

Erythema Multiforme Caused by *Treponema pallidum* in a Young Patient with Human Immunodeficiency Virus Infection[▽]

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Erythema multiforme (EM) is usually caused by drug reactions or virus infection. We report a case of secondary syphilis presenting as EM in an HIV-infected patient, proved by immunohistochemical staining, which is rare in the literature. It is valuable to determine the etiology of EM to optimize treatment.

CASE REPORT

A 26-year-old homosexual man presented to our hospital with a 5-day history of fever episodes and pruritic skin rashes all over. The lesions had initially developed on his upper limbs and then extended to the entire body. He had been healthy except for one episode of chronic diarrhea due to *Giardia* infection that was completely treated 2 months previously and one episode of a perioral herpetic ulcer more than 6 months previously. He had no history of drug use before the occurrence of skin eruptions.

He was well oriented. His body temperature was 37.6°C, blood pressure was 128/66 mm Hg, pulse was 83 per minute, and respiratory rate was 18 per minute. On physical examination, there were numerous discrete, coin-sized annular erythemas with central dusky red areas (target lesions) over his four limbs, trunk, head, and neck (Fig. 1). The involved area was about 90% of the total body surface. Focal confluent patches and crusted erosions were also noted. The cutaneous lesions suggested erythema multiforme (EM). Other physical findings were unremarkable.

Laboratory tests disclosed a white blood cell count of 6,800/mm³ with 3% eosinophils, hemoglobin level of 11.6 g/dl, platelet count of 397,000/mm³, and C-reactive-protein level of 1.69 mg/dl. Serum creatinine and electrolyte levels and tests of liver function were normal. An enzyme-linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) was positive. HIV infection was then confirmed by Western blotting. His CD4 count was 482/mm³, and the HIV viral load was 288,000 copies/ml (Roche Diagnostics, Basel, Switzerland). A venereal disease research laboratory (VDRL) test was positive with a titer of 1:128, and a *Treponema pallidum* hemagglutination assay (TPHA) (11, 13) was reactive with a titer of 1:2,560. A serological survey for recent infections by herpes simplex virus (HSV), cytomegalovirus (CMV), and toxoplasma was negative. Bacterial and fungal cultures from blood were also negative.

A skin specimen was taken from a lesion site. Microscopically, a hematoxylin-and-eosin-stained section showed mild hyperkeratosis, mild parakeratosis, lymphocytic exocytosis, and a

few apoptotic keratinocytes in the epidermis (Fig. 2). Focal vacuolar degeneration of the basal cell layer and superficial perivascular lymphohistiocytic infiltration were also noted. The pathological features were compatible with EM. Further immunohistochemical study with an antispirochete antibody (Biocare Medical, California) (7) showed many intraepidermal spirochetes in the area of vacuolar degeneration (Fig. 3A). However, no spirochetes were detected in the normal paralesional epidermis (Fig. 3B).

After clinicopathological correlation, this HIV-infected patient was diagnosed with *T. pallidum*-induced EM. He was treated with benzathine penicillin G (2.4 million units) by intramuscular injection once weekly for 3 consecutive weeks. His fever episodes and skin lesions gradually subsided, with some desquamation and postinflammatory hyperpigmentation of the skin.

To the best of our knowledge, cutaneous manifestations of secondary syphilis presenting as EM-type eruptions are very rare in HIV-infected patients in the literature. Only one case was reported in a Japanese article in 2005, in which a 28-year-old HIV-infected Australian man was found to have EM-like eruptions with spirochetes detected by immunostaining using an anti-*Treponema pallidum* antibody (12). Two other cases of secondary syphilis-related EM-like lesions were reported for immunocompetent adults (9, 10).

It is valuable for physicians to determine the etiology of EM in order to optimize treatment. An EM-type eruption, a kind of fixed circular erythematous patch with a central necrotic change or blistering, is considered a hypersensitivity reaction to various agents, such as foreign antigens, drugs, or infectious agents (8, 14). Drugs reported to give rise to EM include antibiotics, such as sulfonamides, aminopenicillins, cephalosporins, quinolones, tetracyclines, anticonvulsants, nonsteroidal anti-inflammatory drugs, antifungal agents, and others (1, 2). Infectious agents associated with EM include viruses, bacteria, fungi, parasites, and others (1, 6). HSV infection and adverse reactions to drugs account for the most common causes of EM in HIV-infected patients (4); however, all of these etiologies were excluded in our case.

The pathology of the EM lesion in our case showed typical vacuolar interface dermatitis with scattered necrotic keratinocytes and few perivascular plasma cells. There were no eosinophils in the inflammatory infiltrates. This picture was compatible with the

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FIG. 1. Numerous coin-sized target lesions with confluent patches presenting on the patient's entire body.

diagnosis of EM, rather than the conventional papulosquamous lesion in secondary syphilis, which is characterized by psoriasiform hyperplasia and perivascular plasma cell infiltration (8, 10). Our immunohistochemical staining demonstrated abundant spi-

rochetes in the lesional epidermis (i.e., *T. pallidum*, after correlations with the serological results of VDRL and TPHA), while no spirochetes were identified in the normal paralesional area. This finding might establish the causative role of spirochetes in induc-

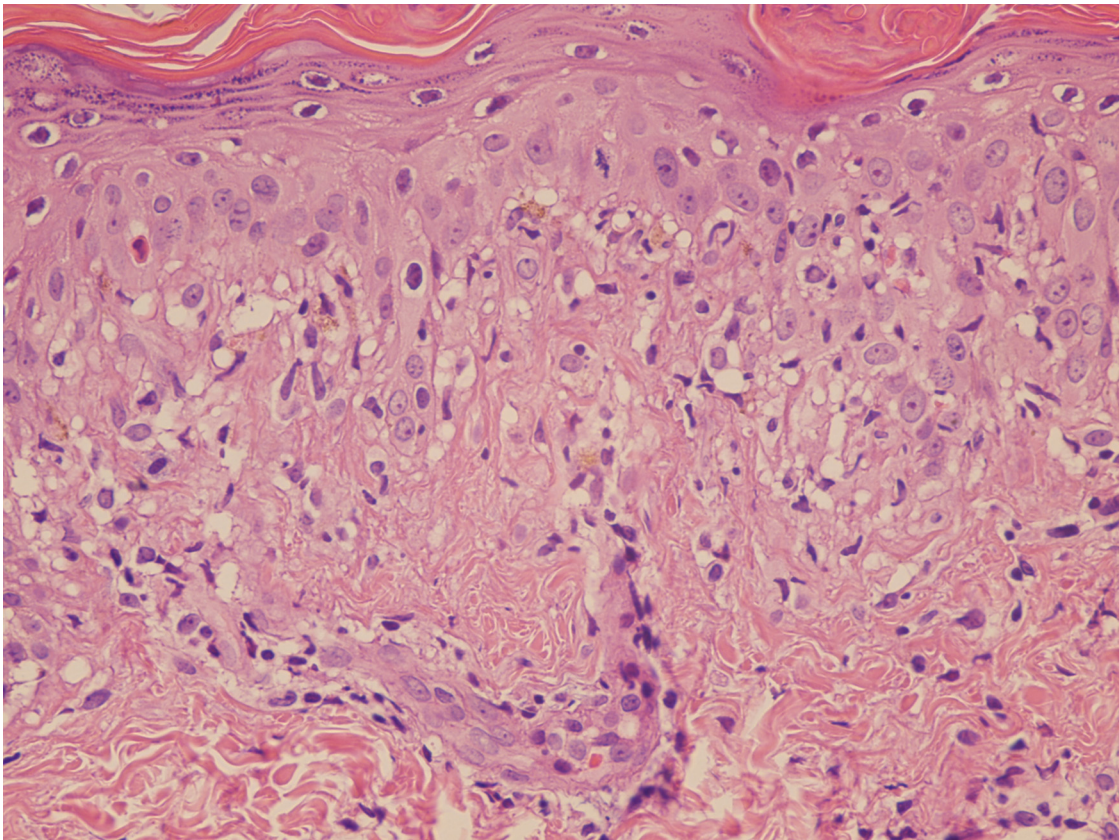


FIG. 2. Vacuolar degeneration of the basal cell layer with a few apoptotic keratinocytes and perivascular lymphohistiocyte infiltration were noted in the lesion (hematoxylin and eosin; original magnification, $\times 400$).

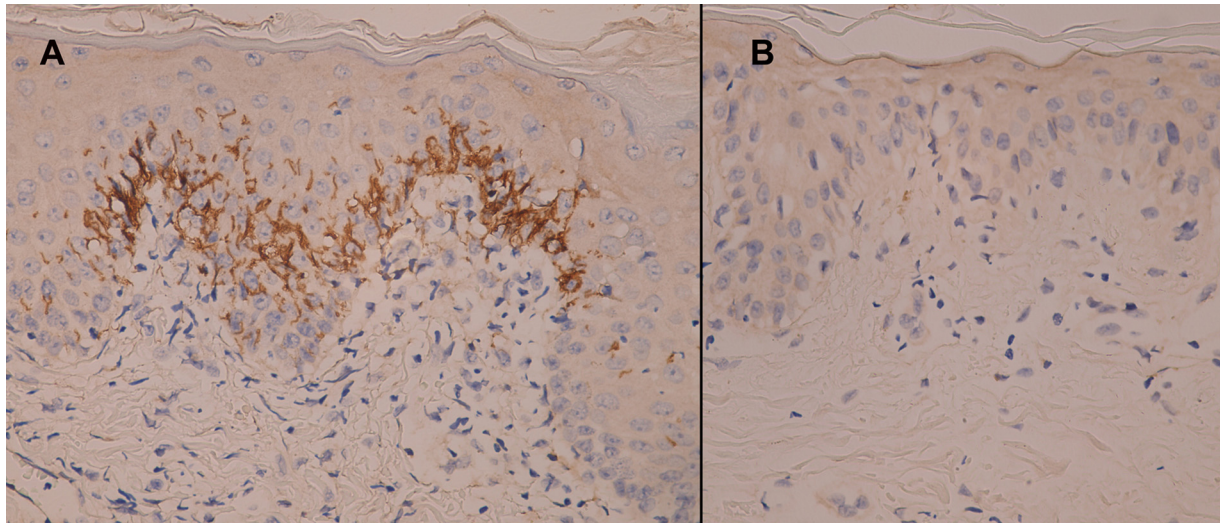


FIG. 3. (A) Abundant intraepidermal spirochetes were identified in the area of vacuolar degeneration (immunohistochemical staining with a polyclonal antibody to spirochetes; magnification, $\times 400$). (B) Spirochetes were not found in the paralesional site, which showed little inflammation in the hematoxylin-and-eosin section (immunohistochemical staining with a polyclonal antibody to spirochetes; magnification, $\times 400$).

ing the change of interface dermatitis and keratinocyte necrosis, which clinically represented the EM eruptions. As a result, this patient responded well to standard penicillin treatment, and his symptoms resolved after treatment.

The traditional method for detecting spirochetes in tissue sections is the silver stain using either the Steiner modification of the Dieterle technique or the Warthin-Starry technique, which is hard to interpret due to marked background staining (7). Immunohistochemical staining with an antispirochete antibody, which consists of a rabbit purified IgG fraction, demonstrates better sensitivity and specificity than silver staining in localizing tissue spirochetes (7). Another useful ancillary tool in the diagnosis of syphilis is PCR. PCR can detect fewer organisms and can be complementary to immunohistochemical staining in identifying *T. pallidum* from skin biopsy specimens (3, 9).

There is a high incidence of coinfection with HIV and *T. pallidum* among homosexual men (5). In HIV-infected patients with EM eruptions and elevated VDRL and TPHA titers, a diagnosis of EM-type syphilis cannot be made solely on the serology results because the eruptions may result from other causes, like viruses or drugs. Hence, we recommend a routine special stain or PCR method in order to identify spirochetes in the EM lesions of HIV-infected patients with elevated VDRL and TPHA titers.

In conclusion, we have reported a case of an HIV-infected patient with EM eruptions. Secondary syphilis should be included in the differential diagnosis when approaching such patients. Further, skin biopsy and special staining are essential for determining the causative relationship between spirochetes and EM lesions, especially when the patient's VDRL and TPHA titers are elevated. Such relationships would influence the treatment policy.

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