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Case Report

A Case Report of Recurrent Erythema Multiforme

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Abstract

Erythema multiforme (EM) is a rare cutaneous or mucocutaneous reaction characterized by "target" lesions, mainly of the face and extremities. The disease is more common in boys and young people than in other subjects. It is benign but can be recurrent, there may be complications, especially in the eyes. Most cases are related to infections, especially herpes simplex virus (HSV) and *Mycoplasma pneumoniae*, while drug-induced EM is rare. We report a case of recurrent erythema multiforme in a young woman, possibly related to HSV.

Keywords: *Mycoplasma pneumoniae*; Erythema Multiforme (EM); Stevens-Jonhson Syndrome (SJS)

Introduction

Erythema multiforme (EM) is a cutaneous or mucocutaneous reaction first described by von Hebra in 1860. Skin lesions are characterized by typical and/or atypical target lesions. The disease is divided into minus (no mucosal lesions, only skin and lip lesions) and major (mucosal lesions).

Previously, the classification between EM, Stevens-Jonhson syndrome (SJS), and toxic epidermal necrolysis (TEN) was still inconsistent due to unclear pathogenesis. There are different opinions on the differential diagnosis of major EM from SJS/TEN. Since 1983, SJS has been considered synonymous with major EM, both with the involvement of more than one mucosa with skin involvement. In 1993-1994, Bastuji-Garin and Roujeau proposed the distinction between the two diseases based on clinical and etiological factors. In major EM, there are mucosal lesions, bullae, and skin lesions less than 10% of the body surface area. But unlike SJS, the skin lesions in major EM are typical and/or atypical target lesions that are elevated compared to normal skin, distributed mainly in the extremities. Stevens-Johnson syndrome is characterized by extensive bullae due to drug reactions, which appear on the background of erythema, necrosis, and pruritus, concentrated mainly on the face and trunk [1]. Etiologically, EM is often associated with herpes simplex virus reactivation, rarely drug-induced, SJS/TEN mainly drug-induced, rarely infection [2,3]. There were some cases in which mucosal lesions are primary, and there was little or no skin damage. This form is known as *Mycoplasma pneumoniae*-related mucositis (MPAM) [4]. Today, EM is considered a separate disease, separated from the SJS/TEN group, with specific clinical features, epidemiology, and pathogenesis. The disease is benign but can be recurrent, there may be complications, especially in the eyes. Most cases are related to infections, especially herpes simplex virus (HSV) and *Mycoplasma pneumoniae*, which are rarely drug-induced.

We report a case of recurrent EM in a young female patient, possibly related to HSV.

Case Report

Clinical features

A 25-year-old female patient was admitted to the hospital because of painful lesions on the skin and oral mucosa. The disease began to appear two years ago, with outbreaks, and then subsided, about once every 2-3 months. Initially, the patient had red papules, and red patches on the trunk, then blisters appeared in the middle of the lesions, quickly spreading to the hands and feet. Accompanied by that, the patient has blisters in the oral mucosa and lips that, when broken, leave painful erosions. Before each episode, the patient had no symptoms of upper respiratory tract inflammation, no fever, and no pain. No history of other diseases, no allergies to drugs or foods.

On admission, the patient had no fever, body temperature of 36.8°C, blood pressure of 110/80 mmHg, and burning pain in skin lesions and oral mucosa. On the lips, some blisters have broken, leaving scaly scabs with a dark brown crust. Some lesions in the roof of the palate resemble aphthous ulcers: ulcers of 3-5 mm, surrounded by a red halo, with white pseudomembranous in the middle. Around the root, there are shallower ulcers with, red background. Other mucosal lesions were not affected. Hands, feet, and trunk with patches, and papules suggest typical target lesions with bullae/vesicles in the middle, varied in size, and uneven. The dorsal region has older lesions, now with epidermal necrotic macules. Nikolsky sign was negative.

Paraclinical features

Laboratory tests: white blood cell counts 13.25 G/L; neutrophil 91.7%. Other blood and urine biochemistry were normal. Serum HSV-1/2 IgM negative; HSV-1/2 IgG positive; serum *Mycoplasma pneumoniae* IgM, IgG negative; PCR (polymerase chain reaction) test for diagnosis of HSV on skin lesions was negative. Cytology of oral mucosal lesions and cutaneous bullous lesions did not show acantholytic cells and multinucleated giant cells. On histopathological images, the epidermis has many dyskeratosis cells, fluid degeneration of the basal membrane, extracellularly; perivascularly dermal infiltration of mononuclear cells, and no eosinophils.

Images 1: Characteristics of the patient's skin and mucosal lesions: erosions and ulcers with brown-black crust on the lips, and aphthous-like ulcers in the oral mucosa; The typical target lesions are large (giant) and varied, some with epidermal necrosis on the arms, legs, and trunk.

Treatment

The patient was diagnosed with EM, which may be microbial or idiopathic, and was treated with methylprednisolone 48 mg/day for 7 days, bilastine 20 mg/day, topical betamethasone cream for cutaneous lesions, topical triamcinolone gel for oral mucosal lesions, gargle with physiological saline. After 7 days of treatment, skin, and mucosal lesions were healed. Prophylactic regimen for patients with acyclovir 400 mg twice daily for 6 months. The patient still had a recurrence of the lesion during treatment, but the severity of the disease was milder, and he did not need to be hospitalized for inpatient treatment.

Discussion

The patient was diagnosed with EM mainly based on clinical features and history. The disease had a recurring nature, in each episode, the interval between the episodes was quite close, and there were both cutaneous and mucosal lesions. Cutaneous lesions suggested typical and/or atypical target lesions. Especially, in this patient, the inflammatory response was quite strong, creating giant target lesions, and forming bullae in the middle (eg, in the knees, and back). Clinically, these skin lesions were sometimes easily confused with fixed drug eruption. But in this patient, when healed, the lesions did not leave persistent hyperpigmented macular. The histopathological features of skin lesions had many points consistent with erythema multiforme (epidermis with many dyskeratoses, fluid degeneration of basal membrane, extracellularly; perivascularly dermal infiltration of mononuclear cells, no have eosinophils). There were no melanin-eating macrophages in the superficial dermis as in fixed drug eruption.

The patient's mucosal lesions had quite a lot of ulcers, erosion, pain, and white pseudomembranous, surrounded by red swollen skin borders, similar to aphthous ulcers or stomatitis caused by HSV. However, in aphthous ulcers, there is usually only a simple oral mucosal lesion, with no skin involvement. Meanwhile, in this patient, oral mucosal lesions were always accompanied by skin lesions. HSV stomatitis is usually at the stage of primary viral infection, common in children, with rather aggressive systemic symptoms such as fever, sore throat, and regional swollen lymph nodes. In this patient, lesions of the oral mucosa had recurred several times, without systemic symptoms. The HSV-1/2 IgM serological test was negative; HSV-1/2 IgG positive did not support acute HSV infection. Because the patient has a lot of skin lesions and the diagnostic tests for *Mycoplasma pneumoniae,* serum IgM and IgG were negative, the diagnosis of *Mycoplasma pneumoniae*-associated stomatitis was excluded.

Regarding the cause of EM in this patient, HSV was the most targeted because of the recurrent nature and distribution characteristics of the lesions; serodiagnosis of HSV-1/2 IgG positive. Erythema multiforme is an acute inflammatory infiltrated by monocytes and lymphocytes. The amount of TCD8+ infiltrates predominately in the epidermis, while the number of TCD4+ predominates in the dermis. There was also an increased number of Langerhans cells. The operation of auto-reactive epidermal T cells plays an important role in the pathogenesis of EM. The trigger in this process is fragments of HSV-DNA in the skin. Viral proteins and DNA are digested by macrophages at the site of HSV injury, producing fragments, and presenting antigens to memory T cells [5]. However, this patient had a PCR negative for HSV. A study of 63 EM patients (with histopathology proving the diagnosis) showed that the HSV-DNA detection rate was 3/11 (accounting for 27.2%) of HSV-associated EM patients with first-time occur; 6/10 (accounting for 60%) EM patients associated with recurrent HSV; 1/4 (accounting for 25%) of patients with idiopathic EM got sick for the first time; and 6/12 (50%) patients with idiopathic recurrent EM; In patients with drug-induced EM or SJS, no cases of HSV-DNA were detected. The overall HSV-DNA detection rate in HSV-related EM patients was 42.9%; in patients with idiopathic EM was 43.8% [6].

Since the patient had no signs of acute infection, while the inflammatory response was very strong, both clinically and histologically, we used systemic and topical corticosteroids for symptomatic treatment. Symptoms improved rapidly after 5-7 days of treatment. To prevent recurrence, we prescribed acyclovir orally 400 mg twice a day for 6 months [7]. During the course of using the prophylactic regimen, the disease still recurred but the severity was milder. This patient was seropositive for HSV-1/2 IgG, so prophylactic oral acyclovir was indicated. Cases of EM of unknown cause or unrelated to HSV are called idiopathic EM. Other anti-inflammatory and immunosuppressive agents may also be used in EM prophylaxis, such as dapsone, azathioprine, or mycophenolate mofetil [8].

Conclusion

Erythema multiforme with diverse cutaneous or mucosal or mucocutaneous lesions often recurs. Diagnosing the cause can be difficult because the disease has a complex immune mechanism and etiology. Treatment is mainly aimed at reducing symptoms and preventing disease recurrence.

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