

# Herpes Associated Erythema Multiforme-A Diagnostic Dilemma

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## Abstract

Erythema multiforme is an acute mucocutaneous disorder, characterized by varying degrees of blistering and ulceration. It comprises variants ranging from a self limited, mild, exanthematous, cutaneous variant with minimal oral involvement. It presents a diagnostic and therapeutic challenge to the clinician. Association between HSV infection and EM has been designated HAEM (Herpes associated erythema multiforme). The incidence of EM has been estimated to be between 0.01 and 1%. It is estimated that 20-40% of cases of erythema multiforme are secondary to herpes simplex virus infection. Both HSV 1 and HSV 2 trigger the erythema multiforme lesions. Prevalence of oral EM varies from 35% to 65% among patients with skin lesions. However, in patients where EM was diagnosed by oral lesions, prevalence of skin lesions ranged only from 25% to 33%. We report a case of recurrent herpes-associated erythema multiforme in a 57 year old female patient managed with prophylactic acyclovir. The patient responded well to this treatment regimen and has been in remission to date.

**Keywords:** Erythema Multiforme, Herpes Simplex Virus, Acyclovir

## Introduction:

Erythema multiforme (EM) is an acute mucocutaneous disorder which appears mostly as symmetrical papules, later developing into "target" or "iris" lesions with an erythematous periphery and a central zone of necrosis.<sup>1</sup> It comprises variants ranging from a self limited, mild, exanthematous, cutaneous variant with minimal oral involvement (EM minor) to a progressive, fulminating, severe variant with extensive mucocutaneous epithelial necrosis (Stevens-Johnson syndrome: SJS; and toxic epidermal necrolysis: TEN), hence the name "multiforme".<sup>2</sup> Originally in 1866 Ferdinand Von Hebra described "erythema multiforme exudativum" as a self limiting cutaneous eruption lasting for several weeks with symmetrically distributed, round,

erythematous skin lesions, some of which evolved with concentric colour changes producing iris or target lesions or blisters.<sup>3</sup>

The peak age at presentation is between 20 and 40 years although 20% of cases occur in children.<sup>4</sup> Drugs, mycoplasma, and herpes simplex virus (HSV) infections were described as the most frequent causes,<sup>4-6</sup> although other causes such as allergy to foodstuffs were also suggested.<sup>5</sup> It is estimated that 15-63% of cases of erythema multiforme are secondary to infection herpes simplex virus.<sup>6</sup>

Before any therapy is prescribed, possible underlying causes, such as medications, diet, infections or systemic diseases should be determined and eliminated. The prophylactic and therapeutic use of acyclovir, in cases of HAEM is a common practice.<sup>7</sup>

### Case Report:

A 57 year old female patient reported to the Department of Oral Medicine and Radiology, Institute of Dental Sciences, Bareilly(U.P.) with the chief complaint of painful ulcers and hemorrhagic crusts on the lower lip since 1 month. History of present illness revealed that this type of ulcers occurred for the first time. The ulcers were painful and hemorrhagic. Patient reported that initially there were blisters on the lips which ruptured to form ulcers and erosions. Patient also complained of swelling and erythema and gave history of mild fever of 1 week duration about 15 days back. On general physical examination patient was of thin built, pale, and was anemic. On extra oral examination there was localized swelling and redness on the lower lip with fragile hemorrhagic crustations (Figure 1). No such history of ulcers elsewhere in the body.

On inspection ulcers were present on the vermillion border of lower lip, roughly measuring around 1x1.5 cm in dimension with diffuse borders and with hemorrhagic overlying crustations. On

palpation all inspectory findings were confirmed and the ulcer was tender, fragile and haemorrhagic on mild palpation.

On Intraoral examination revealed multiple ulcers on the left buccal mucosa, on the gingiva and lateral border of tongue measuring around 0.5x 1.0 mm in dimension with necrotic centre and erythematous halo(Figure 2). On the basis of history and clinical examination a provisional diagnosis of erythema multiforme minor was given with a differential diagnosis of recurrent herpes labialis and paraneoplastic pemphigus was given. Immunohistochemistry was carried out in a private lab which was found to be positive both for HSV1 IgG and HSV2 IgM antibody. Final diagnosis of herpes associated erythema multiforme was given. A one week course of acyclovir 400mg was given five times daily. For symptomatic relief, hexigel and tantum mouthwash was given. After 1 week patient returned with healed ulcers(Figure 3). Patient was recommended to continue the medication for next 6 months.



Figure no. 1: Haemorrhagic crustations on lower lip



Figure no. 2: Ulcers on left buccal mucosa



Figure no. 3: Post operative view

## Discussion:

The term erythema multiforme (EM) is a clinical condition which reflects the broad morphological spectrum of the lesions.<sup>8</sup> A range of usually exogenous factors trigger what appears to be an immunologically related reaction with sub- and intra-epithelial vesiculation.<sup>2</sup> Erythema multiforme has been reported to be triggered by numerous agents, particularly viruses, especially herpes simplex virus (HSV) but other herpesviruses (varicella-zoster virus, cytomegalovirus, Epstein-Barrvirus), adenoviruses, enteroviruses (Coxsackie virus B5, echoviruses), hepatitis viruses (A, B and C), influenza, paravaccinia, parvovirus B19, poliomyelitis, vaccinia and variola have all been implicated.<sup>9</sup> Drugs such as sulphonamides (e.g. co-trimoxazole), cephalosporins, aminopenicillins, quinolones, chlormezanone, barbiturates, oxicam non-steroidal anti-inflammatory drugs, anticonvulsants, protease inhibitors, allopurinol or even corticosteroids may be implicated. Food additives or chemicals such as benzoates, nitrobenzene, perfumes or terpenes have also been reported as aetiological agents.<sup>10</sup>

Autoreactive T-cells triggered by virus infection play an important role in herpes associated erythema multiforme (HAEM) pathogenesis.<sup>11</sup> Both HSV 1 and HSV 2 trigger the Erythema multiforme lesions. A study revealed that the cutaneous lesions of patients with HAEM were infected with HSV-1 in 66.7% of cases, HSV-2 in 27.8% of cases and with both HSV types in 5.6% of cases.<sup>12</sup> The HAEM is a recurrent disease that can be precipitated by sun exposure and does not progress to Stevens-Johnson syndrome. Even in the absence of a clear clinical history of HSV infection, subclinical HSV is likely the precipitating factor, as evidenced by the polymerase chain reaction (PCR) analysis of HSV.<sup>13</sup> Typically, an erythema multiforme (minor or major) lesion begins 10–14 days following the clinical manifestations of an HSV infection. In the HAEM, HSV lesions can precede the appearance of target lesions by 2–17 days.<sup>14</sup> The condition can begin with nonspecific prodromal symptoms such as headache, malaise and fever. Lesions of the EM minor

can be persistent (continuous), cyclical (acute and self limiting) or recurrent, the cyclical and recurrent occur mainly in the HAEM.<sup>15</sup> The EM minor skin lesions usually caused by herpes simplex are predominantly raised and distributed on the extremities and/or the face, with mucosal erosions involving one or several sites.<sup>16</sup>

Typical targets<sup>7</sup> are defined as individual lesions less than 3 cm diameter with a regular round shape, a well-defined border, and two concentric palpable, oedematous rings, paler than the centre disc. The lip is the most common site of preceding HSV infection in cases of HAEM. The oral lesions have predilection for the vermilion border of the lips and the buccal mucosa, generally sparing the gingival.<sup>7</sup> Hemorrhagic crusting of the lips and ulceration mainly of the non-keratinized mucosa characterize oral lesions. When it affects the lips, it results in erosions or serum-hemorrhagic crusts, with pathognomonic blood-stained crusting of erosions on swollen lips, hindering the phonation, the feeding and limiting the oral movement.<sup>17</sup> Other mucous membranes that can be affected, mainly in the HAEM cases, are the eyes, nose, genitalia, esophagus and respiratory tract.<sup>18</sup>

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. The mean duration of the disease is 10 years (range 2–36 years).<sup>19</sup>

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.<sup>12</sup> Serology to identify HSV-1 and HSV-2 and to detect specific IgM and IgG antibodies may confirm a suspected history of HSV infection.<sup>20</sup> HSV-DNA has been detected in between 36% and 81% of patients with the HSV-EM using polymerase chain reaction amplification.<sup>21</sup>

The characteristic histopathological change of EM minor is epidermal cell death, which is termed “satellite cell necrosis”, mimicking apoptotic cell

death. Among some apoptosis inducers, the perforin, a pore-making granule from natural killer cells has been suggested.<sup>22</sup> Another apoptotic mechanism that can also be related is the altered expression of apoptotic regulatory proteins. The intense expression of Bcl-2 protein by the inflammatory cells in EM minor support a role for this protein in the maintenance or persistence of the infiltrate in submucosa. An altered or increased expression of Fas antigen throughout the epithelium in correlation with the inflammatory cell infiltrates has been reported in many skin diseases including EM minor.<sup>23</sup>

The EM minor can be distinguished from SJS by the presence of true target lesions and no mucosal lesions or lesions involving 1 (oral) mucosa site rather than 2 or more mucosal sites, as seen in SJS. The EM minor also resolves without sequels within 2 weeks, whereas SJS often lasts longer than 2 weeks, leaving scars, could also have visceral involvement, with signs and systemic symptoms.<sup>13</sup> The HSV is associated with many cases of EM minor, while SSJ and TEN are caused in 80% of the cases by systemic drugs.<sup>4</sup>

Erythema multiforme major is characterised by involvement of multiple mucous membranes. Generally EM major is a more severe form of the disease than EM minor and, in addition to the oral cavity, the genital, ocular, laryngeal and oesophageal mucosae may be affected. Toxic epidermal necrolysis is a rare clinicopathologic entity, with a high mortality, characterised by extensive detachment of full thickness epithelium usually induced by drugs.<sup>2</sup> No specific treatment is available but supportive care is important; a liquid diet and intravenous fluid therapy may be necessary.<sup>2</sup> 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.<sup>19</sup> Oral acyclovir has been shown to be effective at preventing recurrent HAEM and the protocols may include 200–800 mg/day for 26 weeks.<sup>24</sup> 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.<sup>12</sup> In patients who have recurrent EM associated with HSV, suppressive treatment using acyclovir (400 mg twice a day for 6 months) has also been effective in preventing recurrence. Newer generation anti-herpes drugs such as valacyclovir hydrochloride and famciclovir are also useful in both intermittent and suppressive therapy.<sup>4</sup>

### Conclusion:

An important step in the management of erythema multiforme is recognition and withdrawal or prevention of contact with the causative agent. Although its etiology is not yet well defined, the relationship between erythema multiforme and herpetic infection seems certain. In the case reported here, erythema multiforme triggered by HSV infection was diagnosed, and the disease was controlled with continuous oral acyclovir therapy to prevent recurrences. Patients should be informed about the condition and the importance of preventing recurrences. As there remains no specific diagnostic test, early clinical recognition of disease remains essential to promptly initiate appropriate treatment.

### Referances:

1. Huff JC, Weston WL. Recurrent erythema multiforme. *Medicine (Baltimore)*. 1989 May; 68(3):133-40.
2. Farthing P, Bagan JV, Scully C. Mucosal disease series. Number IV. Erythema multiforme. *Oral Dis*. 2005 Sep;11(5):261-7.
3. Von Hebra. On diseases of skin including exanthemata. London: New Syndeham Society, 1866.
4. Carrozzo M, Togliatto M, Gandolfo S. [Erythema multiforme. A heterogeneous pathologic phenotype]. *Minerva Stomatol*. 1999 May;48(5):217-26.
5. Nesbit SP, Gobetti JP. Multiple recurrence of oral erythema multiforme after secondary herpes simplex: report of case and review of literature. *J Am Dent Assoc*. 1986 Mar;112(3):348-52.

6. Kokuba H, Imafuku S, Huang S, Aurelian L, Burnett JW. Erythema multiforme lesions are associated with expression of a herpes simplex virus (HSV) gene and qualitative alterations in the HSV-specific T-cell response. *Br J Dermatol*. 1998 Jun;138(6):952-64.
7. Katz J, Livneh A, Shemer J, Danon YL, Peretz B. Herpes simplex-associated erythema multiforme (HAEM): a clinical therapeutic dilemma. *Pediatr Dent*. 1999 Sep-Oct;21(6):359-62.
8. Aurelian L, Ono F, Burnett J. Herpes simplex virus (HSV)-associated erythema multiforme (HAEM): a viral disease with an autoimmune component. *Dermatol Online J*. 2003 Feb;9(1):1.
9. Tatnall FM, Schofield JK, Leigh IM. A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. *Br J Dermatol*. 1995 Feb;132(2):267-70.
10. Porter SR, Scully C. Adverse drug reactions in the mouth. *Clin Dermatol*. 2000 Sep-Oct;18(5):525-32.
11. Weston WL. Herpes-associated erythema multiforme. *J Invest Dermatol*. 2005 Jun;124(6):xv-xvi.
12. Osterne RL, Matos Brito RG, Pacheco IA, Alves AP, Sousa FB. Management of erythema multiforme associated with recurrent herpes infection: a case report. *J Can Dent Assoc*. 2009 Oct;75(8):597-601.
13. Weston WL, Morelli JG. Herpes simplex virus-associated erythema multiforme in prepubertal children. *Arch Pediatr Adolesc Med*. 1997 Oct;151(10):1014-6.
14. Farthing PM, Maragou P, Coates M, Tatnall F, Leigh IM, Williams DM. Characteristics of the oral lesions in patients with cutaneous recurrent erythema multiforme. *J Oral Pathol Med*. 1995;24(1):9-13.
15. Malmström M, Ruokonen H, Konttinen YT, Bergroth V, Segerberg-Konttinen M, Hietanen J et al. Herpes simplex virus antigens and inflammatory cells in oral lesions in recurrent erythema multiforme. Immunoperoxidase and autoradiographic studies. *Acta Derm Venereol*. 1990;70(5):405-10.
16. T Isaac Joseph, Geetha Vargheese, Deepu George, and Pradeesh Sathyan. Drug induced oral erythema multiforme: A rare and less recognized variant of erythema multiforme. *J Oral Maxillofac Pathol*. 2012 Jan-Apr; 16(1): 145-148.
17. Kelly JP, Auquier A, Rzany B, Naldi L, Bastuji-Garin S, Correia O et al. An international collaborative case-control study of severe cutaneous adverse reactions (SCAR). Design and methods. *J Clin Epidemiol*. 1995 Sep;48(9):1099-108.
18. Manganaro AM. Erythema multiforme. *Gen Dent*. 1996 Mar-Apr;44(2):164-6.
19. Al-Johani KA, Fedele S, Porter SR. Erythema multiforme and related disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007 May;103(5):642-54.
20. K. A. Kamala, L. Ashok, Rajeshwari G. Annigeri. Herpes associated erythema multiforme. *Contemp Clin Dent*. 2011 Oct-Dec; 2(4): 372-375.
21. Brice SL, Krzemien D, Weston WL, Huff JC. Detection of herpes simplex virus DNA in cutaneous lesions of erythema multiforme. *J Invest Dermatol*. 1989 Jul;93(1):183-7.
22. Inachi, S., H. Mizutani and M. Shimizu. Epidermal apoptotic cell death in erythema multiforme and Stevens-Johnson syndrome. Contribution of perforin-positive cell infiltration. *Arch Dermatol*. 1997; 133: 845-849.
23. Chrysomali, E., F. Lozada-Nur and N.P. Dekker et al. Apoptosis in oral erythema multiforme. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod*. 1997; 83: 272-280.
24. Bowers KE. Oral blistering diseases. *Clin Dermatol*. 2000 Sep-Oct;18(5):513

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