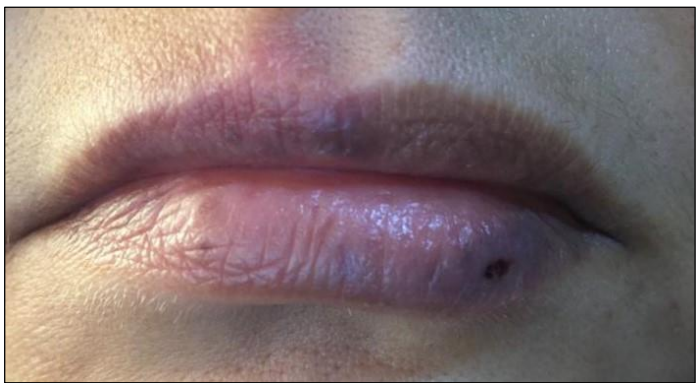

Fig-5: Six week follow up showing complete remission of the ulcerations

The patient when recalled after 2 months, showed marked improvement in her condition with no signs of recurrence. Cutaneous lesions resolved without scarring, but hyperpigmentation persisted. The patient has been followed up for the past two years and has had no recurrence.

IV. DISCUSSION

Erythema multiforme (EM) is an acute, sometimes recurrent, mucocutaneous condition; [2,3] occurring predominantly in young adults, with a slight female predilection; and an uncertain etiopathogenesis that can follow the administration of drugs (10% cases) or infections (90% cases) (3,4). Recurrent erythema multiforme (REM) occurs in about 10% of patients with EM major and up to 30% in EM minor. [8]

EM is a T- cell-mediated immune reaction to precipitating stimuli, leading to a cytotoxic immunological attack on non-self antigen expressing keratinocytes followed by sub-epithelial and intra-epithelial vesicle formation, eventually leading to widespread blistering and erosion. [3]

The mechanism of tissue damage in EM seems to vary in virus-induced EM and drug-induced EM.[4] In HSV associated EM, HSV–DNA fragments in the skin or mucosa trigger the disease leading to a delayed type hypersensitivity reaction; virus fragments get transported to the epithelium by $CD34^{+}$ cells, and T cells accumulate in response to HSV antigens and damaged cells.CD4+ T helper1 (Th1) lymphocytes, produce IFN-γ, characteristic of a delayed type hypersensitivity reaction.(5) In drug-induced EM, reactive metabolites of the particular drug induce the disease and keratinocyte apoptosis is induced by tumor necrosis factor alpha (TNF-α) released from keratinocytes, macrophages, and monocytes leading to tissue damage.[4]

A large proportion of patients (>50%) have no specific precipitating factor; the second largest trigger category being emotional state or stressful conditions.[13]Although the exact mechanism of pathogenesis is not known, it is postulated that the causative agents induce a T-cell mediated immune reaction which results in cytotoxic immunological attack on keratinocytes, which express non-self-antigens, with consequent vesiculation and extensive erosion and blistering.[14]

Studies have reported HSV as the most common precipitating factor for REM infections (nearly 90% cases) and medications (10% cases). [11,13]

Erythema multiforme is usually diagnosed based on the patient's history and clinical manifestation. [10,11] There are no diagnostic or laboratory tests to confirm the diagnosis. [15,16,] Laboratory examination can be done to identify a suspected history of HSV infection. In a study involving 48 patients with REM, 18 patients had positive serological test for HSV, indicating the presence of past infection. The result of serologic test for HSV in our patient, was non-reactive, which suggested no history of HSV infection. A few studies have put forth the possibility that a subclinical infection is likely in many cases of idiopathic recurrent EM [12,14] wherein polymerase chain reaction (PCR) has identified HSV DNA in the biopsies of 6 out of 12 patients with idiopathic EM. (16)

Prodromal symptoms are rare, nonspecific, mild ranging from a cough, rhinitis, low-grade fever, malaise, diarrhoea, myalgia, and arthritis. Most often the lesions are asymptomatic, occasionally itching or burning sensation may appear.[13] Patient characteristics such as gender, age, prodromal symptoms, onset and duration of recurrent EM observed in our patient were similar to those reported in previous studies, with a slightly more advanced age at onset (45 years) and female preponderance (58%).

Approximately 70% of patients with recurrent EM had oral lesions. (6). An important step in the management of recurrent erythema multiforme is recognition and withdrawal of the causative agent; here the drug (tablet Etoricoxib MR) being one of the factors was discontinued, and managed with topical steroids, antihistamines, anti-oxidants, Methyl cobalamin injections improved symptoms in our case. However, current evidence is limited in supporting the hypothesis that early antiviral therapy reduces the time to symptom and lesion resolution [17,18], so administration of antiviral Famciclovir 500 mg (bid)was advocated. Current recommendations include acyclovir, 400 mg, twice daily, valacyclovir,500 mg, twice daily, or famciclovir, 250 mg, twice daily. Continuous antiviral therapy is still the first-line therapy for recurrent-EM.

V. CONCLUSION

There are no specific treatments for the management of REM, but treating suspected etiology remains its primary goal. Treatment of REM is challenging and prolonged and is a multiteam approach, keeping in mind the patients mental and physical health. Patients should be informed about the condition and the importance of preventing recurrences.

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