Secondary Syphilis in an Immunocompromised Kidney Transplant Recipient

Chelsy L. Marty, MD; John L. Snow, MD

As an increasing number of patients undergo successful solid organ transplantation, immunocompromised patients are encountered more commonly in the private practice office. Thus the evaluation of such patients should take into consideration the possibility of infection. We report the case of a kidney transplant recipient who took standard immunosuppressive therapy and presented with cutaneous findings of secondary syphilis. Skin biopsy and serologic testing confirmed the diagnosis. The patient was treated according to current guidelines from the Centers for Disease Control and Prevention. We present a brief review of the clinical presentation, pathologic findings, diagnostic methods, and treatment options for syphilis.

Cutis. 2011;88:284-289.

Case Report

A 44-year-old man presented to the dermatology service with an asymptomatic rash of 4 to 6 weeks' duration. The rash initially developed on the shoulders and chest and then subsequently spread to the entire torso, arms, legs, and face. The patient was asymptomatic. In response to directed questioning, he reported having had a small ulceration on the glans penis that had healed spontaneously 1 to 2 weeks prior to the onset of the rash. He had participated in 1 unprotected sexual contact with a new male partner approximately 8 weeks before he was seen in the clinic.

The patient's clinically significant medical history included a kidney transplant 15 months prior to presentation and ongoing treatment with immunosuppressant medication. He was taking tacrolimus and mycophenolate mofetil and had received 2 recent courses of intravenous prednisolone because of renal biopsy findings suggestive of rejection. He had 1 documented febrile episode after the rash developed that spontaneously resolved.

Physical examination demonstrated pink to light red papules and oval plaques, some with fine white scale, scattered across the face, torso (Figure 1), arms, and legs. They did not appear to follow lines of Blaschko. The dorsal hands and feet showed circular, bright pink, scaling patches (Figure 2). The palms showed a few circular pink patches with scale. The soles of the feet and oral mucosa were uninvolved. The penis showed no evidence of rash, erosion, or ulceration.

Secondary syphilis was suspected and a punch biopsy was obtained. Histologic findings

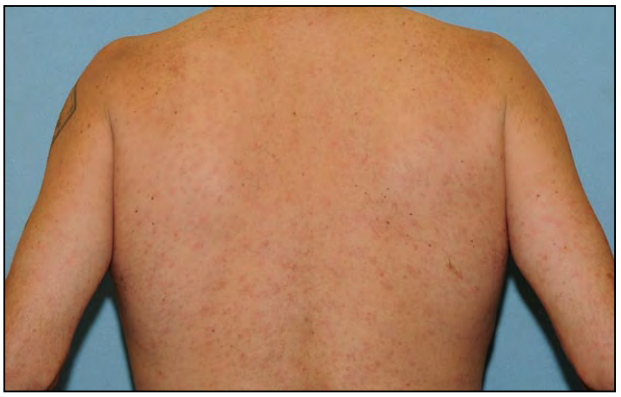

Figure 1. Pink to light red papules and oval plaques with fine white scale were scattered across the patient's back.

From the Department of Dermatology, Mayo Clinic, Jacksonville, Florida.
The authors report no conflict of interest.
Correspondence: Chelsy L. Marty, MD, First Coast Dermatology Associates, 3200 S 3rd St, Ste 200, Jacksonville Beach, FL 32250.

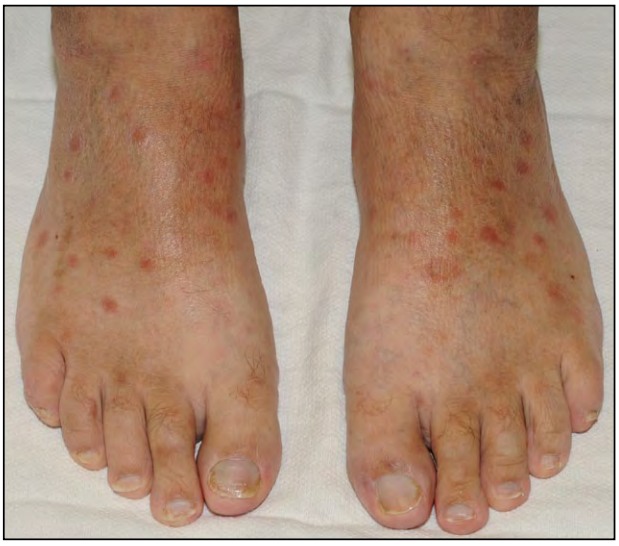

Figure 2. Circular, pink, scaling patches were evident on the patient's feet.

demonstrated a lichenoid interface dermatitis with both superficial and deep perivascular lymphohistiocytic and plasmacytic infiltrate (Figure 3). Numerous spirochetes were demonstrated by immunoperoxidase staining (Figure 4). A rapid plasma reagin test, which had been nonreactive 2 months prior, was 1:1024. Syphilis IgG and IgM antibodies were positive. A test for human immunodeficiency virus (HIV) was negative. The patient had a questionable history of an allergic reaction to penicillin and was treated with doxycycline hyclate twice daily for 4 weeks. Six months after completion of therapy, the patient's rapid plasma reagin result had declined 4-fold and was deemed an appropriate response to therapy.

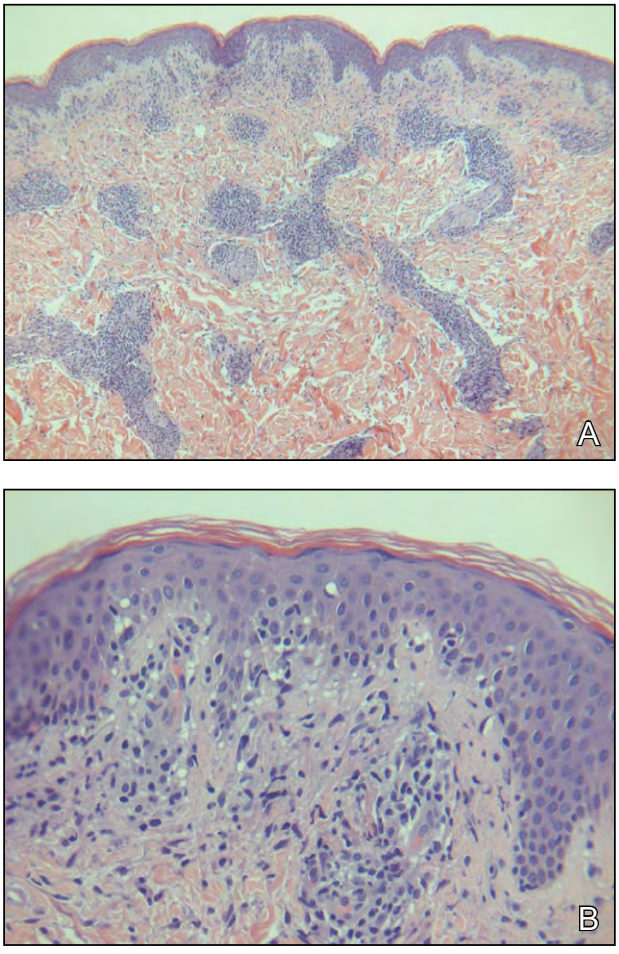

Figure 3. Histologic findings identified lichenoid interface dermatitis with both superficial and deep inflammation (A) and infiltrate consisting of lymphocytes and plasma cells (B)(H&E; original magnifications ×40 and ×200, respectively).

Comment

Syphilis has been written about for centuries, but its association with *Treponema pallidum* was not known until 1905 when Schaudinn and Hoffmann[1] first demonstrated spirochetes in smears of fluid from secondary syphilitic lesions, which was followed by a serum reaction test developed in 1906 by Wassermann et al[2] to aid diagnosis. The United States began to require the reporting of syphilis in 1941 and the decade with the highest reported incidence since then was the 1940s.[3] With the advent of penicillin and public health education about sexually transmitted diseases, the incidence substantially decreased in the following decade to less than 4 cases per 100,000 individuals; since the mid-1950s, the rates have seemed to cycle in recurrent peaks and troughs every 7 to 10 years.[3] The incidence declined to an all-time low

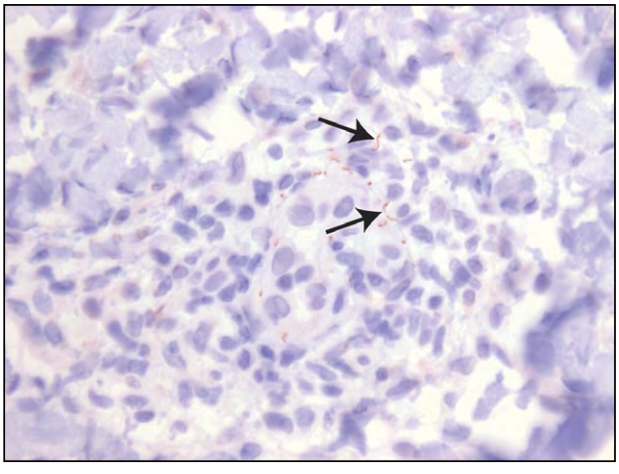

Figure 4. Spirochetes (arrows) from a skin biopsy specimen were demonstrated by immunoperoxidase stain (original magnification ×400).

of 2.1 cases per 100,000 individuals in 2000 but has again begun to increase.[4] Men having sex with men account for 65% of all primary and secondary syphilis cases in the United States.[5] These men also have high coinfection rates of other sexually transmitted diseases or HIV.[6]

Transmission—Treponema pallidum is transmitted through compromised skin or intact mucosa; it can be transmitted by vaginal or anal intercourse, by oral sex, or by kissing near an infectious lesion.[7] On the basis of sex partner tracing studies and prospective studies of prophylactic treatment, transmission rates of primary, secondary, early latent, and late latent syphilis have been estimated to be 18% to 88%. A critical review of prior studies indicated a reported transmission probability per partner of approximately 60%.[8] The second most common mode of transmission is from mother to fetus in utero.[7] The risk from needle sharing appears to be low.[9]

Clinical Presentation—The clinical manifestations of syphilis traditionally have been divided into 3 stages: primary, secondary, and tertiary. After an average incubation period of 3 weeks (range, 3–90 days), a painless, indurated, nonpurulent ulcer or chancre develops at the inoculation site.[7] Depending on the location, the lesion may go unnoticed by the patient. The most common location in men is the penis, usually the coronal sulcus or glans penis; lesions often are found in the anogenital region in homosexual men.[10] The labia majora is the most common location in women. Regional lymphadenopathy often is present. The chancre heals spontaneously in 3 to 6 weeks.[10] As many as 60% of patients never recall having had an ulceration or any other indication of primary syphilis.[11]

Secondary syphilis develops 2 to 12 weeks (range, 2 weeks to 6 months) after initial inoculation; during this time, the primary chancre may still be present or it may have spontaneously healed long before any findings of secondary syphilis.[11] A skin rash is the most common presenting sign of secondary syphilis and it may mimic many other dermatologic conditions. The most characteristic eruption is an asymptomatic, symmetric, macular rash on the torso, palms, or soles. Patients also may have persistent generalized lymphadenopathy, malaise, patchy alopecia, pharyngitis, or mucous membrane lesions.[12]

Latent syphilis is the stage that occurs after symptoms of secondary syphilis have resolved; the patient is asymptomatic but serologic testing is positive. The latent stage lasts until patients undergo therapeutic cure or relapse back to secondary syphilis, or until tertiary syphilis develops.[11] Latent syphilis is divided into early latent infection (lasting up to 1 year) and late latent infection (lasting longer than 1 year but with the patient no longer considered contagious).[13] Patients with early latent disease are still considered infectious because approximately 25% relapse to secondary syphilis.[11]

Tertiary syphilis develops in 15% to 40% of patients who are not treated.[14] Tertiary syphilis includes cardiovascular syphilis, neurosyphilis, and late benign syphilis. Cardiovascular syphilis typically develops 10 to 30 years after initial infection; the most common manifestation is syphilitic aortitis of the ascending aorta.[15]

The clinical manifestations of neurosyphilis are quite varied and often have overlapping stages and presentations. After *T pallidum* infection occurs, the cerebrospinal fluid is affected in approximately 25% of patients.[16] There are then 4 possible outcomes: spontaneous resolution, asymptomatic neurosyphilis, acute meningeal syphilis, or progression to late neurosyphilis. Asymptomatic neurosyphilis is characterized by abnormal laboratory findings in cerebrospinal fluid in the absence of any neurologic signs. Patients with acute meningeal syphilis typically present with severe headache, confusion, nausea, vomiting, and a stiff neck, but no fever. Cranial nerves also can be involved.[11] Patients with late parenchymal neurosyphilis present with general paresis or tabes dorsalis (ie, parenchymatous neurosyphilis). Tabes dorsalis is caused by demyelinization of the posterior column, dorsal roots, and dorsal root ganglia. Patients often report lightning pains in the feet, ankles, and calves; paresthesia; sensory ataxia; pupillary changes, including the classic Argyll-Robertson pupil; or impairment of position and vibration sense that leads to a wide-based gait and positive Romberg sign.[11]

The characteristic finding in late benign syphilis is gumma. Gummata have been described as painless, firm, dusky red nodules ranging in diameter from a few millimeters to several centimeters.[17] They can develop in any organ but most commonly occur in the skin, bone, liver, brain, or heart.[11] Skin findings are found in 70% of patients with late benign syphilis.[10] These lesions can be granulomatous nodules, psoriasiform plaques, or cutaneous gummata that can eventually ulcerate.

Diagnosis—Syphilis usually is suspected on the basis of clinical findings, and diagnosis can be confirmed by examining available tissue specimens and conducting serologic testing. Biopsy of a skin lesion can show findings suggestive of cutaneous syphilis. Spirochetes can be seen with Warthin-Starry silver stain, but background artifact often hinders the detection rate. Oral mucosal biopsies may contain nontreponemal spirochetes that also would highlight with silver stain. Immunohistochemical staining for *T pallidum* is more specific and more sensitive.[18,19]

Polymerase chain reaction also can be used to detect *T pallidum* in skin, serum, cerebrospinal fluid, amniotic fluid, and lesion exudate; however, it is not as sensitive or as specific as immunohistochemical stains.[20] Traditionally, confirmation of *T pallidum* was by direct visualization of treponemes by dark-field microscopy and direct fluorescent antibody. The availability of these techniques is limited in many practices because they require specialized equipment; sensitivity also is limited by the investigator's expertise.

Serologic testing is divided into nontreponemal and treponemal testing. Nontreponemal testing methods include the rapid plasma reagin and VDRL tests; both use the reactivity of human IgG and IgM antibodies to *T pallidum* with the synthetic cardiolipin-lecithin-cholesterol antigen.[21] These tests are best used for initial screening, with subsequent specific treponemal tests to confirm the diagnosis. The sensitivity of nontreponemal tests depends on the stage of syphilis at the time of testing. In primary syphilis, 30% of patients may have a negative test on the initial visit.[22] In secondary syphilis, the sensitivity of nontreponemal tests approaches 100%, but in late syphilis, sensitivity decreases. False-positives are categorized as acute false-positives (reactions of ≤6 months' duration) or chronic false-positives (reactions of >6 months' duration). The causes of an acute false-positive include hepatitis, infectious mononucleosis, chickenpox, pregnancy, viral infection, and laboratory error. The causes of a chronic false-positive include connective-tissue disease, aging, leprosy, and malignancy.[22]

Treponemal tests involve the detection of antibodies directed against treponemal components and are used to verify reactivity in nontreponemal tests. The most commonly used tests are the fluorescent treponemal antibody absorption test and the microhemagglutination–*T pallidum* test. The sensitivity of treponemal tests depends on the stage of syphilis the patient has when tested. In primary syphilis, the sensitivity ranges from 72% to 100%; in secondary syphilis, it approaches 100%; and in early latent and late latent syphilis, it ranges from 71% to 98%.[22] Transient false-positive results have been estimated to occur in approximately 1% of the general population.[23] Treponemal tests are therefore recommended for confirmation testing only rather than for screening, and then only within the context of a reactive nontreponemal test.[22]

Treatment—Patients in the early stages of syphilis are treated with intramuscular penicillin G benzathine. Oral penicillin is not recommended.[24] For patients with a penicillin allergy, alternate therapies include cephalosporins, tetracyclines, and erythromycin, depending on the clinical situation.[11]

At initiation of treatment, patients should be closely monitored for potential development of the Jarisch-Herxheimer reaction, which typically occurs within the first 24 hours.[7] Affected patients become febrile, and malaise, headaches, and myalgia may develop. Other possible associated conditions include pharyngitis, leukocytosis, and local and systemic exacerbation of the stage of syphilis being treated. Treatment with analgesics/antipyretics may help alleviate symptoms, but the routine use of corticosteroids is not recommended.[11]

Serologic tests are used to monitor treated patients for cure. Because treponemal tests often remain positive for life, nontreponemal tests are used to monitor patients for treatment success and are administered sequentially, typically at 6 and 12 months. Even in untreated patients, nontreponemal antibodies will gradually decrease over time, with approximately 30% of patients who have syphilis becoming seronegative for the antibodies during their lifetime.[21] With treatment, the decrease in nontreponemal antibodies occurs more rapidly, and a 4-fold decrease in titer is considered an adequate response to treatment 6 months after treatment of early syphilis (ie, primary, secondary, and early latent) or 12 months after treatment of late syphilis.[24]

HIV Coinfection—Coinfection with HIV has raised new questions about the rates of transmission, the adequacy of laboratory studies for diagnosis, and the clinical course and treatment of syphilis in HIV-positive patients. In the United States, 16% of all patients with syphilis and 28% of men who have been diagnosed with it also are HIV positive.[25,26] An open genital ulcer in primary syphilis may facilitate the acquisition and transmission of HIV because of impaired natural mucosal and epithelial barriers.[27] Syphilis has been estimated to increase HIV acquisition 2- to 4-fold and HIV transmission 2- to 9-fold.[28]

The clinical presentation of a syphilis patient who is coinfected with HIV is generally similar to a patient who is HIV negative.[11] However, patients with neurosyphilis may have a different clinical presentation. It has been suggested that neurosyphilis may occur more frequently and progress more rapidly in HIV-infected patients.[21] For this reason, some groups advocate that HIV-infected patients who are coinfected with syphilis should receive a lumbar puncture in the initial evaluation to evaluate for the possibility of neurosyphilis,[29] which does not follow current Centers for Disease Control and Prevention recommendations for cerebrospinal fluid evaluation in patients infected with syphilis.[24] As a result, there is controversy regarding the role of lumbar punctures in the initial evaluation and subsequent follow-up examinations of HIV-positive patients with serologic

findings of reactive syphilis.[11] For the initial diagnosis, the interpretation of serum nontreponemal and treponemal serologic tests in patients with suspected syphilis is the same as patients with HIV coinfection.[21] Treatment recommendations for a patient with syphilis who is coinfected with HIV are the same as a patient with syphilis who is HIV negative. There currently is some controversy about the treatment of neurosyphilis in HIV-positive patients because more treatment failures have been found in this subgroup despite the use of currently recommended therapies.[11] The concentrations of nontreponemal titers also are more variable in HIV-infected patients and are not reliable for a definitive determination of treatment success. It also may take longer for these patients to demonstrate a decrease in titers after appropriate treatment.[21]

Organ Transplant and Immunosuppression—There have been prior reports of syphilis occurring in 6 organ transplant recipients.[30-35] Three cases developed after a liver transplant,[30,33,34] 2 after a kidney transplant,[31,35] and 1 after a heart transplant.[32] All 6 patients had skin findings of either genital ulceration or the characteristic skin rash common in secondary syphilis. All but 1 patient had laboratory or histopathologic evidence of syphilitic hepatitis.

Our patient presented with the widespread macular rash of secondary syphilis. Directed questioning revealed a recent history of a new sexual partner and a resolved genital lesion. There were no laboratory changes suggestive of syphilitic hepatitis.

Immunosuppressed patients should be treated according to guidelines from the Centers for Disease Control and Prevention, which are based on the syphilis stage. As mentioned, the current recommendation for treatment of the early stages of syphilis is intramuscular penicillin G benzathine.[24] It is unclear if an immunocompromised patient should receive additional therapy. Patients should be closely followed to determine adequate serologic response. Our patient had a history of a penicillin allergy and was treated with doxycycline for 4 weeks.

Conclusion

Dermatologists should consider syphilitic infection in the differential diagnosis of any immunosuppressed patient who presents with skin lesions or a rash. This case illustrates the more classic cutaneous findings of secondary syphilis with a maculopapular eruption and circular scaling patches on the palms.

REFERENCES

1. Schaudinn F, Hoffmann E. Vorlaufiger bericht uber das vorkommen von spirochaeten in syphilitischen krankheitsprodukten und bei papillomen. *Arbeiten K Gesundheits*. 1905;22:527-534.
2. Wassermann von A, Neisser A, Bruck C. Eine serodiagnostische reaktion bei syphilis. *Dtsch Med Wochenschr*. 1906;32:745-746.
3. Nakashima AK, Rolfs RT, Flock ML, et al. Epidemiology of syphilis in the United States, 1941-1993. *Sex Transm Dis*. 1996;23:16-23.
4. Centers for Disease Control and Prevention (CDC). Primary and secondary syphilis—United States, 2000-2001. *MMWR Morb Mortal Wkly Rep*. 2002;51:971-973.
5. Centers for Disease Control and Prevention (CDC). Primary and secondary syphilis–United States, 2003-2004. *MMWR Morb Mortal Wkly Rep*. 2006;55:269-273.
6. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2004 Supplement: Gonococcal Isolate Surveillance Project (GISP) Annual Report—2004. Atlanta, GA: US Department of Health and Human Services; December 2005. http://www.cdc.gov/std/gisp2004/GISP2004.pdf. Accessed November 21, 2011.
7. Kent ME, Romanelli F. Reexamining syphilis: an update on epidemiology, clinical manifestations, and management [published online ahead of print January 22, 2008]. *Ann Pharmacother*. 2008;42:226-236.
8. Garnett GP, Aral SO, Hoyle DV, et al. The natural history of syphilis: implications for the transmission dynamics and control of infection. *Sex Transm Dis*. 1997;24:185-200.
9. Jose B, Friedman SR, Neaigus A, et al. Possible parenteral transmission of syphilis among drug injectors. Presented at: 121st Annual Meeting of the American Public Health Association; October 24-28, 1993; San Francisco, CA. Abstract 3016.
10. Lautenschlager S. Cutaneous manifestations of syphilis: recognition and management. *Am J Clin Dermatol*. 2006;7:291-304.
11. Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. *Clin Microbiol Rev*. 1999;12:187-209.
12. Wolff K, Goldsmith LA, Katz SI, eds. Fitzpatrick's Dermatology in General Medicine. 7th ed. New York, NY: McGraw-Hill Medical; 2008.
13. World Health Organization. Guidelines for the Management of Sexually Transmitted Infections. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf. Accessed November 21, 2011.
14. Clark EG, Danbolt N. The Oslo study of the natural course of untreated syphilis: an epidemiologic investigation based on a re-study of the Boeck-Bruusgaard material. *Med Clin North Am*. 1964;48:613-623.
15. Cole HN, Usilton LJ, Moore JE, et al. Cooperative clinical studies in the treatment of syphilis: the effect of specific therapy on the prophylaxis and progress of cardiovascular syphilis. *J Am Med Assoc*. 1937;108:1861-1866.

16. Marra CM, Gary DW, Kuypers J, et al. Diagnosis of neurosyphilis in patients infected with human immunodeficiency virus type 1. *J Infect Dis*. 1996;174:219-221.
17. Zeltser R, Kurban AK. Syphilis. *Clin Dermatol*. 2004;22:461-468.
18. Hoang MP, High WA, Molberg KH. Secondary syphilis: a histologic and immunohistochemical evaluation. *J Cutan Pathol*. 2004;31:595-599.
19. Lee WS, Lee MG, Chung KY, et al. Detection of *Treponema pallidum* in tissue: a comparative study of the avidin-biotin-peroxidase complex, indirect immunoperoxidase, FTA-ABS complement techniques and the darkfield method. *Yonsei Med J*. 1991;32:335-341.
20. Buffet M, Grange PA, Gerhardt P, et al. Diagnosing *Treponema pallidum* in secondary syphilis by PCR and immunohistochemistry [published online ahead of print June 7, 2007]. *J Invest Dermatol*. 2007;127:2345-2350.
21. Zetola NM, Engelman J, Jensen TP, et al. Syphilis in the United States: an update for clinicians with an emphasis on HIV coinfection. *Mayo Clin Proc*. 2007;82:1091-1102.
22. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev*. 1995;8:1-21.
23. Goldman JN, Lantz MA. FTA-ABS and VDRL slide test reactivity in a population of nuns. *JAMA*. 1971;217:53-55.
24. Centers for Disease Control and Prevention, Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep*. 2006;55:1-94.
25. Centers for Disease Control and Prevention (CDC). Primary and secondary syphilis among men who have sex with men—New York City, 2001. *MMWR Morb Mortal Wkly Rep*. 2002;51:853-856.
26. Blocker ME, Levine WC, St Louis ME. HIV prevalence in patients with syphilis, United States. *Sex Transm Dis*. 2000;27:53-59.
27. Gadkari DA, Quinn TC, Gangakhedkar RR, et al. HIV-1 DNA shedding in genital ulcers and its associated risk factors in Pune, India. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18:277-281.
28. Chesson HW, Pinkerton SD, Voigt R, et al. HIV infections and associated costs attributable to syphilis coinfection among African Americans. *Am J Public Health*. 2003;93:943-948.
29. Marra CM. Déjà vu all over again: when to perform a lumbar puncture in HIV-infected patients with syphilis. *Sex Transm Dis*. 2007;34:145-146.
30. Wolf SC, Kempf VA, Tannapfel A, et al. Secondary syphilis after liver transplantation: case report and review of the literature. *Clin Transplant*. 2006;20:644-649.
31. Taniguchi S, Osato K, Hamada T. The prozone phenomenon in secondary syphilis. *Acta Derm Venereol*. 1995;75:153-154.
32. Farr M, Rubin AI, Mangurian C, et al. Late syphilis in a cardiac transplant patient. *J Heart Lung Transplant*. 2006;25:358-361.
33. Camara B, Kamar N, Bonafe JL, et al. Syphilis-related hepatitis in a liver transplant patient. *Exp Clin Transplant*. 2007;5:724-726.
34. Petersen LR, Mead RH, Perlroth MG. Unusual manifestations of secondary syphilis occurring after orthotopic liver transplantation. *Am J Med*. 1983;75:166-170.
35. Johnson PC, Norris SJ, Miller GP, et al. Early syphilitic hepatitis after renal transplantation. *J Infect Dis*. 1988;158:236-238.