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Case Report

The Overlap of Fixed Drug Eruption and Human Herpes Virus Type II Associated Erythema Multiforme

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Abstract

Observations: We present a 29-year-old woman who admitted to the outpatient clinic with a characteristic vesicular eruption of herpes labialis on her upper lip and erythematous, edematous plaques on her arms. She had a disease background of similar lesions that used to appear at the same sites and recurrences of herpes labialis, as well. Histopathologic examination of the biopsy material obtained from an erythematous plaque on the arm revealed necrosis and reticular degeneration, with sparse neutrophils and lymphocytes in the lumen of splitted epidermis. A perivascular infiltration composed of lymphocytes, sparse polymorphonuclear cells and eosinophils was present in the upper dermis which was in accordance with erythema multiforme. Herpes simplex virus type II DNA was detected on the skin biopsy of an erythematous plaque by polymerase chain reaction (PCR). The lesions of the patient healed after antiviral and oral corticosteroid therapy. Recurrences on the arms and face were noted after discontinuation of the treatment but some of them were leaving brownish macules which were characteristic for fixed drug eruption. After discontinuation of all drugs that the patient take, no further attack appeared.

In the present case it is noteworthy that histologically proven erythema multiforme coexisted by herpes simplex virus type II and additional eruptions were associating from time to time and showed a distinctive course by residual hyperpigmentation. HSV DNA has previously been demonstrated in epidermal cells of erythema multiforme lesions by in situ hybridization and polymerase chain reaction. Erythema multiforme may be provoked by some drugs and needs be differentiated from other types of drug eruptions.

Case Report

A 29-year-old woman admitted to the outpatient clinic with erythematous, vesicular eruption on her upper lip and erythematous, edematous plaques on her inner or outer aspects of her arms in February 2005 (**Figure 1** and **Figure 2**). She had a history of similar lesions which had appeared a year ago on her left arm and which had regressed leaving a brownish-purple macule with a discrete border. She was having recurrences of herpes labialis up to 10 times per every year since her childhood but never used to have genital lesions. On physical examination, small and grouped vesicles on an erythematous base were detected on the upper lip, along with dark red, edematous papules and plaques some of which had target-like appearance on her arms. There was a plaque that had a brownish centre and surrounded by erythema and edema on the left arm. On systemic examination all findings were normal.

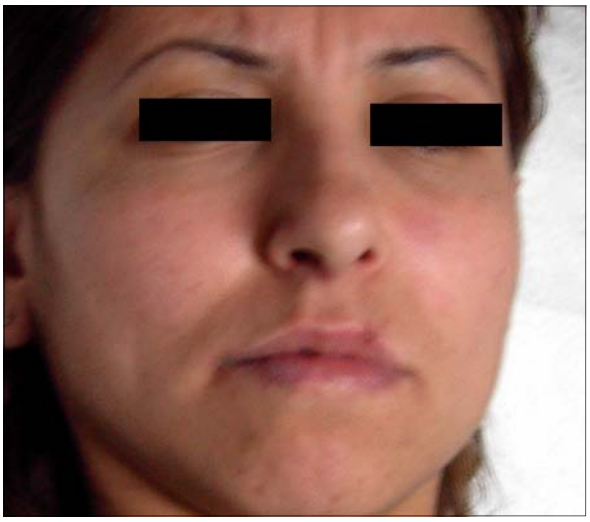

Figure 1. Attack of recurrent herpes labialis

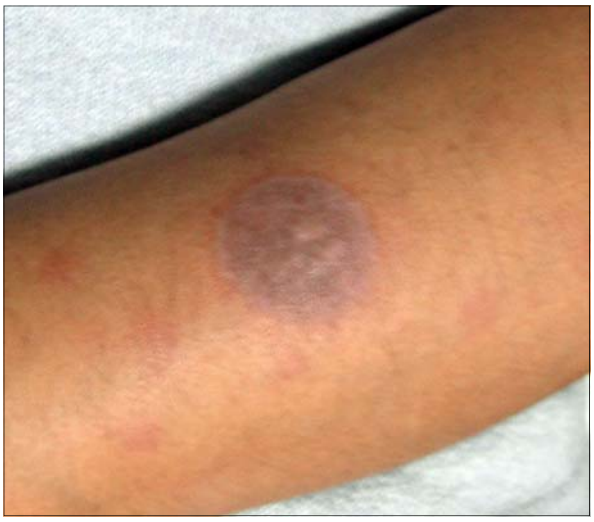

Figure 2. Violaceus and pink-colored patches and plaques coexisting with herpetic lesions

Histopathologic examination of the biopsy material obtained from an erythematous plaque on the right arm revealed necrosis and reticular degeneration, with sparse neutrophils and lymphocytes in the lumen of splitted epidermis. There was an infiltration of mononuclear cells, and some eosinophils around the vessels, and some polymorphous nuclear cells and pigmented macrophages in vessels in the upper dermis (**Figure 3**). On molecular biological evaluation Herpes simplex virus type II DNA was detected on the skin biopsy of an erythematous plaque on right arm by polymerase chain reaction (PCR).

The patient was given oral acyclovir 400 mg three times a day and oral prednisone at a dose of 30 mg per day with the diagnosis of herpes labialis and associated erythema multiforme. A short time after improvement of the lesions, new plaques, mimicking the previous clinical picture, appeared on her arms whereas clinical findings of recurrent herpes labialis were absent. The patient was diagnosed as erythema multiforme and oral corticosteroid therapy was reinitiated. Three attacks with 1 to months' intervals were seen after treatment with increasing number of inflamed lesions that regressed leaving brownish purple macules on her face and arms (**Figure 4**). The latter lesions were thought to be due to fixed drug eruption since the patient denoted that that they appeared after administration of nonsteroidal anti-inflammatory drugs during premenstrual periods. No further attacks were recorded after inhibition of all drugs that the patient used to take were stopped.

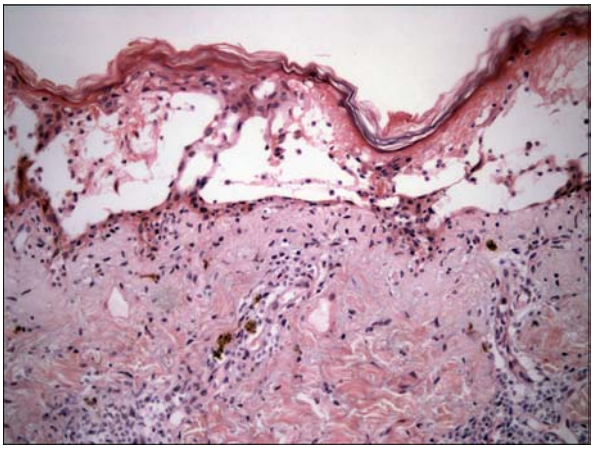

Figure 3. Subepidermal blister and inflammatory infiltration in the upper dermis (HE X 100)

Discussion

The term erythema multiforme (EM) is a clinical condition which reflects the broad morphological spectrum of the lesions.[1] It is characterized by a polymorphous eruption composed of symmetrically distributed macules, papules, bullae, and typical target lesions with a central vesicle or bulla. The lesions have a propensity for the distal parts of the extremities and the oral mucosa [**1, 2**]. Histopathological features in-

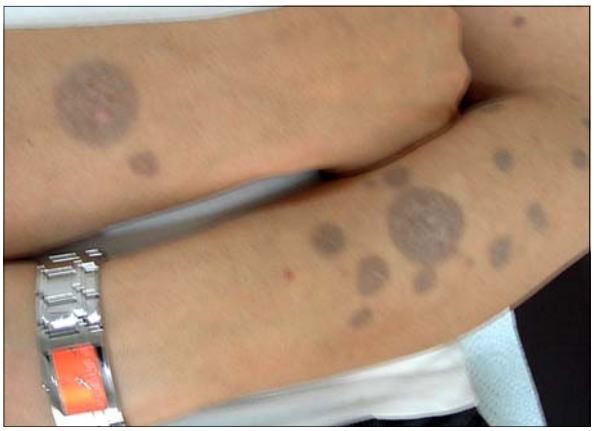

Figure 4. Dark colored discrete lesions which appeared as drug eruptions

clude accumulation of mononuclear cells around upper dermal blood vessels, endothelial swelling, and epidermal damage with hydropic degeneration of basal cells and focal keratinocyte necrosis. Exocytosis of lymphocytes and mononuclear cells is characteristic [**1**]. It is estimated that 15-63% of cases of erythema multiforme are secondary to infection herpes simplex virus [**2**]. Autoreactive T-cells triggered by virus infection play an important role in herpes associated erythema multiforme (HAEM) pathogenesis. Disease development begins with viral DNA fragmentation and the transport of the DNA fragments to distant skin sites by peripheral blood mononuclear cells (PBMCs) [**1, 3**]. HSV genes within DNA fragments deposited on the skin are expressed, leading to recruitment of HSV-specific CD4+ Th1 cells that respond to viral antigens with production of interferon-γ (IFN-γ). This step initiates an inflammatory cascade that includes expression of IFN-γ induced genes, increased sequestration of circulating leukocytes, monocytes and natural killer (NK) cells, and the recruitment of autoreactive T-cells generated by molecular mimicry or the release of cellular antigens from lysed cells. The PBMCs that pick up the HSV DNA, their ability to process it, the viral proteins expressed in the skin and the presence of epitopes shared with cellular proteins may determine whether a specific HSV episode is followed by HAEM development. The polymerase chain reaction (PCR) assay for HSV DNA detection in lesional skin and staining with antibodies to IFN-γ and TNF-α, are important criteria for the diagnosis of skin eruptions and improved patient management [**1**].

Drug-associated EM (DIEM) is a mechanistically distinct EM subset that involves expression of tumor necrosis factor α (TNF-α) in lesional skin [**1**]. Fixed drug eruption is localized sharply circumscribed cutaneous drug reaction that recurs in exactly the same location on repeated exposure [**4, 5**]. Both the skin and mucous membranes may be involved. Typically there are one or more sharply defined round, slightly edematous plaques, ranging in size from several millimeters to many centimeters. The lesions fade over months, but typically leave behind subtle gray-brown post-inflammatory hyperpigmentation. Histopathologically an acute lesion will show an intense lichenoid inflammation with an accumulation of lymphocytes at the epidermal-dermal junction. There is hydropic degeneration of the basal cells and there may be a subepidermal blister. In older or especially in recurrent lesions, melanophages rich in melanin are found in the superficial dermis [**4**].

Erythema multiforme and fixed drug eruption can histopathologically be identical and course of the disease may be helpful for the correct diagnosis. This case is a striking example that shows the importance of reassessment of further changes in reactive skin diseases induced by different factors.

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