Seronegative Secondary Syphilis in 2 Patients Coinfected With Human Immunodeficiency Virus

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Critical Situations: Dermatology in the Acute Care Setting

REPORT OF CASES

CASE 1

A 45-year-old man infected with the human immunodeficiency virus (HIV) presented with a 3-month history of violaceous oval macules and papules on the trunk and extremities (Figure 1) as well as multiple lichenoid papules over the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints and elbows (Figure 2). Brownish-red scaly patches were observed on the palms. His most recent CD4 cell count was 158 cells/mL, and his viral load was 175,102 copies/mL.

The patient’s history was significant for Kaposi sarcoma, treated with liposomal doxorubicin, and syphilis, which was treated 15 years earlier with 3 courses of intramuscular penicillin G. The patient had recently developed hypercholesterolemia, induced by highly active antiretroviral therapy, and subsequently had a myocardial infarction. Secondary syphilis was suspected, but findings from the rapid plasma regain (RPR) test, performed with appropriate dilution to rule out a prozone reaction, were negative.

Biopsy specimens of the abdomen and dorsal surface of the right hand both revealed a bandlike and perivascular lymphohistiocytic infiltrate with scattered plasma cells, acanthosis, and exocytosis (Figure 3). Warthin-Starry staining revealed several silver-impregnated microorganisms (Figure 4). Spirochetes were not seen on examination of the retina or cerebrospinal fluid. A treponemal-specific serologic test, such as the fluorescent treponemal antibody absorption test, was deferred because this patient had a history of syphilis infection. The patient experienced rapid and complete resolution of his cutaneous disease with 3 weekly courses of intramuscular penicillin G at a dose of 2.4 million IU.

CASE 2

A 36-year-old HIV-positive man presented to the dermatology clinic with a 1-year history of pruritic weeping buttock lesions. He had been previously treated by his primary care physician with topical corticosteroids and had completed a 7-day course of famciclovir without resolution. His most recent CD4 cell count was 213 cells/mL, and his viral load was “undetectable” (<50,000 copies/mL). His medical history was significant for treatment of genital herpes with acyclovir in 2002. The patient had negative RPR findings in 2001.

Physical examination revealed 4 moist erythematous nodules on the buttock and in the intergluteal folds (Figure 5). There were no other remarkable cutaneous or oral lesions. A viral culture was negative for herpes simplex virus, and the patient was empirically treated with a 7-day course of valacyclovir without improvement.

A skin biopsy specimen showed a superficial and deep perivascular and lichenoid lymphoplasmacytic infiltrate with eosinophils and histiocytes. The immunoperoxidase stain for Treponema pallidum revealed multiple microorganisms in dilated endothelial cells (Figure 6). Warthin-Starry staining also revealed silver-staining fragments consistent with spirochetal organisms (Figure 7).

Serologic findings at the County Health Department for RPR and microhemagglutination assay for T pallidum were negative. The cerebrospinal fluid was not evaluated. The patient received his first course of treatment with 2.4 MU of intramuscular penicillin G, and subsequent treatment was continued at the County Health Department.

Treponema pallidum is a fastidious organism that does not grow in routine laboratory cultures. Therefore, in immunocompetent patients, diagnosis of secondary syphilis relies largely on nontreponemal serologic tests such as the RPR or the Venereal Disease Research Laboratory that measure serum IgG and IgM antibody reactivity to a cardiolipin-cholesterol-lecithin antigen. These nontreponemal tests are virtually 100% sensitive in immunocompetent patients with secondary syphilis. However, the sensitivity of these serologic assays may be lowered in immunosuppressed individuals, notably in those coinfected with HIV, thus complicating the diagnosis of secondary syphilis. Given that serologic testing for the diagnosis of secondary syphilis may be unreliable in patients coinfected with HIV, it is essential to perform a skin biopsy in patients who test serologically negative but remain clinically suspect.

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Syphilis, the "great imitator," has reemerged as a public health threat. Since reaching a low in 2000, the rates of primary and secondary syphilis are again on the rise, almost exclusively among men who have sex with men. Analysis of the National Surveillance Data for 2002 by the Centers for Disease Control and Prevention reveals that the number of reported cases of primary and secondary syphilis increased by 12.4%. Furthermore, coinfection with HIV is also increasing, making diagnosis of syphilis even more elusive in that HIV modifies the natural history and clinical manifestations of this disease.

Coinfection with HIV can also affect the results of non-treponemal and treponemal tests owing to altered immunologic responses to T pallidum. This may result in false-negative or false-positive serologic findings. Biological false-positive reactions in HIV-seropositive patients may result from polyclonal B-cell activation in early HIV infection. In late HIV infection, false-negative results are seen as a result of dysfunctional B-cells that fail to mount an appropriate antibody response against newly encountered T pallidum antigens. The frequency of this occurrence, however, is unknown.
Several case reports have described HIV-infected patients diagnosed as having seronegative secondary syphilis on the basis of *T pallidum* detection in cutaneous biopsy specimens by electron microscopy and Warthin-Starry stain. Given that the rates for syphilis are again on the rise in this country, we remind clinicians of the diagnostic challenge of this reemerging public health threat by presenting 2 cases of HIV-infected patients diagnosed as having seronegative secondary syphilis on the basis of spirochete identification via Warthin-Starry silver stain and/or the immunoperoxidase technique.

The Centers for Disease Control and Prevention recommends the use of direct microscopic examinations of lesion or biopsy material when clinical findings suggest syphilis but serologic test results are negative. Histologically, the usual method for detecting spirochetes in tissue sections is with the Warthin-Starry silver stain. This method, however, can be technologically difficult, time-consuming, and challenging to interpret. Electron microscopy can also be used to detect *T pallidum* in tissue, but this requires the availability and associated expenses of an electron microscope, which limits this method of detection. As demonstrated in the present article, one valuable method to detect *T pallidum* in tissue sections is the use of immunoperoxidase antibodies. In a study of biopsy specimens taken from patients with secondary syphilis, Phelps et al reported an immunoperoxidase staining sensitivity of 90%, which was equivalent to pathology findings (90%) and more sensitive than conventional silver staining (60%) and serologic analyses (70%).

Coinfection with syphilis and HIV is on the rise, and failure to accurately diagnose secondary syphilis can lead to devastating clinical sequelae for patients and their partners. Thus, dermatologists should perform a tissue biopsy to establish diagnosis when faced with this clinical dilemma.

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REFERENCES


Submissions

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