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## Clinical and Virological Comparison of 3 Patients with Erythema Multiforme

*Sir,*

Erythema multiforme (EM) is a polymorphous self-limited, often recurrent eruption that can follow drug administration or infection with various agents including herpes simplex virus (HSV). HSV-associated EM (HAEM) is presently distinguished from other EM eruptions based on clinical severity or the presence of target lesions and oral mucosa involvement. Here we describe 3 patients whose management was complicated by adherence to sole clinical criteria.

### CASE REPORTS

#### *Patient 1*

Patient 1 is a 28-year-old Caucasian man seen in July 1992 a few days after onset of recurrent HSV labialis with symmetrical target lesions on the hands, feet, knees and penis but no oral mucosa involvement. He was placed on a 5-day course of 40 mg prednisone/day and acyclovir 1 g daily for a week before reducing the latter drug to a maintenance dosage of 600 mg. With this treatment, the patient had no recurrent eruptions until March 1994 when he presented 5 days after an EM eruption that followed a HSV episode. Biopsy of the EM lesion on his lateral left palm showed ulcerated and focally necrotic epidermis with dyskeratotic keratinocytes adjacent to the ulcer. The underlying upper epidermis contained a band-like lymphohistiocytic infiltrate. The patient's HSV recurrences were suppressed for the next year on an oral dose of acyclovir of 400 mg daily. In June 1995 he discontinued the medication and promptly developed a recurrent HSV episode that was not accompanied by EM. Three additional episodes of recurrent HSV ensued within the next 3 months, during which the patient developed target lesions on the wrists, but was free of mucosal involvement.

#### *Patient 2*

Patient 2 is a 44-year-old Caucasian woman who had 1 episode of HSV labialis in 1989. She noticed an erythematous lesion of grouped vesicles on her hip in August 1991. Within a few days small target lesions

appeared on her lower legs but they spontaneously remitted within a week. One year later, in August 1992 the hip and leg lesions recurred. A Tzanck smear of the hip lesion was positive for multinucleated cells. The patient was placed on oral acyclovir at divided doses ranging from 1.2 to 1.6 g/day, but in spite of therapy, leg and arm lesions appeared 4 or 5 times over the next 5 years. They were not associated with a clinical recurrence of the HSV lesions, exposure to the sun, intercurrent disease, medication or reduction in the dose of daily acyclovir. Mucosal lesions were not seen. In late October 1997 the patient noticed several erythematous papules and plaques ranging from 2 to 4 mm in diameter over the lower arms and legs which were not accompanied by hip vesicles. No vesiculation was present, but the wrist lesion was crusted slightly in the centre. Target lesions were not seen. Biopsies of 2 lesions on the right dorsal wrist and hand showed an interface lichenoid lymphohistiocytic infiltration. A subepidermal bulla was seen in the 1992 specimen, but epidermal necrosis was a feature of both 1997 specimens. Significant apoptosis was present in all lesions.

#### *Patient 3*

Patient 3 is a 44-year-old Caucasian woman with a history of recurrent HSV located in the centre of her lower lip confirmed by virus isolation. At the end of September 1996 she noticed a lip lesion 4 days after ingesting naproxen for menstrual pain. It was at a different site from her HSV recurrences and was followed by a limited number of erythematous macules on her upper chest and distal hands. The following month the patient presented with a 2 mm diameter unilocular tense vesicle on the right lip commissure. An aspirate obtained within 24 h of onset was negative for virus isolation. Within 36 h, the patient developed a classical HAEM picture, with ulcerative blood crusted lesions which covered the mucosae of the entire lower and central lip and scattered areas of the upper lip. Multiple target lesions appeared rapidly on her upper chest, arms and hands. An active lesion above the left elbow was biopsied and the patient was begun on 30 mg prednisone daily. After 4 days, acyclovir (1 g/day) was added for an additional week because of poor clinical response. In late October and November, the patient had additional episodes of target eruptions, each progressively

more severe. In the last episode, she had generalized hyperaesthesia within 1 h of taking the medicine and multiple lesions on her hands, arms, chest, and back as well as vaginal and pharyngeal lesions with complete denudation of the lower lip mucosae. She then recalled the association of naproxen intake with onset of clinical disease. Oral prednisone was administered and recovery occurred within 8 days. She has subsequently discontinued all naproxen intake with no outbreak of her eruption.

#### *HSV tests*

EM lesional skin from the 3 patients was negative for HSV isolation, even by co-cultivation which is used to isolate latent neuronal virus. EM lesional skin from patients 1 and 2 was positive for HSV DNA by PCR with primers for DNA polymerase (Pol), but not other genes (1–4), suggesting that HAEM tissues do not contain the entire viral genome. HSV DNA does not persist in the skin, because skin obtained from patient 1 at 13 months after EM resolution was negative and some HSV episodes were not accompanied by HAEM. The proximal area of the same dermatome as the acute HAEM lesional skin was free of HSV DNA, suggesting that DNA is not disseminated to the skin by axonal transport. Dissemination is limited and patchy as evidenced by the absence of HSV DNA from random samples of normal skin and perilesional skin obtained during HAEM episodes. HSV DNA is probably disseminated by circulating macrophages, but it remains speculative whether acral distribution is determined by capillary lumen size or fostered by the lower ambient skin temperature. Significantly, EM lesional skin from patients 1 and 2 was positive for HSV RNA while HSV DNA-containing healed skin was negative for viral RNA, suggesting that HSV expression is involved in HAEM development (3, 4).

#### DISCUSSION

Causal diagnosis is essential for patient management. For example, patient 2 had a history of Tzanck-positive HSV lesions and PCR of her EM plaques was positive for HSV DNA. However, target lesions were the exception. By contrast, based on the presence of target lesions, patient 3 had HAEM. However, her EM lesions were negative for HSV DNA and RNA, and the initial HSV lesion suspected to be a HAEM antecedent was inconsistent with HSV recurrence and negative

for virus isolation. A drug aetiology was favoured by the history of antecedent naproxen ingestion, the increasing severity of the body eruption with successive doses of naproxen and the disappearance of the episodes after the drug was discontinued. Had our position been that target lesions are the sole pathognomonic criterion for HAEM, naproxen would have never been discontinued, with increasingly severe monthly episodes. We conclude that target lesions, oral mucosa involvement and local histopathology do not differentiate the EM aetiology. PCR for HSV DNA differentiates between various EM syndromes, and is positive in the majority of HAEM cases. Nonetheless, all criteria are not found in all cases and multiple clinical and laboratory criteria must be used in making a causal diagnosis of EM.

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