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Case Report

Herpes Simplex Associated Erythema Multiforme – A Case Report and Review

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ABSTRACT:
Erythema multiforme is a self-limiting acute mucocutaneous benign condition characterised by occurrence of blisters and ulcers. The hallmark of the disease is the presence of "target lesions". There have been several factors like infections, systemic diseases that can trigger EM, but an infection with Herpes Simplex virus captures a different place in the books of etiology of this disease. The association of EM trigerred due to HSV infection is referred to as herpes associated erythema multifome (HAEM). The incidence reported of this disease is between 0.01-1%.[1] Diagnosing an EM is of great challenge to the clinician due to its compromising variants from being self limited, mild, exanthematous, and cutaneous with minimal oral involvement.. This article discusses a case of HAEM in a 30 year old female patient and also discusses the pathophysiology and treatment of the disease.
Keywords- erythema multiforme, HAEM, target lesions, acyclovir.

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INTRODUCTION

Erythema multiforme (EM) is a self limiting disease. It is a mucocutaneous hypersensitivity reaction caused due to or trigerred due to infections or certain drugs or medications.[1] Though EM can be caused due to a wide range of factors but the most common factor is with a preceding viral infection with herpes simplex virus.[2] Erythema Multiforme mainly affects the teenagers and young adults with an age group of 20-40 years, but it can be late in onset as late as 50 years of age or even more.[3,4] The disease is known to have a more male predilection than females with a ratio of 3:2.[3,5] Several drugs are known to cause erythema multiforme including antibacterial, sulfonamides, penicillins, cephalosporins, quinolones, anticonvulsants, analgesics, non-steroidal anti-inflammatory drugs, antifungals.[3] Erythema multiforme can be classified as minor, major, Steven-Johnson syndrome or toxic epidermal necrolysis. (Table 1)

The minor form being the mildest one while toxic epidermal necrolysis being the severe one.[3,4,6] Erythema Multiforme is a benign condition which may resolve spontaneously if the patient is re exposed to the trigerring factors of the disease.[7] It may have varied muco-cutaneous presentations clinically. Erythema multiforme can be characterized by acute onset of ulcers on the skin and ulcers or blisters on the mucous membrane.[7] The hallmark of this disease is the presence of cutaneous lesions commonly referred to as "target lesions" or "iris" and may or may not be present in all the cases.[7] There may be appearance of lesions which appear as irregular red macules , papules or vesicles which further may enlarge to form plaques on the skin. There may be formation of crustations and blisters in the centre of skin lesions resulting in concentric rings which resembles a "bull's eye". Fever, malaise, headache, cough sore throat, polyarthralgia and lymphadenopathy mat be the symptoms which can be observed as much as before 1 week before the actual appearance of surface erythema or blisters.[3,8] The most common site of involvement of oral lesions for erythema multiforme is the lips and buccal musosa wherein the lesions may appear as erythematous macules and further followed by epithelial necrosis, formation of ulcers and bullae with an irregular border and a strong inflammatory halo.[3] Haemorrhagic crustations may also be seen on the lips.[4,6] Before any long term therapy, erythema multiforme should be managed by eliminating the underlying causes such as medications, diet, certain infections or any systemic diseases. The first drug of choice for erythema multiforme with a herpes simplex origin is Acyclovir used prophylactically and therapeutically as a preventive drug.[9,10]

CASE REPORT

A 30 year old female patient presented to the department of oral medicine & radiology with a complaint of burning in her mouth and multiple recurrent ulcers since 2 months. She was apparently alright before 2 months from the date of reporting. Then she experienced painful ulcers in her mouth. The pain was insidious in onset and was progressive in nature along with the progressing ulcers. The painful ulcers were also associated with burning sensation in the mouth. There was no history of fever, mouth trauma, chemical and thermal burns & urticaria. Her past medical history revealed history of constipation for which she had not taken any medications while her past dental history revealed having history of recurrent multiple ulcers since her childhood for which she had taken some home remedies and ayurvedic treatment. The patient reported no history of hospitalization, her family history was non-contributory, with all her vital signs being within normal range. Extraoral examination revealed symmetrically distributed erythematous papules of size approx. 2cms with well defined border, round in shape seen over the left arm and the legs suggestive of typical "***target lesions"*** (Figure 1A-C). There was presence of blood filled crustations on the lower lip along with ulceration. (Figure 2)

On intraoral examination, the soft tissue examination revealed ill defined irregularly spread erythematous erosive areas along with yellowish slough seen on the left and right buccal mucosa and the right and left retromolar region. Erythema seen over the soft palate and the tonsillar area and tongue- appeared to be coated and pale. (Figure 3)

On hard tissue examination, there were pit fissure caries with 47,48 and proximal caries with 27. Patient was further advised some laboratory investigations which revealed a normal complete blood count and erythrocyte sedimentation rate (ESR). Her serology tests confirmed that the patient was positive for HSV as there was fourfold rise in antibody titer. Hence depending on the history, clinical examination and laboratory investigations, we arrived at the diagnosis of recurrent herpes associated erythema multiforme (HAEM). The patent was given a 5-day course of Levocetrizine 5mg, along with an antacid Rantac 150mg along with a topical steroid ointment Turbocort for local application, multivitamin syrup and was advised to maintain hydration and sufficient intake of nutritious foods and vegetables (green leafy) and strict stoppage of all previous medications and was followed after a time period of three days. On her first follow up, the lesions appeared to be growing. (FIGURE 4A-D) Hence the patient was referred to a physician of the general hospital of our college where she was prescribed Tab. Ofloxacin-Ornidazole, Tab. Albendazole, Tab Lactobacillus, Tab. Cetrizine, Inj. Becomplex IM stat for a course of 5 days. She was also given steroid Wysolone (Swish & throw) and a local anaesthetic for 5 days. On the second follow up, the lesions appeared to be reduced at some sites and at some sites they apperaed to be persistent. (Figure 5A-E) Hence she was told to continue with the same medications which were given to her during the follow up except a change in the adminitration of the steroid Wysolone which was given this time as swish and swallow for again 5 days. On third follow up, the oral lesions appeared to be reduced and healed for upto 90%, hence she was given only steroid Wysolone (swish and throw) and was again recalled after 5 days. (Figure 6 A-E)Target lesions present on the extremities also healed completely. (Figure 7A-D)

On the fourth follow up, completely healed target lesions were seen but there was recurrence of lesions on some sites of the oral cavity and as the patient was not completely responding to the treatment given before, hence she was prescribed antivirals drug, Acyclovir (200mg), Becosules syrup, a probiotic (Sporolac-DS), laxative (Tab. Dulcolax) and a local anaesthetic for oral lesions for 7 days.

On the fifth follow up, the oral lesions healed completely as the patient responded well to antiviral drug, probiotics, laxatives, anthelmintic, oral local anaesthetic gels and other supplementary medications. (Figure 9A-H) No recurrence was reported later.

TABLE 1- Differential features of erythema multiforme major, Stevens-Johnsons syndrome and toxic epidermal necrolysis3

Category of erythema multiforme	Features
Erythema multiforme minor	Typical target lesions, raised atypical target lesions, minimal mucous membrane involvement and, when present, at only 1 site (most commonly the mouth). Oral lesions; mild to severe erythema, erosions and ulcers. Occasionally may affect only the oral mucosa. < 10% of the body surface area is affected.
Erythema multiforme major	Cutaneous lesions and at least 2 mucosal sites (typically oral mucosa) affected. < 10% of the body surface area involved. Symmetrically distributed typical target lesions or atypical, raised target lesions or both. Oral lesions usually widespread and severe.
Stevens-Johnson syndrome	Main difference from erythema multiforme major is based on the typology and location of lesions and the presence of systemic symptoms. < 10% of the body surface area is involved. Primarily atypical flat target lesions and macules rather than classic target lesions. Generally widespread rather than involving only the acral areas. Multiple mucosal sites involved, with scarring of the mucosal lesions. Prodromal flu-like systemic symptoms also common.
Overlapping Stevens-Johnson syndrome and toxic epidermal necrolysis	No typical targets; flat atypical targets are present. Up to 10%–30% of the body surface area affected. Prodromal flu-like systemic symptoms common.
Toxic epidermal necrolysis	When spots are present, characterized by epidermal detachment of > 30% of the body surface and widespread purpuric macules or flat atypical targets. In the absence of spots, characterized by epidermal detachment > 10% of the body surface, large epidermal sheets and no macules or target lesions.

Adapted from Al-Johani et al.[3] with permission from Elsevier, with additional information from reference 2.

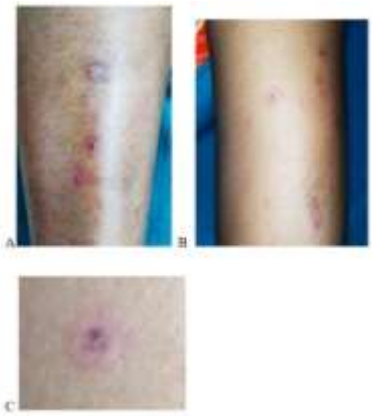

FIGURE 1- Erythematous papules with well defined border suggestive of typical "target lesions", seen over- (A) right leg ; (B) left arm (C) enlarged view of target lesions.

FIGURE 2 – Blood filled crustations along with ulcerations seen over the lower lip.

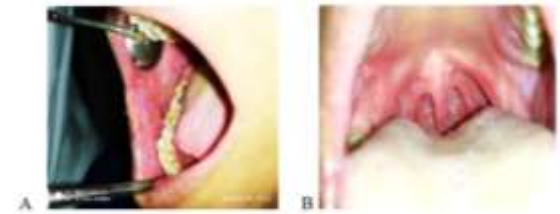

FIGURE 3- (A) erythematous erosive areas along with yellowish slough seen on the right buccal mucosa and right corner of mouth, (B) Erythema seen over the soft palate and the tonsillar area.

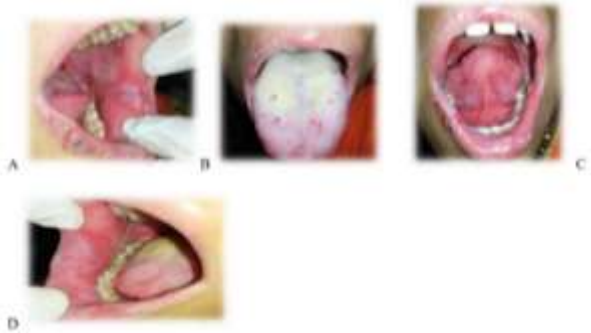

FIGURE 4 - FOLLOW UP 1 – (A)slightly reduced ulcerations on left buccal mucosa , (B) increased coating on dorsal surface of tongue, (C) ulcers seen over ventral surface of tongue along with haemorrhagic crusts on the labial mucosa of lower lip and on the vermillion border of lower lip (D) reduced ulcertion on the right buccal mucosa.

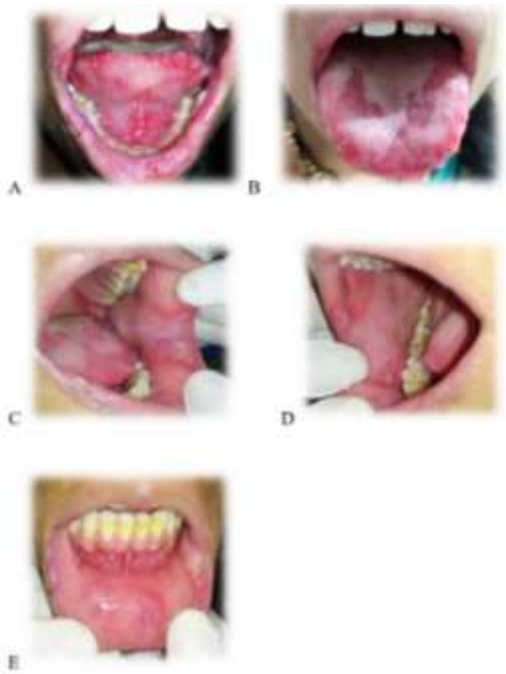

FIGURE 5- FOLLOW UP 2 , (A) increase in ulcerations over the lateral borders and ventral surface of tongue, (B) reduced coating on tongue giving it a geographic appearance, (C) persistent ulceration on left buccal mucosa, (D) reduced ulceration on the right buccal mucosa, (E) reduced ulceration on the lower labial mucosa.

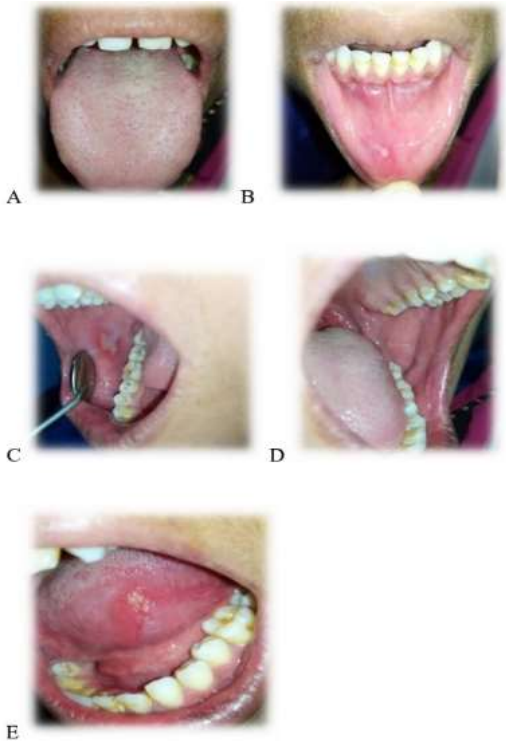

FIGURE 6- FOLLOW UP 3, (A) coating of tongue complete reduced, (B) reduced ulcerations on the lower labial mucosa, (C) single ulcer seen on the right buccal mucosa, (D) completely reduced ulcerations on left buccal mucosa, (E) single ulcer on the left lateral border of tongue.

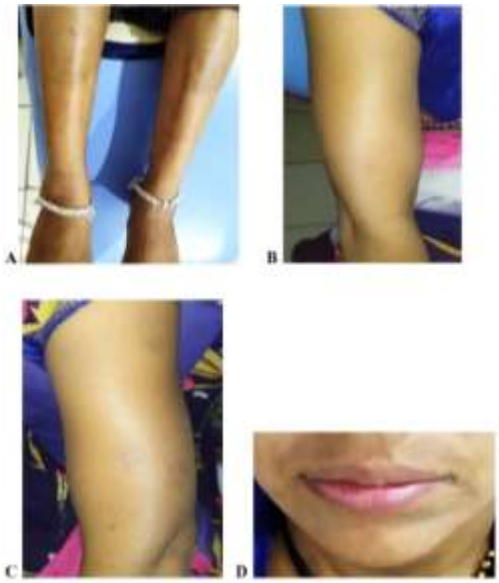

FIGURE 7- (A-C) completely healed target lesions seen over the extremities and (D) completely healed haemorrhagic crustations over the upper and lower lip.

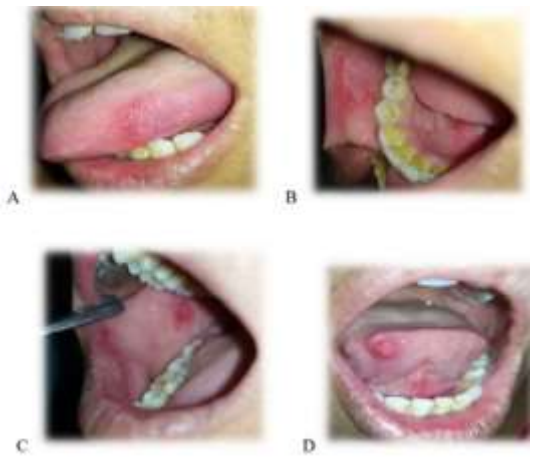

FIGURE 8- FOLLOW 4, recurrence of ulcers on, (A) left lateral border of tongue, (B) right buccal musoca, (C) right retromolar area, (D) right side on ventral surface of tongue.

DISCUSSION

Erythema Multiforme (EM) is an acute mucocutaneous self limiting disease leading to skin eruptions, irrespective of the oral or other mucous membrane involvement.[1,3] The etiopathogenesis of this disease remains uncertain.[1] EM is usually seen as a succeeding disease post administration of drugs or infections[1], although HSV remains the most common predisposing feature for the occurrence of EM.[1,11] In about 60% of the patients diagnosed with recurrent herpes associated erythema multiforme (HAEM), the DNA of Herpes simplex virus can be found . The DNA of HSV virus can also be found in patients diagnosed clinically of erythema multiforme of idiopathic origin using polymerase chain reaction (PCR) of skin biopsy specimens.[12] One of the studies revealed that in 66.7% of the cases the cutaneous lesions of patients with EM

were infected with HSV-1 & HSV-2 in 27.8% of cases and both HSV-1 and HSV-2 in 5.6% of the cases.[13] The lesions of EM can be seen after 10-14 days following the clinical manifestations of HSV infection.[3]
Some authors in their studies have found that HAEM has a consistent pathogenesis along with a delayed hypersensitivity reaction.[14,15]

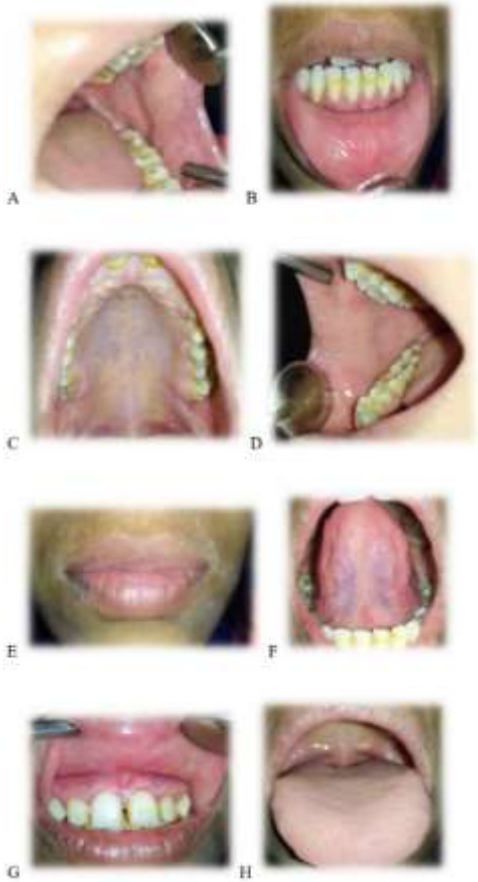

Figure 9- Follow Up 5, Complete Healing Of Ulcerations Seen On (A) Left Buccal Mucosa, (B) Lower Labial Mucosa (C) Hard And Soft Palate, (D) Right Buccal Mucosa, (E) Healed Haemorrhagic Crustations On Upper And Lower Lip, (F) Ventral Surface Of Tongue, (G) Upper Labial Mucosa, (H) Complete Regression Of Coating On Tongue

In the beginning of the disease there is transportation of the HSV DNA fragments by the circulating peripheral blood mononuclear CD34+ cells or the Langerhans cell precursor to keratinocytes which leads to deposition of HSV specific CD4+ T_H 1 cells.[3] Interferon-γ (INF-γ) which is released by the CD4+ cells then initiates the inflammatory cascade in response to the viral antigens and the destruction of immunomediated epidermis begins.[14,15,16] PCR is a great technique to detect HSV DNA in lesions of HAEM, while reverse transcriptase PCR or immunohistochemistry also proves to be an efficient technique for the identification of HSV genes using antibodies to specific viral genes. Presence of INF-γ in HAEM lesions can signify involvement of virus.[13]

Diagnosis of HAEM lesions is easier when there are target lesions preceding or coexisting HSV infection in a patient of HAEM. Presence of typical target lesions and oral lesions in a suspected HAEM patient can be a basis for clinical diagnosis.[1] In the present case, oral lesions as well as typical target lesions were seen. Oral lesions were seen over the buccal mucosa, labial mucosa, lips, tongue, haemorrhagic crusts were seen on the upper and lower lips. Target lesions were seen over the extremities which healed eventually after taking antiviral medication.
The treatment of erythema multiforme is dependent on the severity of the lesions.[1] In mild cases of EM which heal within 2-6 weeks, a local anaesthetic, a local wound care, topical analgesic for controlling pain along with liquid diet is indicated.[1] For severe cases of EM, intravenous fluid therapy with intensive management can be a treatment of choice.[3,11] Oral antihistamines and topical steroids can also be given in conjunction to provide symptomatic relief. In some patients systemic corticosteroids are needed, irrespective of the fact that the evidence for supporting their use is limited. [11,17]
Recurrence can be seen in approximately 20-25% of the cases, even though the disease resolves immediately in 10-20 days, still patients may experience 2-24 episodes in an year. The drug of choice for the treatment of HAEM is Acyclovir, an antiviral, which can be given in a dose of 200mg, 5 times a day for 5 days, but only if the therapeutic scheme is started initially.[3,11,14] In cases of constant recurrence of the disease, a continuous low dose of oral acyclovir may prove effective. The administration of oral acyclovir in a protocol dosage of 200-800mg/day for 26 weeks may be effective in preventing the recurrence of HAEM. If Acyclovir fails to heal the disease, Valacyclovir in a dose of 500mg twice a day can be started as the next antiviral drug for the treatment of HAEM.[18]
The present case was treated with a combination of different groups of drugs at various stages of the disease including oral antihistamines, oral analgesics, oral corticosteroids, local anaesthetics, prebiotics, laxatives, antivirals, topical anaesthetics were given in their preferred doses to the patient and the lesions healed eventually after antiviral therapy with Acyclovir in the doses of (200mg- 5times a day for 5 days). No recurrence is noted till date.

CONCLUSION

The key step towards managing Erythema Multiforme lies in avoidance of contact with the causative age
nt. Though the relationship between HAEM & EM is not yet well defined due to its uncertain etiology, yet it remains certain. Cases of EM triggered due to HSV infections are treated with a combination of systemic acyclovir and topical /oral corticosteroids in order to prevent recurrences. In the case reported here, the patient was initially managed by corticosteroids given orally and later was put on systemic acyclovir in the later stages of the disease.

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