# Management of Erythema Multiforme Associated with Recurrent Herpes Infection: A Case Report

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## ABSTRACT

Erythema multiforme is an acute mucocutaneous disorder, characterized by varying degrees of blistering and ulceration. We report a case of recurrent herpes-associated erythema multiforme managed with prophylactic acyclovir. An 11-year-old boy had lesions in the oral cavity and lips, which had been diagnosed as erythema multiforme minor. Four months later, the patient had desquamative gingivitis with erythematous lesions and necrotic areas in the skin. This episode was not related to drug intake, which suggests that the erythema multiforme was a result of herpetic infection. This hypothesis was supported by positive serology for herpes simplex virus. Five months later, the patient returned with new oral, skin and penis mucosal lesions. The diagnosis was confirmed as herpes simplex virus-associated erythema multiforme major. The episode was treated with acyclovir, and acyclovir was used prophylactically for 7 months to control the disease.

For citation purposes, the electronic version is the definitive version of this article: www.cda-adc.ca/jcda/vol-75/issue-8/597.html

Erythema multiforme is an acute mucocutaneous hypersensitivity reaction with a variety of etiologies. It is characterized by a skin eruption, with or without oral or other mucous membrane lesions.[1-3] It can be induced by drug intake (**Box 1**) or several infections, in particular herpes simplex virus (HSV) infection,[1] which has been identified in up to 70% of erythema multiforme cases.[4]

When HSV infection is implicated, the diagnosis is herpes-associated erythema multiforme. In these cases, recurrent episodes of erythema multiforme are usually related to HSV infection.[5] A study by Ng and colleagues[6] detected HSV DNA in 50% of patients with recurrent idiopathic erythema multiforme.

Erythema multiforme typically affects teenagers and young adults (20–40 years), but the onset may be as late as 50 years of age or

**Box 1** Drugs and infectious agents most commonly associated with erythema multiforme and related disorders[3]

**Drugs**
Antibacterial; sulfonamides, penicillins, cephalosporins, quinolones; anticonvulsants; analgesics; nonsteroidal anti-inflammatory drugs; antifungals

**Infectious agents**
Herpes simplex virus; Epstein-Barr virus; *Cytomegalovirus*; varicella-zoster virus; *Mycoplasma pneumoniae*; hepatitis viruses; *Mycobacterium*; streptococci; fungal agents; parasites

**Table 1** Differential features of erythema multiforme minor, erythema multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis[a]

| 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).<br>Oral lesions; mild to severe erythema, erosions and ulcers.<br>Occasionally may affect only the oral mucosa.<br>< 10% of the body surface area is affected. |
| Erythema multiforme major | Cutaneous lesions and at least 2 mucosal sites (typically oral mucosa) affected.<br>< 10% of the body surface area involved.<br>Symmetrically distributed typical target lesions or atypical, raised target lesions or both.<br>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.<br>< 10% of the body surface area is involved.<br>Primarily atypical flat target lesions and macules rather than classic target lesions.<br>Generally widespread rather than involving only the acral areas. Multiple mucosal sites involved, with scarring of the mucosal lesions.<br>Prodromal flu-like systemic symptoms also common. |
| Overlapping Stevens-Johnson syndrome and toxic epidermal necrolysis | No typical targets; flat atypical targets are present.<br>Up to 10%–30% of the body surface area affected.<br>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.<br>In the absence of spots, characterized by epidermal detachment > 10% of the body surface, large epidermal sheets and no macules or target lesions. |

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

more.[2] The disease is more common in males than females in a ratio of 3:2.[7]

Recently, erythema multiforme has been classified as minor, major, Stevens-Johnson syndrome or toxic epidermal necrolysis, where erythema multiforme minor is the mildest type of lesion and toxic epidermal necrolysis the most severe[2,3] (**Table 1**).

Erythema multiforme is associated with an acute onset and, usually, mild or no prodromal symptoms. Fever, lymphadenopathy, malaise, headache, cough, sore throat and polyarthralgia may be noticed as much as 1 week before the onset of surface erythema or blisters.[8] Lesions may appear as irregular red macules, papules and vesicles that collapse and gradually enlarge to form plaques on the skin. Moreover, crusting and blistering sometimes occur in the centre of the skin lesions, resulting in concentric rings resembling a "bull's eye" (target lesion). On the other hand, oral lesions are usually erythematous macules on the lips and buccal mucosa, followed by epithelial necrosis, bullae and ulcerations with an irregular outline and a strong inflammatory halo. Bloody encrustations can also be seen on the lips.[2,3]

In this report, we discuss the case of an 11-year-old boy who was clinically diagnosed with erythema multiforme associated with herpes infection. The disease was controlled by the prophylactic use of acyclovir to prevent further recurrence.

## Case Report

An 11-year-old boy visited the stomatology clinic at the Federal University of Ceará with complaints of painful ulcers and hemorrhagic crusts on the lips. He reported having pharyngitis and a fever 1 week previously. The patient had started treatment with azithromycin and amoxicillin, after which he developed ulcers and a hemorrhagic crust on the lower lip. An oral examination identified ulcerative lesions involving the bilateral buccal mucosa and the labial mucosa

**Figure 1:** Ulcers and hemorrhagic crusts on the lower lip during the first diagnosed episode of erythema multiforme minor.

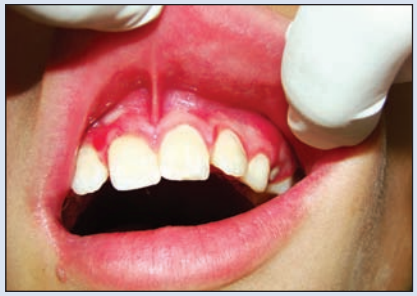

**Figure 2:** Desquamative gingivitis during the second episode of erythema multiforme, 4 months after the first.

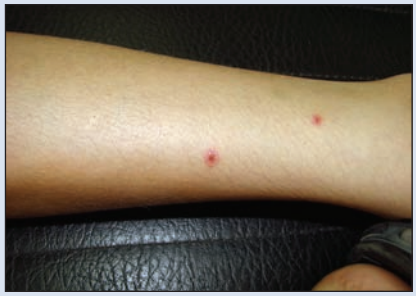

**Figure 3:** Eruptions and erythematous lesions with necrotic areas on the legs seen during the second episode.

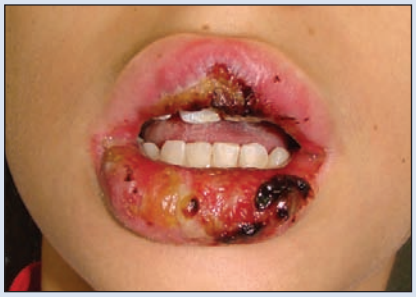

**Figure 4:** Ulceration and hemorrhagic crusts in the vermilion zone of the lips during the third episode, which was diagnosed as herpes-associated erythema multiforme.

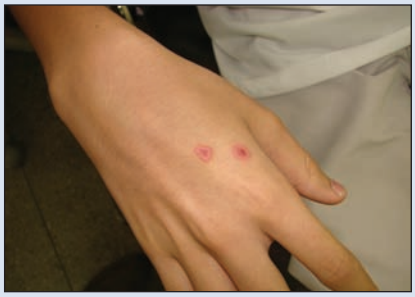

**Figure 5:** Round skin lesions with necrotic centre (target lesions) seen on the hands during the third episode of erythema multiforme.

(**Fig. 1**). The patient reported that a similar incident had occurred 2 years previously. Currently, he had no skin injuries, and the clinical features suggested erythema multiforme minor. Accordingly, he was treated for his symptoms, and the lesions healed within 14 days.

Four months later, the patient returned to the stomatology clinic with a diffuse gingivitis manifested as pure desquamative gingivitis (**Fig. 2**). He had also developed eruptions and erythematous lesions with necrotic areas on his trunk and legs (**Fig. 3**), and a single vesicle lesion was seen on the perilabial skin. On that occasion, the patient denied drug therapy, and it was suggested that a herpetic infection had triggered the erythema multiforme. Serology tests confirmed that the patient was positive for HSV (IgG and IgM positive), and he was treated with a 7-day course of acyclovir (1,000 mg/day), a topical dexamethasone elixir and acetaminophen. With this combined course of treatment, the disease was controlled.

Five months later, the patient returned with new oral lesions characterized by diffuse ulcerations in the oral mucosa, involving the bilateral buccal mucosa and the labial mucosa, and hemorrhagic crusts on the vermilion zone of the lips (**Fig. 4**). These lesions limited his oral hygiene and intake of food, but intravenous rehydration was not necessary. The patient also presented with target lesions of a regular round shape on his legs, arms, hands and trunk (**Fig. 5**). Mucosal ulcerations on the penis were also found, and the patient reported that they had appeared after unprotected exposure to the sun.

At this point, the disease was diagnosed as erythema multiforme major associated with HSV, and the patient was treated with a 10-day course of acyclovir (1,000 mg/day), acetaminophen and a topical dexamethasone elixir. After 14 days of treatment, skin and oral lesions were controlled. Because of the recurring episodes, acyclovir was given prophylactically for 7 months, starting with 800 mg/day and reduced in the last month to 400 mg/day. Renal and liver functions were monitored during the course of treatment, and no abnormalities were found. In addition, no oral or skin lesions developed during the 7 months of treatment, and the disease is currently under control.

## Discussion

Erythema multiforme is an acute, sometimes recurrent, mucocutaneous condition of uncertain etiopathogenesis that can follow the administration of drugs or

infections. Infection with HSV is the most common feature in the development of erythema multiforme minor. Herpes-associated erythema multiforme (HAEM) can be found several days or weeks following an episode of HSV. Both HSV types 1 and 2 have been shown to precipitate HAEM,[3] and health history, clinical observations and prospective studies indicate that most cases of erythema multiforme are preceded by infection with HSV,[9] although it is important to emphasize that HSV infection may be clinically silent.[10] HSV DNA has been detected in 60% of patients clinically diagnosed with recurrent HAEM and in 50% of patients with recurrent idiopathic erythema multiforme using polymerase chain reaction (PCR) of skin biopsy specimens.[6] Another study[11] 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. Typically, an erythema multiforme (minor or major) lesion begins 10–14 days following the clinical manifestations of an HSV infection. The lip is the most common site of preceding HSV infection in cases of HAEM.[12] In the present case, the serology for HSV was positive, confirming that the erythema multiforme was associated with an HSV infection. However, it is important to emphasize that HSV was identified only during the second episode of the disease and that HAEM was confirmed at the third episode.

Several studies[1,13] 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+ $T_H1$ 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.[1,13,14] 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 PCR or immunohistochemistry using antibodies to specific viral genes. Detection of IFN-γ in HAEM lesions can also be used as evidence of virus involvement.[1] 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.[2]

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 case, diffuse ulcerations in the oral mucosa involving the buccal mucosa, the labial mucosa and hemorrhagic crusts on the lips as well as the classic skin lesions were seen. Pronounced systemic signs and symptoms (cutaneous and mucosal lesions) suggested the diagnosis of erythema multiforme major. Histopathologic examination revealed a pattern that is characteristic of erythema multiforme, but is not pathognomonic.[2] Subepithelial or intraepithelial vesiculation is usually seen in association with necrotic basal keratinocytes, and subepithelial edema and intense inflammatory infiltration (lymphocytes, neutrophils and often eosinophils) are present; again, these features are characteristic of erythema multiforme, but not pathognomonic. Often, the inflammatory infiltrate is arranged in a perivascular orientation that is typically seen in erythema multiforme.[4] Changes affecting both the epithelium and supporting connective tissue were seen in the present case. All the symptoms together, including the clinical and histologic features as well as the patient's HSV-positive status and symptom recurrences, confirmed the diagnosis of HAEM.

Treatment of erythema multiforme depends on the severity of the clinical features. Mild forms usually heal in 2–6 weeks; local wound care, topical analgesics or 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.[4,15] Oral antihistamines and topical steroids may also be necessary to provide symptom relief.[16] Systemic corticosteroids have been used successfully in some patients, but evidence to support their use for erythema multiforme is limited.[3]

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).[3,4]

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.[3] Oral acyclovir has been shown to be effective at preventing recurrent HAEM,[10] and the protocols may include 200–800 mg/day for 26 weeks.[4,10,17,18] 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.[19] During the second and third episodes in this case, the patient was treated with acyclovir (1,000 mg/day), and prophylactic use of acyclovir was prescribed to prevent recurrences. The dosage of an antiviral medication may be reduced once the patient is free of recurrences for 4 months, and the drug may eventually be discontinued.[2] In our case, the patient was treated for 7 months with acyclovir, starting with 800 mg/day followed by a reduction in the last month to 400 mg/day.

## 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.

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***Acknowledgements:** The authors wish to acknowledge Dr. Raquel Carvalho Montenegro for her help with the preparation of this manuscript.*

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*The authors have no declared financial interests.*

*This article has been peer reviewed.*

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