Syphilitic Palmoplantar Keratoderma and Ocular Disease: A Rare Combination in an HIV-Positive Patient

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The estimated time to complete this activity is 1 hour.

GOAL

To understand atypical manifestations of concomitant infection with syphilis and human immunodeficiency virus (HIV) to better manage patients with the conditions

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Recognize the clinical symptoms and signs of syphilis, particularly in patients with HIV.
2. Discuss laboratory testing for syphilis and inconsistencies seen in patients with HIV.
3. Differentiate among treatment regimens based on cutaneous findings, extracutaneous disease, HIV status, and allergies.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and general practitioners.

CME Test and Instructions on page 311.

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Approximately 349 million individuals worldwide are actively infected with syphilis. The incidence of syphilis in North America and Europe is low but has been rising in recent years. The rate of concomitant infection with human immunodeficiency virus (HIV) and syphilis also has been increasing. Concomitant infection with HIV can cause syphilis to have atypical characteristics. These atypical

findings can involve the skin as well as organs that rarely are affected in HIV-negative individuals such as the eyes. We present a case of syphilis causing palmoplantar keratoderma and ocular disease in a patient with HIV infection, and discuss the differences in diagnosis and treatment of patients with both diseases.

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Syphilis is a sexually transmitted disease caused by the organism *Treponema pallidum* that can affect nearly every organ system in the body.[1,2] Rates of concomitant infection of human immunodeficiency virus (HIV) and syphilis have been increasing.[3,4] Diagnosis in this patient population can be difficult. Patients with HIV and syphilis have a higher prevalence of persistent positive and false-negative test results for syphilis when assessed with both the standard tests, including the rapid plasma reagin (RPR) and VDRL test, and the more specific antibody tests, such as the microhemagglutination assay–*T pallidum* (MHA-TP) for *T pallidum* antibodies and fluorescent treponemal antibody absorption test.[4-7] The cutaneous characteristics of syphilis can be atypical in a patient who is HIV positive.[2] Organs that rarely are affected in HIV-negative individuals, such as the eyes, are more commonly affected in HIV-positive patients.[8,9] We present a case of a rare combination of syphilitic palmoplantar keratoderma and ocular disease in a patient with previously undiagnosed HIV.

Case Report

A 30-year-old black man was admitted to the hospital for headache and blurry vision. The patient reported having right retro-orbital pain for 3 days and sudden onset of blurry vision in his right eye for 1 day. He also reported skin discoloration over most of his body of 6 months' duration. His medical history was unremarkable and he was not taking any medications. Social history was remarkable for unprotected sex with 1 male partner. The patient denied any history of sexually transmitted diseases or intravenous drug use. Review of systems was remarkable for a 20-lb unintentional weight loss over 1 month as well as night sweats.

Physical examination revealed a thin man with hyperpigmented, finely scaling, dark brown macules and patches on his trunk and upper and lower extremities (Figure 1). His palms and soles were markedly hyperkeratotic and had hyperpigmented macules (Figure 2). Extensive examination of the mucous membranes, hair, nails, and genitals was otherwise unremarkable. He had no lymphadenopathy or hepatosplenomegaly. On ophthalmologic examination, visual acuity was 20/400 OD and 20/25 OS with correction. Both pupils were round and reactive without an afferent pupillary defect. Slitlamp examination revealed mild conjunctivitis in both eyes, moderate anterior uveitis in the right eye, and mild interstitial keratitis in the left cornea (Figure 3). Fundal examination of the right eye was remarkable for healthy appearing optic nerves, healthy retinal vessels, and a hyperpigmented

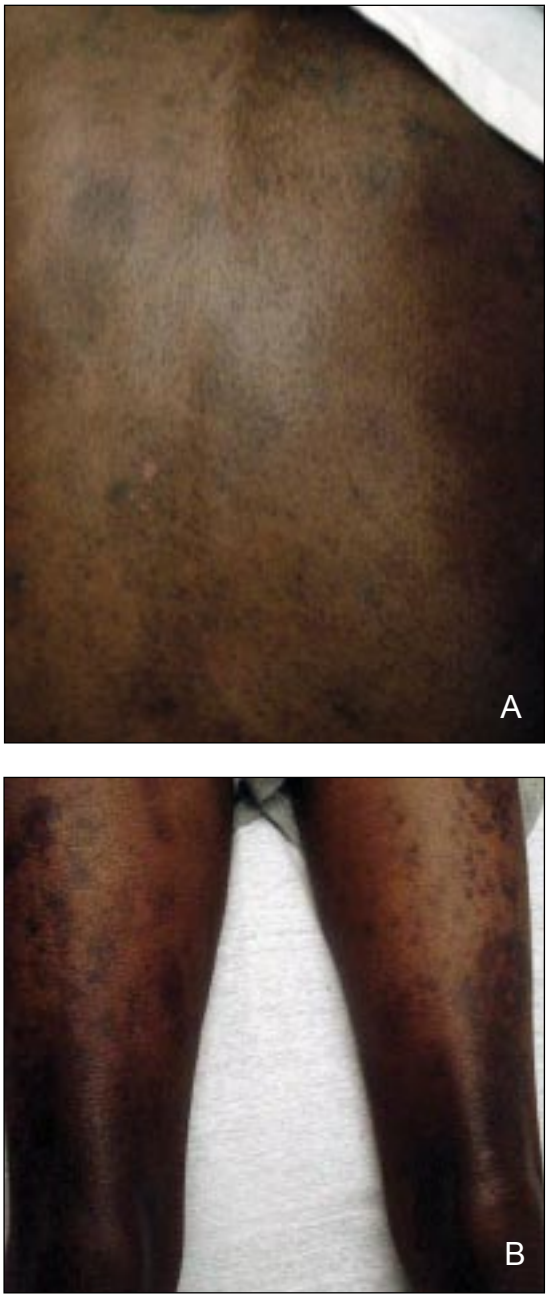

Figure 1. Hyperpigmented, finely scaling, dark brown macules and patches on the back (A) and thighs (B).

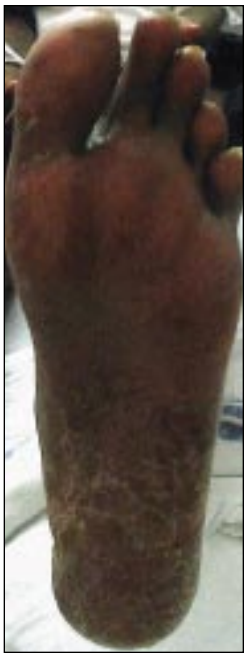

Figure 2. Markedly hyperkeratotic and hyperpigmented macules with diffuse thick scaling on the toes and sole of the foot.

lesion in the macula consistent with retinitis (Figure 4).

Laboratory studies revealed the following values: white blood cell count, $3.8\times10^3/\mu L$ (reference range, $3.8–10.8\times10^3/\mu L$); erythrocyte sedimentation rate, 134 mm/h (reference range, 0–20 mm/h); and C-reactive protein, 7.5 mg/L (reference range, 0–6 mg/L). An RPR titer was reactive at 1:256, and an MHA-TP test confirmed infection with *T pallidum*. Results of a rapid HIV test were positive and confirmed by an HIV antibody test and an HIV Western blot analysis. An immunodeficiency panel showed a T4:T8 ratio of 0.0 (reference range, 0.9–3.4) and absolute CD4 lymphocyte count of 17.0/μL (reference range, 560–1840/μL). A lumbar puncture was performed and a VDRL test of the spinal fluid was nonreactive. A skin biopsy of a hyperpigmented scaling patch on the anterior thigh demonstrated a lichenoid and perivascular lymphoplasmacytic infiltrate with pigment incontinence. Special stains for organisms were not performed.

The patient was diagnosed with and treated for secondary syphilis with ocular involvement as well as HIV infection. Treatment included intravenous penicillin G benzathine 4 million units every 4 hours for 14 days followed by 3 weekly intramuscular injections of 2.4 million units of penicillin G benzathine. He was started on prednisolone acetate 1% drops in both eyes and homatropine 5% drops in the right eye.

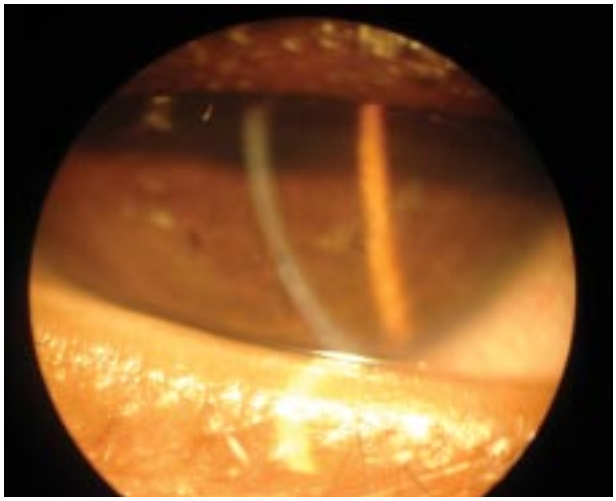

Figure 3. Slitlamp examination of the left eye demonstrated faint corneal opacities consistent with interstitial keratitis of the cornea.

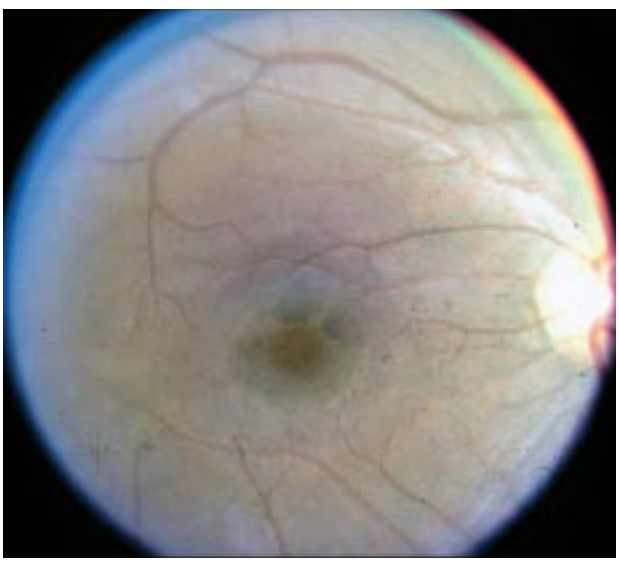

Figure 4. Examination of the right eye was remarkable for healthy appearing optic nerves, healthy retinal vessels, and a hyperpigmented lesion in the macula consistent with retinitis.

On reevaluation 2 weeks later, his palms and soles were less hyperkeratotic and the patches on his body were no longer scaling but remained hyperpigmented. His conjunctivitis and interstitial keratitis were improved and his visual acuity returned to 20/20 OD and OS. Repeat dilated examination showed a persistent hyperpigmented lesion in the macula of the right eye.

Comment

Syphilis is an infectious disease caused by the spirochete *T pallidum*. Approximately 349 million individuals

worldwide are actively infected with syphilis.[3] The incidence of syphilis in North America and Europe is low, estimated to be approximately 5 in 100,000, but has been rising in recent years.[2,3] Coinfection with HIV is not uncommon in patients with syphilis. Genital ulcers, such as the chancre of syphilis and herpes simplex virus, may increase the likelihood of transmission of HIV from one partner to another.[10,11] Blocker et al[12] have reported that the median seroprevalence for concomitant HIV infection is 15.7%, with men affected more commonly than women (27.5% vs 12.4%). The odds ratio for HIV infection in populations with syphilis is 8.8 for men and 3.3 for women.[12] Simultaneous infection with HIV can alter the symptoms, diagnostic tests, and treatment of syphilis compared to patients without HIV.

Patients with HIV and syphilis are more likely to have an asymptomatic primary stage, present with secondary syphilis, and have a chancre persist during secondary syphilis.[1,2,4,13] Some authors believe the course of syphilis in patients with HIV may be more dangerous versus patients without HIV.[2,14,15] For example, lues maligna is a rare ulceronodular type of syphilis that is more common in patients with HIV infection.[16,17] Ocular and central nervous system involvement also are more common in patients with syphilis and HIV.[18-20]

Another rare manifestation of secondary syphilis is palmoplantar keratoderma with thick hyperkeratotic scaling of both the palms and soles.[21-25] These findings resemble psoriasis, keratoderma blennorrhagicum, or inherited keratodermas. This type of syphilitic keratoderma with diffuse involvement of the palms and soles must be distinguished from a second type of syphilitic keratoderma (keratoderma punctatum syphiliticum), which has discrete punctate lesions.[24,25] Syphilitic keratodermas can be distinguished from other keratodermas by the presence of concomitant stigmata of secondary syphilis, positive testing for syphilis, and improvement with treatment of syphilis. Three case reports of diffuse syphilitic palmoplantar keratoderma aside from our own have been published based on a search of the literature using the MEDLINE database (1966–present) for the terms *syphilis* and *keratoderma* as well as a search of the references from the retrieved articles. Three of 4 total cases reported occurred in patients with HIV and syphilis. The same 3 patients also reported visual changes and were diagnosed with ocular syphilis.[21-23] The combination of palmoplantar keratoderma and ocular symptoms should prompt testing for syphilis as well as HIV, as the findings are atypical and coinfection with both is increasingly common.

Ocular syphilis is an uncommon manifestation affecting less than 5% of patients with either secondary[8,26] or tertiary syphilis.[20] Visual changes, including painless loss of vision, floating spots, enlarged blind spots, and occasionally symptoms of meningeal inflammation,[2,8,9] are common in tertiary neurosyphilis and rare in secondary syphilis.[27] Ocular involvement of secondary syphilis and tertiary neurosyphilis is protean and can affect every structure of the eye. The most common findings of anterior chamber involvement are anterior uveitis and conjunctivitis, while interstitial keratitis is rare in acquired disease but more common in congenital disease.[8,27] Posterior chamber involvement consists of vitritis, optic neuritis, and chorioretinitis, all of which can be treated with systemic antibiotic therapy.[20,27,28] Acute syphilitic posterior placoid chorioretinitis, originally described in HIV-positive patients with syphilis, was thought to be specific to this population but has been described in patients without HIV and in patients receiving corticosteroids during syphilis treatment.[26,29] Steroids are used during treatment of syphilis to prevent the Jarisch-Herxheimer reaction or as therapy for optic neuritis. Because of the increased incidence of ocular involvement in HIV-positive patients with syphilis and differences in treatment, practitioners should have a low threshold to obtain an ophthalmic evaluation.[22]

Serologic tests most often are used to diagnose syphilis, though dark-field microscopy also can be used.[2] With increasing rates of HIV and syphilis, inconsistencies in serologic testing have been identified. Case reports have identified important differences for both nontreponemal and *Treponema*-specific tests in patients with HIV infection. The *Treponema*-specific tests—MHA-TP and fluorescent treponemal antibody absorption—have an increased prevalence of false-negative results after therapy.[30,31] Nontreponemal tests—RPR and VDRL—can have higher rates of falsely reactive results,[30,32] can fail to fall with therapy,[33] and may have falsely nonreactive results due to the prozone effect.[5,34,35] The prozone effect causes a false nonreactive result because of very high levels of syphilis antibodies that interfere with the assay.[5,35,36] Although there have been case reports of diagnostic test failures, it is not believed that there is enough evidence to change the use of standard serologic tests for HIV-positive patients.[27] Also, given the increased prevalence of HIV in patients with syphilis and vice versa, it is recommended that reciprocal testing be done for patients who present with either disease.[2,4,30]

Treatment of syphilis is based on the duration and extent of infection. The Centers for Disease Control and Prevention has published guidelines on treatment of HIV-positive and HIV-negative patients.[36] Patients with primary or secondary syphilis are treated with intramuscular penicillin G benzathine, regardless of their HIV status. Lumbar puncture to assess the cerebrospinal fluid is not necessary for these early-stage, asymptomatic patients. A lumbar puncture should be done if a patient presents with ocular or other nervous system signs, concomitant HIV infection, tertiary syphilis, or treatment failure. Ocular syphilis often coexists with tertiary neurosyphilis; however, tests of the cerebrospinal fluid are specific but not sensitive. Also, because antibiotic penetration of the blood-ocular barrier can be poor, patients with ocular syphilis often are treated with regimens for neurosyphilis.[27,36] Treatment of neurosyphilis consists of intravenous penicillin G benzathine 3 to 4 million units every 4 hours for 10 to 14 days, regardless of HIV status. Alternative therapies for patients who are allergic to penicillin include doxycycline and amoxicillin.[4,27,36] However, the Centers for Disease Control and Prevention recommends considering desensitization in patients with HIV coinfection and/or neurosyphilis. In these patient populations, extended treatment with intramuscular penicillin G benzathine weekly for 3 weeks has been advocated to ensure complete treatment.[36]

Conclusion

The prevalence of syphilis is increasing in the United States and abroad. Infection with syphilis can increase transmission of HIV, and concomitant infection with both also is increasing, so practitioners should have a low threshold to do reciprocal testing. Manifestations of syphilis are more likely to be atypical in patients with HIV. Syphilis also may involve organs not typically involved in patients who are immunocompetent. As a result, referral to specialists, including ophthalmologists, may help to confirm the diagnosis and alter treatment. It also is important to consider the possibility of false-positive and false-negative test results in this population and to pursue repetitive testing. A biopsy or assistance from laboratory staff and infectious disease specialists also may be helpful to confirm a diagnosis of syphilis. Our case of syphilitic palmoplantar keratoderma and ocular disease demonstrates a rare combination of findings in syphilis. Testing for syphilis should be considered in patients with keratoderma and ocular symptoms. Also, this constellation of findings is uncommon in syphilis and should initiate HIV testing.

REFERENCES

1. James WD, Berger TG, Elston DM, eds. *Andrews' Diseases of the Skin: Clinical Dermatology*. 10th ed. Canada: WB Saunders; 2005.
2. Kinghorn GR. Syphilis. In: Cohen J, Powderly WG, eds. *Infectious Diseases*. 2nd ed. London, England: Mosby; 2004:807-816.
3. Gerbase A, Stein C, Levison J, et al. Global burden of sexually transmitted diseases (excluding HIV) in the year 2000. World Health Organization Web site. http://www.who.int/healthinfo/statistics/bod_sexuallytransmitteddiseasesotherthanHIVAIDS.pdf. Accessed November 11, 2009.
4. Lynn WA, Lightman S. Syphilis and HIV: a dangerous combination. *Lancet Infect Dis*. 2004;4:456-466.
5. Taniguchi S, Osato K, Hamada T. The prozone phenomenon in secondary syphilis. *Acta Derm Venereol*. 1995;75:153-154.
6. Hicks CB, Benson PM, Lupton GP, et al. Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma. a diagnostic dilemma. *Ann Intern Med*. 1987;107:492-495.
7. Augenbraun M, Rolfs R, Johnson R, et al. Treponemal specific tests for the serodiagnosis of syphilis. Syphilis and HIV Study Group. *Sex Transm Dis*. 1998;25:549-552.
8. Aldave AJ, King JA, Cunningham ET Jr. Ocular syphilis. *Curr Opin Ophthalmol*. 2001;12:433-441.
9. Deschenes J, Seamone CD, Baines MG. Acquired ocular syphilis: diagnosis and treatment. *Ann Ophthalmol*. 1992;24:134-138.
10. Arora PN, Sastry CV. HIV infection and genital ulcer disease. *Indian J Sex Transm Dis*. 1992;13:71-73.
11. Bruisten SM, Cairo I, Fennema H, et al. Diagnosing genital ulcer disease in a clinic for sexually transmitted diseases in Amsterdam, The Netherlands. *J Clin Microbiol*. 2001;39:601-605.
12. Blocker ME, Levine WC, St. Louis ME. HIV prevalence in patients with syphilis. United States. *Sex Tranm Dis*. 2000;27:53-59.
13. Health Protection Agency. Recent developments in syphilis epidemiology. *CDR Weekly*. 2003;13. http://www.hpa.org.uk/CDR/archives/2003/cdr3103.pdf. Published July 31, 2003. Accessed February 20, 2008.
14. Johns DR, Tierney M, Felsenstein D. Alteration in the natural history of neurosyphilis by concurrent infection with human immunodeficiency virus. *N Engl J Med*. 1987;316:1569-1572.
15. Passo MS, Rosenbaum JT. Ocular syphilis in patients with human immunodeficiency virus infection. *Am J Ophthalmol*. 1988;106:1-6.
16. Sands M, Markus A. Lues maligna, or ulceronodular syphilis, in a man infected with human immunodeficiency virus: case report and review. *Clin Infect Dis*. 1995;20:387-390.
17. Kumar B, Muralidhar S. Malignant syphilis: a review. *AIDS Patient Care STDS*. 1998;12:921-925.

18. Bordón J, Martínez-Vázquez C, Alvarez M, et al. Neurosyphilis in HIV-infected patients. *Eur J Clin Microbiol Infect Dis*. 1995;14:864-869.
19. Doris JP, Saha K, Jones NP. Ocular syphilis: the new epidemic. *Eye*. 2006;20:703-705.
20. Chao JR, Khurana RN, Fawzi AA, et al. Syphilis: reemergence of an old adversary. *Ophthalmology*. 2006;113:2074-2079.
21. Waugh MA. Reiter's disease with keratoderma in a man with papulosquamous secondary syphilis. *Br J Vener Dis*. 1972;48:295-299.
22. Radolf JD, Kaplan RP. Unusual manifestations of secondary syphilis and abnormal humoral immune response to *Treponema pallidum* antigens in a homosexual man with asymptomatic human immunodeficiency virus infection. *J Am Acad Dermatol*. 1988;18(2, pt 2):423-428.
23. Kishimoto M, Lee MJ, Mor A, et al. Syphilis mimicking Reiter's syndrome in an HIV-positive patient. *Am J Med Sci*. 2006;332:90-92.
24. Kerdel-Vegas F, Kopf AW, Tolmach JA. Keratoderma punctatum syphiliticum: report of a case. *Br J Dermatol*. 1954;66:449-454.
25. Chapel TA, Blum D. Horny syphilis. *Cutis*. 1978;22:55-59.
26. Gass JD, Braunstein RA, Chenoweth RG. Acute syphilitic posterior placoid chorioretinitis. *Ophthalmology*. 1990;97:1288-1297.
27. Browning DJ. Posterior segment manifestations of active ocular syphilis, their response to a neurosyphilis regimen of penicillin therapy, and influence of human immunodeficiency virus status on response. *Ophthalmology*. 2000;107:2015-2023.
28. Friberg TR. Syphilitic chorioretinitis. *Arch Ophthalmol*. 1989;107:1676-1677.
29. Zamani M, Garfinkel RA. Corticosteroid-induced modulation of acute syphilitic posterior placoid chorioretinitis. *Am J Ophthalmol*. 2003;135:891-894.
30. Nandwani R, Fisher M; Medical Society for the Study of Venereal Diseases HIV Special Interest Group. Clinical standards for the screening and management of acquired syphilis in HIV-positive adults. *Int J STD AIDS*. 2006;17:588-593.
31. Janier M, Chastang C, Spindler E, et al. A prospective study of the influence of HIV status on the seroreversion of serological tests for syphilis. *Dermatology*. 1999;198:362-369.
32. Nandwani R, Evans DT. Are you sure it's syphilis? a review of false positive serology. *Int J STD AIDS*. 1995;6:241-248.
33. Malone JL, Wallace MR, Hendrick BB, et al. Syphilis and neurosyphilis in a human immunodeficiency virus type-1 seropositive population: evidence for frequent serologic relapse after therapy. *Am J Med*. 1995;99:55-63.
34. Haslett P, Laverty M. The prozone phenomenon in syphilis associated with HIV infection. *Arch Intern Med*. 1994;154:1643-1644.
35. Jurado RL, Campbell J, Martin PD. Prozone phenomenon in secondary syphilis. has its time arrived? *Arch Intern Med*. 1993;153:2496-2498.
36. Workowski KA, Berman SM. Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines. *Clin Infect Dis*. 2007;44(suppl 3):S73-S76.