Herpes associated erythema multiforme

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Abstract

Erythema multiforme is an acute and a self-limiting mucocutaneous hypersensitivity reaction triggered by certain infections and medications. One of the most common predisposing factors for erythema multiforme is infection with herpes simplex virus. Herpes associated erythema multiforme (HAEM) is an acute exudative dermatic and mucosal disease caused by the infecting herpes simplex virus. It has recurrence and idiorestriction, characterized by increasing of CD4+T leukomonocyte. This article reports a case of HAEM in a 9-year-old girl, with a review of relevant literature, and discusses the pathophysiology and treatment of erythema multiforme triggered by herpes simplex virus

Keywords: Clinical features, erythema multiforme, herpes associated, management, oral, skin

Introduction

Erythema multiforme (EM) is an acute mucocutaneous hypersensitivity reaction with a variety of etiologies. It is characterized by skin eruptions, with or without oral or other mucus membrane lesions.[1,2] It can be induced by drug intake or several infections, immune conditions and food additives [Table 1].

EM typically affects young adults (20–40 years) and 20% of cases occur in children. The disease is more common in males than females and is precipitated by preceding herpes infection in up to 70% of cases.[3]

EM begins 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.[3,4] 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 center 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.[2,3,5] Based on the degree of mucosal involvement and the nature and distribution of skin lesions, EM is classified into a number of different variants [Table 2]. Herein, we report of case of EM triggered by herpes simplex virus (HSV) infection.

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Case Report

A 9-year-old girl presented to us with history of swelling, pain and ulceration on upper and lower lip since 1 week. Her history of present illness revealed that she had fever and sore throat 1 week back, followed by vesicle formation and ulcerations on lips. Oral lesions appeared first followed by dermal lesions. Oral lesions were associated with pain which was moderate and intermittent in nature and aggravated on mastication. Past medical history revealed similar attack 3 months back. The patient reported no prolonged drug intake and hospitalization, and her family and drug history were noncontributory, with all her vital signs being within normal range.

Extraoral examination revealed multiple fluid-filled vesicles on right elbow with central crustation [Figure 1]. Both right and left cervical lymph nodes were palpable, tender and soft to firm in consistency. On intraoral examination, multiple diffuse ulcerations of upper and lower labial mucosa were present. Swelling of upper and lower lips, fissuring and cracking of right and left corners of mouth with hemorrhagic crests were also noted and were tender on palpation [Figures 2 and 3].

Laboratory investigation revealed normal complete blood

Table 1: Triggering or predisposing factors of erythema multiforme

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
Immune conditions	BDG, hepatitis B immunization, sarcoidosis, graft versus host disease, inflammatory bowel disease, systemic lupus erythematous
Food additives or chemicals	Benzoates, nitrobenzoates, perfumes or terpenes, ammoniated mercury, oxybenzone, phenylbutazone, nickel, nitrogen mustard, capsicum, herbal medicine, rosewood

Table 2: Sub-classes of erythema multiforme and their clinical features

Sub-types of erythema multiforme	Clinical features
Erythema multiforme minor	Typical target lesions, raised atypical target lesions, minimal mucus membrane involvement and, when present, at only one 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 two mucosal sites (typically oral mucosa) are affected <10% of the body surface area is 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 are 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 is affected Prodromal flu-like systemic symptoms are common
Toxic epidermal necrolysis	When spots are present, it is characterized by epidermal detachment of >30% of the body surface and widespread purpuric macules or flat atypical targets. In the absence of spots, it is characterized by epidermal detachment >10% of the body surface, large epidermal sheets and no macules or target lesions

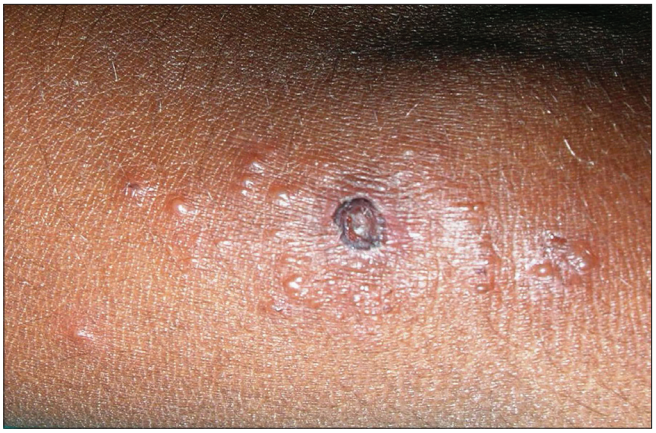

Figure 1: Multiple fluid-filled vesicles with central black color crustation present on right elbow

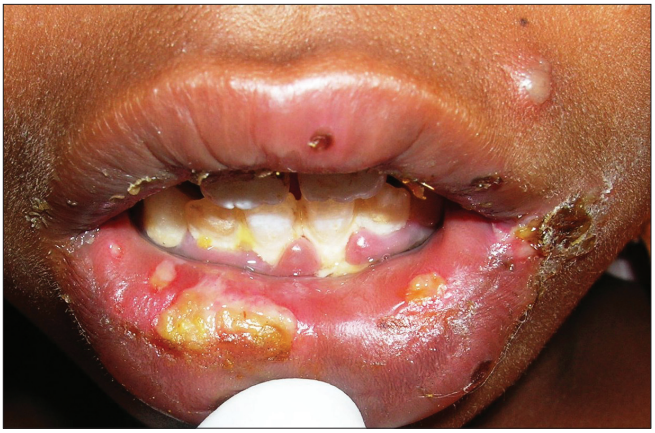

Figure 2: Swelling and ulcers of lower lip with hemorrhagic crust at left corner of mouth

count and erythrocyte sedimentation rate (ESR). Serology tests confirmed that the patient was positive for HSV and there was fourfold rise in antibody titer. Depending on the history, clinical examination and laboratory investigations, we arrived at the diagnosis of recurrent herpes associated erythema multiforme (HAEM). The patent was treated with a 7-day course of acyclovir (1000 mg/day), a topical dexamethasone elixir and acetaminophen. Within a week, the oral lesions healed and skin lesions healed with transitory hyperpigmentation [Figure 4].

Discussion

EM is an acute, sometimes recurrent, mucocutaneous condition of uncertain etiopathogenesis. It usually follows the administration of drugs or infections. Infection with HSV

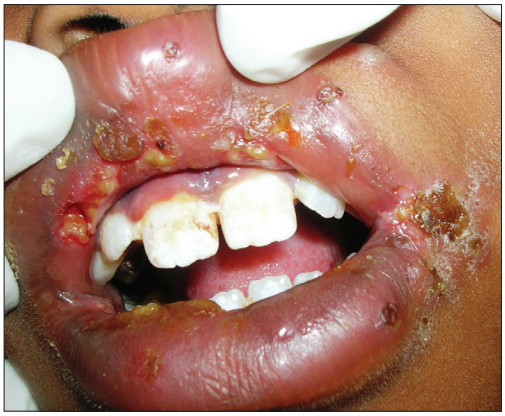

Figure 3: Hemorrhagic ulcers with swelling of upper lip

is the most common predisposing feature in the development of EM minor. Both HSV types 1 and 2 have been shown to precipitate EM.[3] HSV DNA has been detected in 60% of patients clinically diagnosed with recurrent HAEM and in 50% of patients with recurrent idiopathic EM using polymerase chain reaction (PCR) of skin biopsy specimens.[6] Another study revealed that the cutaneous lesions of patients with EM 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.[7] Typically, an EM (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.[4] In the present case, the serology for HSV was positive, confirming that the EM was associated with an HSV infection.

Several studies have demonstrated that the pathogenesis of HAEM is consistent with a delayed hypersensitivity reaction.[1,8] 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.[7-9] 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.[5] Serology to identify HSV-1 and HSV-2 and to detect specific IgM and IgG antibodies may confirm a suspected history of HSV infection.[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 labial mucosa and hemorrhagic crusts on the lips as well as the classic skin lesions were also seen.

Treatment of EM depends on the severity of the lesions.

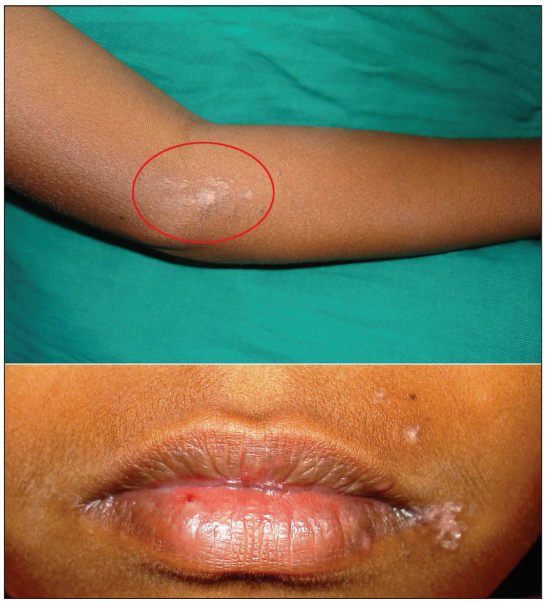

Figure 4: Healing of oral and skin lesions after 1 week treatment with systemic acyclovir

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.[3,4] 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.[3,5]

Recurrence is seen in approximately 20–25% of EM cases. Although the disease resolves spontaneously in 10–20 days, patients may experience 2–24 episodes a year. 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 EM keeps recurring, a continuous low dose of oral acyclovir is necessary.[3,4,9] Oral acyclovir has been shown to be effective in preventing recurrent HAEM, and the protocols may include 200–800 mg/day for 26 weeks. If acyclovir treatment fails, valacyclovir can also be prescribed (500 mg twice a day).[4,10]

Conclusion

In the case reported here, EM triggered by HSV infection was diagnosed, and such cases should be managed by systemic acyclovir and topical corticosteroids.

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