Prominent Osseous and Unusual Dermatologic Manifestations of Early Syphilis in Two Patients with Discordant Serological Statuses for Human Immunodeficiency Virus Infection

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Numerous case reports of atypical and/or severe forms of syphilis in individuals coinfected with human immunodeficiency virus (HIV) have led many authorities to conclude that HIV exacerbates early syphilitic infection. Herein we report prominent osseous and unusual dermatologic manifestations of early syphilis in two individuals whose serostatuses for HIV infection were discordant. Our cases emphasize the need for caution before conclusions are drawn from anecdotal data about the interactions between HIV infection and syphilis.

Case Reports

Case 1

A 27-year-old woman presented to Parkland Memorial Hospital (Dallas) because of a 1-month history of headache, fever, ulcerative rash, and bilateral shin and heel pain. The patient's medical history was remarkable for an admission 15 months earlier because of similar complaints, at which time a diffuse rash consisting of papules and small ulcers, a serum VDRL test titer of 1:256, and a reactive microhemagglutination assay for Treponema pallidum were noted.

A cutaneous punch biopsy from an ulcer on the back was performed at that time and showed histopathologic changes consistent with lues maligna, and spirochetes were visualized by Warthin-Starry silver staining. Cultures of the biopsy specimen for acid-fast bacilli and fungi were negative, while routine cultures yielded only coagulase-negative staphylococci in thioglycollate broth. An HIV ELISA was negative. Tibial radiographs were negative, but a bone scan showed increased activity in the left anterolateral tibia and the left distal fibula at the lateral malleolus.

The patient received treatment for 5 days with nafcillin (12 g/d) and ceftizoxime (2 g/d) intravenously, followed by a single intramuscular injection of benzathine penicillin (2.4 million units [MU]), resulting in symptomatic improvement. The patient then was lost to follow-up.

At the time of the second admission, she acknowledged having had unprotected intercourse with three different partners since her previous discharge from the hospital. She also acknowledged long-standing use of cocaine intranasally, but she denied intravenous drug use. She had not recently traveled outside of the Dallas-Ft. Worth area and had never traveled outside the United States.

On physical examination during the present admission, the patient's temperature was 38°C. Scattered papules, pustules, and ulcers (figure 1) were noted. Her shins and heels were erythematous and tender, and she was unable to ambulate because of pain. There were no other remarkable physical findings.

Pertinent laboratory data included the following values: serum VDRL test titer, 1:256; WBCs, 6.3 × 10^9/L, with 23% lymphocytes; erythrocyte sedimentation, 109 mm/h; CSF, normal; and HIV ELISA, negative. Dark-field examination of one of the ulcers was negative. A punch biopsy of a right-back lesion showed an inflammatory dermal infiltrate consisting predominantly of lymphocytes and plasma cells; fat necrosis of the subcutis also was noted.

All special stains were negative, while routine cultures and those for acid-fast bacilli and fungi yielded only light growth of coagulase-negative staphylococci in thioglycollate broth.
Figure 1. Ulcerative lesion below the left breast of patient 1, an HIV-negative woman with syphilis.

Radiographs of the lower extremities showed periosteal elevation of the mid-left tibia consistent with periostitis, and a bone scan showed increased uptake in both mid-tibias, in the left calcaneus, in the left-second-proximal interphalangeal joint, and in the tarsal bones of the right foot. MRI of both tibias showed abnormal signal on T1 spin-echo images in the middle thirds of both tibias (left > right), with extensive periosteal thickening; a second focus of increased signal was also noted in the distal left tibia (figure 2).

Intravenous penicillin G at a dosage of 16 MU/d was administered for 14 days, resulting in marked diminishment of both skin lesions and bone pain. Immediately before discharge, the patient was given 2.4 MU of benzathine penicillin intramuscularly. She was scheduled to receive additional injections at weekly intervals as an outpatient but was lost to follow-up.

Case 2

A 34-year-old homeless black female was admitted to Parkland Memorial Hospital because of a 2-month history of progressive fever, chills, night sweats, weight loss, and painful skin lesions. The patient admitted to unprotected sexual activity in the recent past with one sex partner who was healthy. Her medical history included treatment for syphilis in 1980 by intramuscular injection of penicillin, but documentation of this treatment could not be found.

On physical examination the patient had a temperature of 37.8°C, and she appeared cachectic. Oral erythematous papules were noted on her hard palate. Tender, erythematous subcutaneous nodules were observed on her face (figure 3), shins, and right distal humerus. These nodules were firm and affixed to bone; the largest measured 6 cm in diameter. The remainder of the examination findings were unremarkable.

Laboratory data included an erythrocyte sedimentation rate of 118 mm/h, a serum VDRL test titer of 1:128, and a reactive microhemagglutination assay for T. pallidum. The CSF VDRL test was reactive at a titer of 1:1, but other CSF parameters were within normal limits. A serum ELISA for HIV was positive, and the result was confirmed by immunoblotting; the CD4 lymphocyte count was 130/mm³. Both PPD and anergy panels were negative at 72 hours. Blood cultures and fungal isolators did not yield any growth. Chest roentgenographic findings were within normal limits. No lesions were noted on skull radiographs, but tibial radiographs showed cortical thickening of the mid-diaphyseal regions (right > left) (figure 4). Serologies for histoplasmosis, coccidioidomycosis, and blastomycosis were negative, and cryptococcal antigen was not detected in either serum or CSF.

A fine-needle aspirate of a mandibular lesion was negative for bacterial, mycobacterial, and fungal growth. A punch biopsy of a nodule overlying the left tibia showed only telangiectasia. An incisional biopsy of a nodule overlying the right lower extremity demonstrated granuloma, often perivascular, consisting of epithelioid histiocytes and multinucleated giant cells surrounded by lymphocytes and plasma cells (figure 5):
Figure 3. Nodular skin lesions on the forehead and right preauricular area of patient 2, an HIV-positive woman with syphilis.

Figure 4. Radiograph showing changes of osseous syphilis (arrowhead) in the mid-left tibia of patient 2.

Discussion

The two cases of acquired syphilis presented herein raise interesting issues regarding osseous and dermatologic manifestations of syphilis, the basis for syphilis staging, and, most important, the impact of concurrent HIV infection on the natural history of this sexually transmitted spirochetal disease.

Syphilitic osteitis follows invasion of the medullary space by *T. pallidum* during hematogenous dissemination of early syphilis [10]. The perivascular inflammatory response induced by the spirochetes causes periostitis, osteochondritis, or frank osteomyelitis, depending on the part of the affected bone. More advanced vascular changes may lead to secondary ischemia and caseation necrosis.

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The patient’s hospital course was remarkable for a Jarisch-Herxheimer reaction several hours following the initiation of therapy with intravenous penicillin G (12 MU/d). Thereafter she tolerated therapy, and her constitutional symptoms as well as her nodules diminished during a 10-day course of intravenous therapy; this regimen was followed by intramuscular benzathine penicillin (2.4 MU), administered weekly for 3 consecutive weeks. She also received prophylaxis with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia. Approximately 6 months after discharge, she was seen in the obstetrics/gynecology clinic of Parkland Memorial Hospital, at which time her skin lesions had resolved and she was free of pain. The serum VDRL test titer was 1:16, the CSF VDRL test was nonreactive, and other CSF parameters were within normal limits. At 9 months after her discharge from the hospital, she remained asymptomatic and had a serum VDRL test titer of 1:16.

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The most common type of skeletal lesion in early syphilis is periostitis, with the tibia being the site most frequently involved; the sternum, skull, and ribs also are commonly affected [11]. In contrast to periostitis, destructive bone lesions are rare in early syphilis; they occurred in only 15 of 10,000 patients with early syphilis seen at the John Hopkins Hospital (Baltimore) between 1919 and 1940 [12]. In that series, the most common sites of destructive lesions were the skull and the sternoclavicular junction.

Early syphilitic periostitis may not be evident on plain radiographs, as in the initial presentation of our first case, and increased sensitivity with technetium bone scintigraphy has been reported [13]. Radiographic manifestations of osteitis or osteomyelitis include destructive or proliferative changes or a combination of the two [14]. MRI nicely demonstrated the extent of osseous involvement in case 1. To our knowledge, MRI findings in a case of bony syphilis have not been described previously.

Given the relative rarity of syphilitic osteitis, it is not surprising that the appropriate therapeutic regimen for this form of the disease has never been determined in clinical trials. It is noteworthy that our first patient may have relapsed after receiving benzathine penicillin G in addition to several days of therapy with intravenous nafcillin and ceftriaxone. Nafcillin probably has poor activity against T. pallidum [15]. Ceftriaxone, on the other hand, has excellent treponemicidal activity in vitro [16] and has an established track record for the treatment of early syphilis [17, 18]. However, results with this agent in the treatment of complicated forms of syphilis (e.g., neurosyphilis) have been somewhat disappointing [19]. On the basis of the exquisite susceptibility of T. pallidum to penicillin G [20], as well as our experience and that of others [21], we believe that syphilitic osteitis, regardless of stage, should be treated with at least a 10-day regimen of high-dose intravenous penicillin G.

The dermatologic manifestations in both of our patients also were impressive. While the cutaneous lesions of secondary syphilis may resemble almost any generalized eruption, the vast majority are macular, papular, papulosquamous, and pustular [22]. Nongenital ulcerative lesions are relatively uncommon but may accompany pustular syphilids or occur as lues maligna, as in case 1 [6]. In the AIDS era, lues maligna has been linked with HIV infection [24, 25]; however, it is important to note that this rare but severe form of secondary syphilis was well recognized in the preantibiotic era [4].

The second case manifested an even rarer cutaneous manifestation of secondary syphilis, nodules [22]. Nodular lesions of secondary syphilis, which often show granulomatous changes in addition to typical histopathologic features of syphilis (e.g., perivascular monocytic and plasma cell infiltrates), may be confused with sarcoidosis, tuberculosis, leprosy, and deep mycoses [26, 27]. In our case, these other infectious entities were ruled out by appropriate stains and cultures of the biopsy specimen for other pathogens and by the patient’s response to penicillin therapy, which included a classic Jarisch-Herxheimer reaction.

It is often thought that the stages of syphilis have distinct clinical manifestations that are easily differentiated. Our cases demonstrate that syphilis staging is often subjective. Inasmuch as the locations of the osseous lesions in our first patient were identical during both admissions, we have presumed that the second presentation represented a relapse of unsterilized osseous nidi, with subsequent hematogenous dissemination to the skin rather than reinfection. Moreover, although cutaneous ulcers and osteitis are well-recognized complications of tertiary syphilis [22], the widespread distribution of lesions in this patient was far more consistent with early disease.

The second case was even more problematic. She had not had clear-cut recent exposure, and, as noted previously, the nodular skin lesions were atypical for secondary syphilis. CSF abnormalities, including a reactive CSF VDRL test, are of limited usefulness in staging because they occur in both early and late syphilis [22, 28].
The presence of granulomas in skin biopsy specimens suggested granulomatous disease to some of our pathologists. However, granulomas in dermal lesions are common in cases of early as well as late syphilis [29–31]. While it is possible that this patient had tertiary disease, we believe that the multiple, symmetric osseous and cutaneous lesions, the rapid onset of disease, and the high VDRL test titer were most consistent with secondary syphilis.

On the basis of reports published in the AIDS era, some authorities have concluded that the cellular immune defect of HIV infection exacerbates early syphilis [1, 2]. Although the majority of these cases involve neurological complications, atypical skin and bony manifestations also have been attributed to HIV infection [2, 5, 25, 32]. It is interesting that controlled studies of syphilis and HIV infection have not supported the conclusion that HIV infection dramatically impacts the natural history of syphilis.

Gourevitch et al. [33] found in a controlled prospective study that HIV infection did not alter the stage at presentation, clinical course, serological manifestations, or response to treatment of syphilis. Hutchinson et al. [34] retrospectively compared the clinical presentations of early syphilis in a cohort of more than 700 patients with and without concomitant HIV infection. HIV-infected patients were more likely to present with secondary syphilis and had more persistent chancres; however, the dermatological manifestations of secondary syphilis were similar in the two groups, and neurological complications were not observed more frequently in those with HIV infection.

Finally, in a recently completed prospective, multicenter study conducted by the Centers for Disease Control and Prevention, no clinically significant differences in clinical manifestations or therapeutic response during a 1-year follow-up period were noted in patients with early syphilis who did or did not have HIV infection [35]. Presently, we have little understanding of the host and microbiological factors that lead to varied clinical manifestations of syphilis. Also poorly understood is how the humoral and cellular arms of the immune system interact to control T. pallidum infection in humans. While case reports can be useful in identifying potentially important associations, conclusions based on anecdotal data need to be confirmed by controlled studies.

If our second case had been viewed in isolation, there would have been a strong temptation to postulate a relationship between the unusual clinical manifestations and HIV infection. Juxtaposition of this case with our first, however, serves as a reminder that severe forms of early syphilis are not restricted to HIV-infected individuals.

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References

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