

Erythema Multiforme-like Secondary Syphilis in a HIV-positive Bisexual Man

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Accepted April 15, 2010.

Erythema multiforme (EM) is self-limiting inflammatory disease, characterized clinically by “target” or “iris” skin lesions, and pathologically by vacuolar alteration of basal cells with many necrotic keratinocytes in the epidermis. Pathological confirmation is often required to differentiate EM from many other diseases that may manifest targetoid lesions. EM often occurs in association with various drugs or infections, most commonly herpes simplex virus (HSV) and, less commonly, mycoplasma or other infections (1). Recent studies showed that HSV-associated EM (HAEM) begins with fragmentation of HSV DNA, followed by transport of the DNA fragments to distant skin sites by peripheral blood mononuclear cells (2, 3). Although syphilis and EM are relatively common, syphilis-associated EM appears to be very rare. We describe here a case with such rare association.

CASE REPORT

In September 2009, a 20-year-old man presented with a 4-day history of a pruritic eruption. Examination revealed oral ulcers and coalescing erythematous to violaceous maculopapules with targetoid morphology on the trunk and proximal extremities (Fig. 1). EM was the provisional diagnosis. Histopathology of a targetoid lesion showed vacuolar interface dermatitis with many necrotic keratinocytes, consistent with EM (Fig. 2A). His drug history was unremarkable. HSV serology was checked, along with the skin biopsy. Serology for HSV types 1 and 2 was IgG-positive but IgM-negative. A week later, he was found to have oral candidiasis as well as multiple scaly erythematous plaques on the palms and soles, raising the suspicion of secondary syphilis and HIV infection, which were confirmed by positive syphilis serology (VDRL 1:256; TPHA 1:5120) and HIV antibody by Western blot. CD4 count was reduced to 209/ml. Further inquiry revealed a 3-year history of unsafe bisexual contacts with multiple partners, and a penile ulcer noted in mid-July. Biopsy of a sole lesion showed psoriasiform dermatitis with infiltration of lymphocytes and neutrophils in the epidermis and papillary dermis without necrotic keratinocytes, features compatible with secondary syphilis. Immunohistochemistry (IHC) stain (1:100, CP135A, Biocare Medical®, CA, USA) demonstrated numerous spirochetes in the sole specimen (not shown) but few in the EM specimen (Fig. 2B). Additional PCR study was performed on the genomic DNA extracted from paraffin tissue sections using primers designed



Fig. 1. Acute onset of generalized, coalescing erythematous to purpuric maculopapules with targetoid morphology (inset).

for *Treponema pallidum* *polA* (4). A specific band of 377-bp product (confirmed by direct DNA sequencing) was detected in both specimens (Fig. 2C). Because of a weakly positive penicillin skin test, the patient was treated with doxycycline 100 mg twice daily for 28 days. The rash improved greatly in 5 days. Two months later the VDRL titre was 1:128.

DISCUSSION

In this report, we described a pathology-confirmed case of EM occurring in a HIV-positive bisexual young man with serology- and pathology-confirmed secondary syphilis. We are aware of only 3 other cases of EM-like lesions in association with syphilis, which were confirmed by VDRL titres of 1:32 or higher and positive demonstration of spirochete microorganisms or *T. pal-*

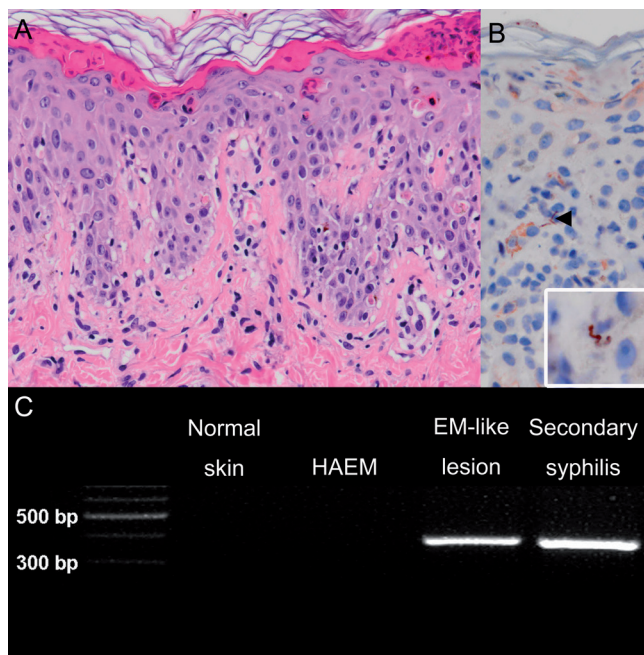


Fig. 2. (A) Histopathology of a targetoid lesion revealed vacuolar alteration of basal cells with many necrotic keratinocytes. (B) Immunohistochemical stain for *T. pallidum* demonstrated a few spirochetes in the epidermis (arrowhead and inset). (C) Polymerase chain reaction (PCR) study for *T. pallidum* *polA* detects a specific band (377 bp) in the EM-like lesion and the secondary syphilis lesion (sole), while the controls (normal skin and HAEM) show negative results. EM: erythema multiforme; HAEM: herpes simplex virus-associated erythema multiforme. (A, haematoxylin and eosin (H&E), $\times 200$; B, immunohistochemistry stain, $\times 200$; inset, $\times 400$).

lidum *polA* DNA by IHC stain or PCR study, respectively (5–7). All 3 patients were immunocompetent, and the inflammatory infiltrate in the skin lesions lacked plasma cells. Of these cases, only the case of congenital syphilis with bullous targetoid lesion (6) showed typical findings of EM; specifically, prominent vacuolization of the basal cells with many necrotic keratinocytes. The histology of the other two cases lacked these typical features (5, 7); therefore, in our view, they may represent examples of annular or targetoid secondary syphilis. Although EM is commonly associated with recurrent HSV infection, there was no history of past or recent HSV infection, or HSV skin lesions clinically in our patient. Our patient was immunocompromised with HIV infection. Interestingly, EM has been reported as a presenting manifestation of acute HIV infection on rare occasion (8, 9). However, the HIV infection in our patient was more advanced, with a low CD4 count of 209/ml, approaching the AIDS stage.

The present case is unique, in that there were two types of skin lesions that could be distinguished clinically and pathologically; namely, secondary syphilis lesions without necrotic keratinocytes on the palms and soles, and numerous targetoid lesions with typical EM histology elsewhere. The direct association between these two processes was supported by finding spirochetes and *T. pallidum*-specific *polA* DNA in both types of lesions.

The mechanism involved in the *T. pallidum*-induced EM is unclear. The finding of a few spirochetes in the EM lesion in our case suggests an antecedent bacteraemia. We surmise that the EM lesions might have either developed *de novo* or evolved from the pre-existing maculopapular lesions of early secondary syphilis. Previously, the lymphocytic infiltrate in HAEM has been shown to be CD4+ predominant, in contrast to CD8+ predominance in drug-associated EM (3). The EM lesion in our patient showed a CD8+ predominant infiltrate (not shown), which might simply reflect the patient's abnormal lymphocyte subpopulations due to his HIV infection. On the other hand, the HIV-induced altered immunity might have led to an abnormal local immune response to *T. pallidum*. In conclusion, the present case highlights that EM may occur in association with secondary syphilis and cause confusion between the two diseases. Syphilis should be considered in the differential diagnosis in HIV patients presenting with EM or targetoid skin lesions.

ACKNOWLEDGEMENT

We thank Mei-Hui Yang for performing the PCR study.

The authors declare no conflict of interest.

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