
Aadya Sharma¹, Harkanwal Preet Singh²*, Prabhleen Kaur³, and Ishita Gupta⁴

¹Department of Oral and Maxillofacial Surgery, SGT Dental College, Hospital and Research Centre, Gurgaon, Haryana, India.
²Department of Oral Pathology and Microbiology, Dasmesh Institute of Research and Dental Sciences, Faridkot, Punjab, India.
³Medical Officer, PHC Gopalpur, Block Kalo Majra, Patiala, Punjab, India.
⁴Department of Oral Medicine and Radiology, SGT Dental College, Hospital and Research Centre, Gurgaon, Haryana, India.

ABSTRACT

Erythema multiforme (EM) is a rare acute mucocutaneous disease which has oral manifestations. It is clinically characterized by a “minor” form and a “major” form. It presents a diagnostic dilemma because the oral cavity has the ability to produce varied manifestations. Primary attacks of oral EM are confined to the oral mucosa but the subsequent attacks can produce more severe forms of EM involving the skin. Hence, it is important to identify and distinguish them from other ulcerative disorders involving oral cavity for early management. This article reports an unusual case of Erythema multiforme with oral and lip lesions along with typical target eye lesion at extremities. We emphasize on its early diagnosis and timely management.

INTRODUCTION

Erythema multiforme (EM) is a rare acute mucocutaneous condition caused by a hypersensitivity reaction with the appearance of cytotoxic T lymphocytes in the epithelium that induce apoptosis in keratinocytes, which leads to satellite cell necrosis [1]. It consists of a polymorphous eruption of macules, papules, and characteristics target lesions (central bullae or vesicle with surrounding concentric rash) distributed with a propensity for the distal extremities [2].

It is classified into minor and major type. 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. Steven Johnson syndrome is a more severe condition characterized by wide spread small blisters on torso and mucosal ulcerations with atypical skin target lesions triggered by drug intake. Typical target skin lesions are necessary along with mucosal ulcerations to consider diagnosing them as EM minor and major [3]. We, hereby report a case of Erythema multiforme with oral and skin lesions in 15 year old boy of Asian ethnic.

MATERIALS AND METHODS

Case Report

A 15 year-old boy presented with history of swelling, pain and ulceration on upper and lower lip since 2 week. (Figure 1)
Initially there were small ulcers which latter transformed into large extensive ulcerated areas. Patient gave history of fever and sore throat 1 week back, followed by vesicle formation and ulcerations on lips. Oral lesions appeared first followed by skin lesions. Oral lesions were associated with severe intermittent pain which was aggravated on mastication. No any relevant medical history was observed. The patient reported no prolonged drug intake and hospitalization. Family and drug history were non-significant. All the vital signs were within normal range. Extra-oral examination showed ulcerations and crustation on lower and upper lip (Figure 1) and multiple fluid-filled round vesicles with central necrotic areas (target lesions) with erythematous halo present on hands (Figure 2) and arms. (Figure 3)

Bilateral submandibular lymph nodes were enlarged and tender. On intraoral examination, multiple diffuse irregular ulcerations of upper and lower labial mucosa and also on palate and ventral surface of tongue. (Figure 4)
Figure 4: Intra-oral photograph showing diffuse ulceration on palate and tongue.

Hemorrhagic crusts were also noticed on lower lip which was tender on palpation. Haematologic investigations revealed normal complete blood count. Serology tests showed positivity for Herpes simplex virus and there was fourfold rise in antibody titer. In the light of available evidences, final confirmatory diagnosis recurrent herpes associated erythema multiforme (HAEM) was given. The patent was treated with a 10-day course of acyclovir (1000 mg/day), a topical dexamethasone elixir and acetaminophen. Oral and skin lesions healed completely within 2 weeks. (Figure 5)

Figure 5: Intra-oral photograph showing complete resolution of lesion.

Patient was followed for 6 months without any evidence of recurrence.

DISCUSSION

EM is an acute, sometimes recurrent, mucocutaneous condition of uncertain etiopathogenesis. It usually follows the administration of drugs or infections. Infection with HSV is the most common predisposing feature in the development of EM minor. Both HSV types 1 and 2 have been shown to precipitate EM \cite{4}. HSV DNA has been detected in 60% of patients clinically diagnosed with recurrent HAM and in 50% of patients with recurrent idiopathic erythema multiforme using polymerase chain reaction (PCR) of skin biopsy specimens \cite{5}. Major differences between drug induced and viral induced erythema multiforme is discussed in table 1 \cite{6}.

Several studies have demonstrated that the pathogenesis of HAEM is consistent with a delayed hypersensitivity reaction. The disease begins with the transport of HSV DNA fragments by circulating peripheral blood mononuclear CD34+ cells (Langerhans cell precursors) to keratinocytes, which leads to the recruitment of HSV-specific CD4+ TH1 cells. The inflammatory cascade is initiated by interferon-γ (IFN-γ), which is released from the CD4+ cells in response to viral antigens, and immunomediated epidermal damage subsequently begins. PCR has been employed to detect the presence of HSV DNA in HAEM lesions and tissues, and HSV genes can also be identified with reverse transcriptase. Serology to identify HSV-1 and HSV-2 and to detect specific IgM and IgG antibodies may confirm a suspected history of HSV infection, although it is not necessary for diagnosis \cite{7, 8}. In present case serologic test showed positivity for HSV.

An intriguing question is why most HSV patients do not develop HAEM Some studies have implicated HLA alleles B15(B62), B35, A33, DR53, DQB1*0301 and DQw3 in HAEM development; other HLA alleles (viz. A1) were associated with the propensity to develop recurrent HSV lesions. Moreover, the incidence of DQB1*0302 was increased in HAEM patients with mild mucous membranes involvement; whereas, an association with DQB1*0402 was seen in the disease form showing severe mucous membrane involvement. However, longitudinal studies indicate that HAEM does not follow all the recurrent HSV episodes experienced by a given patient, and the factors
that determine which HSV episode will result in HAEM causation are still unknown. Most likely, HAEM development is determined by the efficacy of HSV DNA dissemination to distant skin sites and its fragmentation during transport.

**Table 1: Differences between drug induced and viral induced erythema multiforme**

<table>
<thead>
<tr>
<th>Features</th>
<th>HEAM (Herpes simplex virus associated erythema multiforme)</th>
<th>DIEM (Drug induced erythema multiforme)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative Agent</strong></td>
<td>HSV ½</td>
<td>Drugs</td>
</tr>
<tr>
<td><strong>Disease course</strong></td>
<td>Acute, Self-limited, recurrent (7-21 days after HSV lesion)</td>
<td>Acute, self-limited not recurrent, does not follow HSV lesion</td>
</tr>
<tr>
<td><strong>Prodrome</strong></td>
<td>Absent/moderate</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Predilection sites</strong></td>
<td>Acral extremities, Target lesions, common</td>
<td>Acral extremities, Face, Target lesions rare, Blisters</td>
</tr>
<tr>
<td><strong>Skin lesion</strong></td>
<td>Absent/minimal</td>
<td>Prominent</td>
</tr>
<tr>
<td><strong>Mucosal involvement</strong></td>
<td>Absent/moderate</td>
<td>Present/Severe</td>
</tr>
<tr>
<td><strong>Constitutional symptoms</strong></td>
<td>None</td>
<td>Infrequent (pneumonia, hemorrhage, GI, renal failure)</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>None</td>
<td>5-15%</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>None</td>
<td>Exocytic KC necrosis; acrosyringeal concentration of necrotic KC; less pronounced edema; mononuclear infiltrate and CD8+ T cells</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td>Focal necrotic KC; moderate/pronounced edema; mononuclear infiltrate with predominant CD4+ T cells</td>
<td>Lesional skin negative for HSV DNA (PCR); positive for TNF-α (immunohistochemistry)</td>
</tr>
<tr>
<td><strong>Laboratory diagnosis</strong></td>
<td>Lesional skin positive for HSV DNA (PCR) and IFN-γ (immunohistochemistry)</td>
<td>Lesional skin negative for HSV DNA (PCR); positive for TNF-α (immunohistochemistry)</td>
</tr>
</tbody>
</table>

The diagnosis of HAEM is clinical and is easier when the patient develops target lesions with a preceding or coexisting HSV infection. The finding of typical skin or oral lesions (or both) in a patient with suspected HAEM supports the clinical diagnosis. In our present case, diffuse ulcerations in the oral mucosa involving the buccal mucosa, palate, labial mucosa and hemorrhagic crusts on the lips as well as the classic skin lesions were seen. Treatment of EM depends on the severity of the lesions. Mild forms usually heal in 2-6 weeks; local wound care, topical analgesics and anesthetics for pain control and a liquid diet are often indicated in these situations. For more severe cases, intensive management with intravenous fluid therapy may be necessary. Oral antihistamines and topical steroids may also be necessary to provide symptom relief. Systemic corticosteroids have been used successfully in some patients, but evidence to support their use for EM is limited [4, 8, 9]. Recurrences are seen in approximately 20%-25% of erythema multiforme cases. Although the disease resolves spontaneously in 10-20 days, patients may experience 2-24 episodes a year [10].

HAEM is often effectively managed with acyclovir (200 mg, 5 times a day for 5 days), but only if the therapeutic scheme is started in the first few days. If erythema multiforme keeps recurring, a continuous low dose of oral acyclovir is necessary. If acyclovir treatment fails, valacyclovir can also be prescribed (500 mg twice a day). The latter has greater oral bioavailability and is more effective at suppressing recurrent HAEM [11].

**CONCLUSION**

Albeit, etiology of EM is not well defined, it seems to be having definite relationship between erythema multiforme and herpetic infections. We emphasize that for its effective management causative agent should be first recognized and then should be immediately removed. In the case reported here, erythema multiforme triggered by HSV infection was diagnosed, and the disease was managed with continuous oral acyclovir therapy to prevent recurrences.

**REFERENCES**