

Unusual Presentation of Secondary Syphilis in 2 HIV-1 Positive Patients

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Due to diverse clinical and histopathological presentations, diagnosis of secondary syphilis can occasionally prove challenging.¹ This is especially true in the setting of human immunodeficiency virus (HIV) infection. Variable clinical presentations of secondary syphilis in HIV disease may result in an incorrect diagnosis and an inappropriate treatment regimen.²⁻¹⁰ Similarly, the histology of secondary syphilitic lesions may show considerable variation, depending on the clinical morphology of the eruption. We report 2 cases of secondary syphilis in HIV-1-infected patients with cutaneous lesions of variable clinical presentation and an unusual lymphoid infiltrate simulating mycosis fungoides.

Case Reports

Patient 1—A 28-year-old black male, HIV-1-positive since 1996 (CD4 count, 505/cu mm), presented with a 6-week history of a nonpruritic eruption that began on the trunk and later involved the extremities and genitalia. Initially, the patient was treated with topical selenium sulfide and later with fluconazole with some clearing of the truncal lesions. The patient denied a history of recent anogenital ulcers. However, he reported having protected intercourse



FIGURE 1. Hyperpigmented macules, patches, and papules on the trunk (Patient 1).

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approximately 6 months prior to the appearance of the rash. Past medical history was significant for alopecia areata, which had been diagnosed 8 months previously and treated with intralesional triamcinolone. Rapid plasma reagin (RPR) tests, venereal disease research laboratory (VDRL) tests, and fluorescent treponemal antibody (FTA) tests were all negative on 2 occasions within the 8 months prior to onset of the rash. The patient was being treated with no other medications.

Physical examination revealed hyperpigmented macules, patches, and slightly erythematous, flat-topped papules on the trunk, distal arms, and palms (Figure 1). Genital lesions consisted of annular and nonannular, flat-topped, large, moist, slightly scaly, oval or round erythematous plaques on the scrotum (Figure 2) and a fissure in the gluteal cleft. No alopecia, oral lesions, or lymphadenopathy were noted. Skin scrapings from a truncal lesion were examined with a potassium hydroxide preparation and were negative for hyphae.

Two skin biopsies were performed from the right wrist and scrotum. The wrist biopsy revealed psoriasiform epidermal hyperplasia with hyperkeratosis and focal parakeratosis. A dense, bandlike infiltrate obscuring the dermoepidermal junction was observed in the upper dermis, and a moderately dense perivascular lymphocytic infiltrate was present in the mid and deep dermis (Figure 3). The blood vessels were dilated and lined with prominent, plump endothelial cells. The dermal infiltrate was composed of lymphocytes, histiocytes, and occasional plasma cells. Larger lymphocytes, atypical in appearance with hyperchromatic nuclei and hyperconvoluted nuclear membranes, were scattered throughout the infiltrate and showed prominent epidermotropism (Figures 4 and 5). In the epidermis, these atypical lymphocytes were dispersed as single units and small groups of 2 to 4 cells. A smaller number of large mononuclear cells with vesicular nuclei and prominent nucleoli were also noted in the dermal infiltrate.

Biopsy of the scrotal lesion revealed irregular epidermal hyperplasia with hyperkeratosis and parakeratosis. The dermal infiltrate was perivascular and lichenoid with obliteration of the dermoepidermal junction. Focal vacuolar changes of the basal cell layer, rare necrotic keratinocytes, and pigmentary incontinence were observed. Neutrophils, associated with spongiosis and microabscesses, were present in the corneal and upper spinous layers of the epidermis. The dermal infiltrate consisted of lymphocytes, histiocytes, and plasma cells. Large atypical lymphocytes, some with hyperchromatic nuclei and hyperconvoluted nuclear membranes, were scattered throughout



FIGURE 2. Flat-topped and annular large plaques on the scrotum (Patient 1).

the dermal infiltrate and extended into the epidermis. In addition, large mononuclear cells with pale eosinophilic cytoplasm, pleomorphic, vesicular nuclei, and prominent nucleoli were scattered in the dermal infiltrate. The blood vessels, like those of the wrist lesion, were dilated and lined by plump endothelial cells.

In both biopsy specimens, spirochetes were demonstrated in the dermal infiltrate with Warthin-Starry stain. These microorganisms, however, were more numerous in the genital biopsy (Figure 6). The majority of the infiltrating cells in both biopsy specimens showed immunoreactivity for T-lymphocyte markers (CD3 and UCHL-1). Only a minority of lymphocytes showed reactivity for B-cell markers (L26). About 50% to 60% of the infiltrating lymphocytes represented helper T-lymphocytes (OPD4 reactive). The large mononuclear cells with vesicular

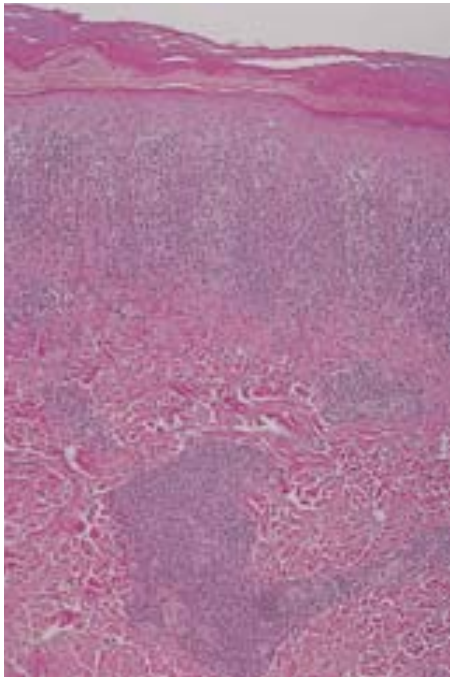


FIGURE 3. Psoriasiform epidermal hyperplasia, a dense, bandlike infiltrate in the upper dermis that obscures the dermoepidermal junction, and a moderately dense perivascular lymphocytic infiltrate in the mid and deep dermis (H&E, original magnification $\times 25$).

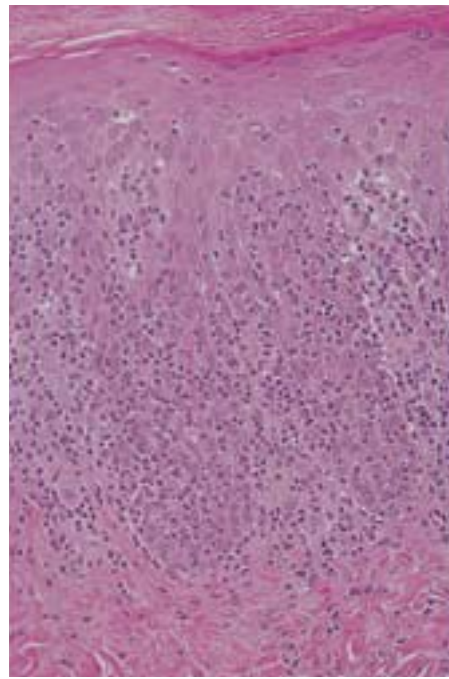


FIGURE 4. Intraepidermal atypical lymphocytes (H&E, original magnification $\times 50$).

nuclei were positive for histiocytic marker (KP1). There was no evidence of dominant monoclonal band in the T-cell receptors gamma and beta rearrangement assays (polymerase chain reaction) in either biopsy specimen.

Serologic tests revealed reactivity of the RPR and FTA tests and positive reaction of the VDRL test at a titer of 1:32, confirming the diagnosis of syphilis. Viral and wound cultures of the gluteal fissure were positive for herpes simplex virus 1 and group β -hemolytic streptococci. Cerebrospinal fluid analysis was not performed due to the patient's refusal to undergo a lumbar puncture.

The patient was treated with 2.4 million units IM of benzathine penicillin weekly and doxycycline 100 mg twice a day, both for 3 weeks. After 1 week of treatment, a marked resolution of some truncal and palmar sites and partial clearing of the genital lesions were noted. Four months later the patient presented with complete resolution of the rash, and 8 months later with normalization of the serologic tests. The gluteal fissure resolved with oral acyclovir therapy.

Patient 2—A 38-year-old black male, HIV-1-positive since 1990 (CD4 count, 200/cu mm), presented with a pruritic eruption that had developed on his trunk and, over a 1-week period, had spread to his

extremities, palms, and soles. The patient denied a history of anogenital ulceration. Past medical history was significant for oral thrush. He was being treated with zidovudine and didanosine.

Physical examination revealed multiple scaling, hyperpigmented papules, and a few plaques on the trunk and extremities, including the palms and soles. The mucous membranes were normal. Patchy alopecia of the scalp and generalized lymphadenopathy were noted.

A biopsy specimen of the upper extremity revealed acanthosis with elongation of rete ridges and focal parakeratosis. A moderately dense infiltrate consisting of lymphocytes, histiocytes, and plasma cells was observed in the upper dermis. Mild lymphocytic epidermotropism was noted. The dermal vascular proliferation with ectasia and prominent endothelial cell lining was surrounded by the lympho-plasma cell infiltrate with predominance of plasma cells, which occurred in clusters in some places. A small number of atypical lymphocytes with hyperchromatic nuclei and irregular nuclear contours were seen in the dermal infiltrate and in the epidermis. Spirochetes were demonstrated in the tissue specimen with Warthin-Starry stain.

Serologic tests revealed a reactive RPR test at a

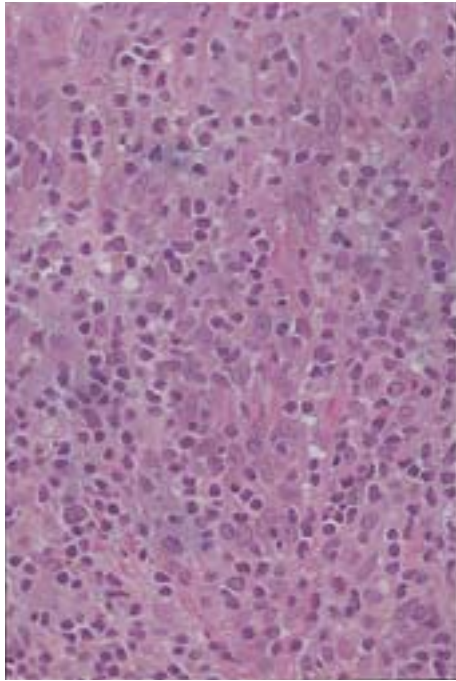


FIGURE 5. Large atypical lymphocytes with hyperchromatic nuclei and hyperconvoluted nuclear membranes in the epidermis (H&E, original magnification $\times 132$).

titer of 1:128 and a positive FTA test (3+) with normal analyses of the cerebrospinal fluid.

The patient was treated with 2.4 million units IM of benzathine penicillin weekly for 3 weeks, with resolution of the rash. Subsequently, the patient was lost to follow-up.

Discussion

A diagnosis of secondary syphilis was suspected in each of these 2 cases on the basis of clinical presentation and was confirmed by serologic tests. Each diagnosis was supported by the presence of numerous spirochetes on Warthin-Starry stain. The biopsy specimens, however, unexpectedly showed atypical lymphoid infiltrates with epidermotropism simulating mycosis fungoides.

The histopathologic features of secondary syphilis are variable depending on the clinical morphology of the lesions, such as macular, papular, or papulosquamous. There is, however, considerable overlap among these various forms.¹¹ The histopathologic features of macular lesions are nonspecific, and plasma cells may or may not be seen. In papular lesions, the lymphocytic infiltrate appears bandlike in the upper dermis and extends around the blood vessels of the deep dermis. Plasma cells are frequently present. In late papular lesions, the infiltrate is denser and more diffuse, with prominent plasma cell infiltrate. Dermal edema,

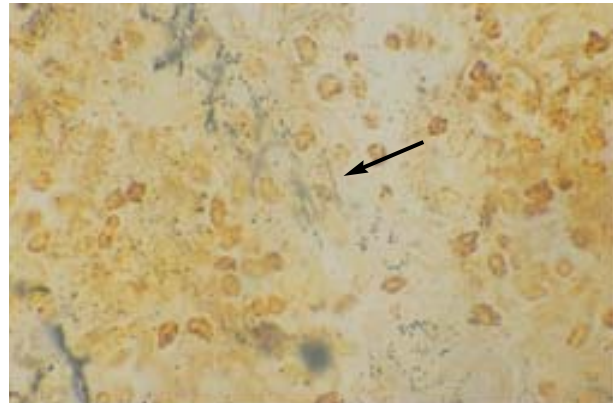


FIGURE 6. Warthin-Starry stain and spirochetes (arrow) (Warthin-Starry, original magnification $\times 250$).

perivascular and periadnexal lymphohistiocytic and plasmacytic infiltrate, vascular proliferation with dilatation, and prominent swollen endothelial cells are commonly described in syphilis.^{1,12}

According to Jeerapaet and Ackerman,¹² vascular changes are the most consistent findings in syphilis. Epidermal changes of parakeratosis; epidermal hyperplasia; lichen planuslike or psoriasiform, spongiform pustules; and exocytosis were described in about 18% to 23% of cases. Superficial and deep perivascular lymphocytic infiltrates with plasma cells and superficial bandlike infiltrate blurring the dermoepithelial junction were also common.

Despite these common findings, classically described histopathologic changes of syphilis are not always present.¹¹ Plasma cells may be absent in early stages and later appear as the disease progresses. About 33% of cases¹⁰ show an absence of plasma cells. All reported cases of HIV-1-associated secondary syphilis in which histopathologic features were described demonstrated features similar to those seen in immunocompetent patients.⁷ Findings of typical epidermal changes and dermal bandlike and superficial and deep mixed perivascular lymphoid infiltrate with plasma cells and plump endothelial cells are comparable to those seen in immunocompetent patients.^{3,5-7} No correlation was found between the nature and intensity of the inflammatory infiltrate, number of spirochetes, syphilis serologic titers, and CD4 cell counts in those cases for which these data were available.⁷

An atypical lymphoid infiltrate is described only rarely in secondary syphilis and 3 cases of secondary syphilis that exhibited a striking resemblance to malignant lymphoma were also described.⁹ The biopsies showed a dense infiltration of lymphocytes, histiocytes, and plasma cells. Scattered throughout were large, pleomorphic, monochromatic cells with hyper-

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chromatic nuclei and prominent nucleoli. Epidermotropism of mononuclear lymphoid cells with microabscesses was noted in these cases. Another case of large, hyperchromatic, mononuclear cells in a small proportion of the lymphohistiocytic and plasma cell infiltrate was noted in one biopsy of 57 cases of secondary syphilis.¹³ Patient 1 demonstrated similar features of a dense, dermal, lymphocytic infiltrate with marked epidermotropism. The lymphocytes were slightly enlarged and exhibited hyperchromatic nuclei with irregular nuclear contours resembling those seen in mycosis fungoides. In addition, large mononuclear cells with vesicular nuclei and prominent nucleoli were observed and were more numerous in the biopsy from the genital lesion. Plasma cells, infrequent in the wrist lesion, were more numerous in the genital lesion. Patient 2 demonstrated a similar lymphoid infiltrate with atypical features. But, in this case, the infiltrate was less dense and exhibited a lesser degree of atypia.

Atypical lymphoid infiltrates suggestive of mycosis fungoides have been reported in HIV-1–positive patients adjacent to skin lesions of Kaposi's sarcoma,¹⁴ in pseudolymphoma,¹⁵ and in 5 cases of T-cell cutaneous infiltrate without demonstrable T-cell clonality in 3 of 5 cases tested.¹⁶ None of these patients, however, carried a diagnosis of syphilis. To our knowledge, atypical lymphoid infiltrates have not been reported in secondary syphilis lesions in the setting of HIV-1 disease.

In summary, our 2 cases emphasize that atypical lymphoid infiltrates simulating mycosis fungoides can occur in secondary syphilis lesions in the setting of HIV-1 disease. The reports of atypical clinical presentations of secondary syphilis in patients with HIV-1 disease should prompt clinicians to obtain Warthin-Starry stains and syphilitic serologic tests when atypical lymphoid cutaneous infiltrates are found. Not doing so can lead to a missed diagnosis of syphilis and result in inappropriate treatment. Although rare, mycosis fungoides has also been reported in the setting of HIV-1 disease,^{17,18} and further histopathologic, immunohistochemical, and molecular studies would be warranted to also rule out this possibility.

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