Mr D is a 38-year-old African American man in whom AIDS had been diagnosed in 2001; he had responded well to antiretroviral therapy, with a recent CD4+ cell count of 376/µL and an HIV RNA level less than 50 copies/mL. He presented to our clinic complaining of a mildly tender "lump" on the left side of his neck, which he first noticed a week ago. He denied fever, chills, sweats, cough, anorexia, weight loss, and urinary symptoms but had a sore throat for 2 days.

The patient recently quit his job as a hairstylist and traveled throughout Western Europe. He admitted to sexual contact, including unprotected oral sex with an anonymous male escort. His past medical history included treatment for disseminated *Mycobacterium avium* infection with intra-abdominal abscesses, depression, chronic hepatitis C (a liver biopsy showed low-grade inflammation), and gonorrhea.

The patient was a well-developed man in no acute distress. He was afebrile. Neck examination was significant for a large, soft, mobile and mildly tender posterior cervical lymph node, approximately 2.5 cm. He also had bilateral, shoddy anterior cervical lymph nodes. His axillary lymph nodes were enlarged to 2 cm and were nontender, soft, and mobile. His oropharynx was clear. He had several enlarged, mildly tender, inguinal lymph nodes that were approximately 1 to 2 cm.

His antiretroviral drug regimen included fosamprenavir, ritonavir, and abacavir/lamivudine coformulation. He was also taking zolpidem. He has a past history of allergic rash after taking trimethoprim/sulfamethoxazole.

Results of laboratory tests included normal liver function tests; white blood cell (WBC) count, 4300/µL (normal, 3400 to 11,200); hemoglobin level, 16.8 g/dL (normal, 13.3 to 17.7); lactate dehydrogenase level, 233 U/L (normal, 96 to 200); rapid plasma reagin (RPR) titer, 1:256; and a positive test result for fluorescent treponemal antibody (FTA-ABS).

Given the elevated RPR titer, the patient was referred for lumbar puncture, but he missed several appointments and ultimately refused the procedure. Since he had no neurological signs or symptoms and had a previously nonreactive titer approximately 6 months earlier, the decision was made to treat with 3 weekly intramuscular injections of benzathine penicillin G. His RPR titer decreased more than 4-fold in 6 months to 1:8.

SYPHILIS AND HIV

Syphilis, caused by the spirochete *Treponema pallidum*, is known as the "great imitator" because of its complex and diverse manifestations of disease. In HIV-infected persons, syphilis may have a more prolonged and aggressive clinical course. The results of serological testing may be aberrantly high, or a test may fail to elicit a response.\(^1\) Syphilis can facilitate the transmission and acquisition of HIV, through either interruption of the natural mucosal barrier or local inflammation, and some studies have shown transient decreases in CD4\(^+\) cell count and increases in plasma viral load during active syphilis infection.\(^1\)\(^5\)

EPIDEMIOLOGY

In 2000, the rate of primary and secondary syphilis in the United States was the lowest ever recorded, with 2.1 cases per 100,000 population.\(^6\) Since then, there has been a steady increase, with 3.3 per 100,000 population in 2006. The number of cases of primary and secondary syphilis increased in this period, from 5979 to 9756. The biggest increase was seen in men who have sex with men (MSM), who accounted for approximately 65% of the total number of cases reported. The cases in the MSM population have been further characterized by high rates of HIV coinfection,
high-risk sexual behavior, and the use of illicit drugs (such as methamphetamine), as well as by use of the Internet as a venue for anonymous sexual encounters. Since 1997, there have been increasing rates of syphilis outbreaks among MSM in several major US cities, including New York, Seattle, Chicago, San Francisco, Los Angeles, and Miami. In each of these outbreaks, high rates of HIV coinfection were documented, ranging from 20% to 73.\(^9\)\(^{12}\)

**CLINICAL PRESENTATION**

Besides through sexual contact, syphilis can be transmitted via other close contact, such as by kissing when an active perioral lesion is present; perinatally (congenital syphilis); and rarely, via transfusion.\(^1\)\(^3\) The natural course of disease can be divided into the following stages: incubation period; primary stage; secondary, or disseminated, stage; latent phase; and, in up to one third of infected persons, a late tertiary stage.

The median incubation period is 3 weeks but can vary from 3 to 90 days.\(^1\)\(^3\)

A chancre, which develops at the site of inoculation, is the hallmark of the primary stage.\(^1\)\(^3\) Because chancres are painless and can be located in difficult-to-visualize areas, they can go unnoticed with disease progression. Commonly affected areas are the cervix, mouth, perianal area, and anal canal. Multiple or large chancres may occur, especially in persons infected with HIV.\(^7\) There may be atypical lesions or an absence of a primary skin lesion in up to 60% of cases.\(^1\)\(^3\) The variations in presentation of primary syphilis depend on the number of treponemes inoculated, the immune status of the patient, and whether the lesion becomes secondarily infected. Lesions of primary syphilis usually resolve spontaneously in 2 to 8 weeks but may persist, especially in immunocompromised persons, such as those with HIV infection.\(^1\)\(^3\)

If untreated, syphilis progresses to the secondary stage via hematogenous dissemination, with eventual parenchymal, constitutional, and/or mucocutaneous disease. This occurs at a mean of 6 weeks (range, 2 to 12 weeks) after initial contact. This stage can overlap with the primary syphilis stage in approximately one third of patients, but in HIV-coinfected patients, primary and secondary syphilis overlap in up to 75% of cases.\(^1\)\(^4\) There is high treponemal and antigen load in the body. Spirochetes can be detected in skin and lymph nodes and even in the CNS and the aqueous humor of the eye.\(^1\)\(^3\)

A rash is present in 50% to 80% of cases.\(^1\) The secondary syphilis rash starts as pink to red, discrete lesions, 3 to 10 mm in diameter on the trunk and on the palms and soles. These lesions are nonpruritic and macular, maculopapular, or pustular.\(^1\)\(^3\) The rash may also mimic other dermatological diseases (ie, psoriasis) or may present as patchy alopecia. Condylomata lata may occur at any moist body site, especially in the perianal area. Oral mucous patches are common.\(^1\)\(^5\) All the lesions that involve the skin are very infectious. Constitutional symptoms occur frequently as well and include low-grade fever, malaise, pharyngitis, laryngitis, anorexia, weight loss, arthralgias, and general painless lymphadenopathy. Enlargement of epidermal lymph nodes is a unique finding that should always suggest the diagnosis. The CNS can be involved in up to 40% of cases, with headache and meningismus.\(^1\)\(^3\)

During this second stage, virtually any organ system can be involved, eg, musculoskeletal system with synovitis, osteitis, periostitis, and the GI tract with hepatitis, elevated alkaline phosphatase level, and proctitis—especially in patients with a history of anal intercourse. Immune complex glomerulonephritis and proteinuria may also occur. HIV-infected persons are predisposed to symptomatic neurosyphilis during this stage—so-called early neurosyphilis.\(^1\)\(^6\) Studies have shown that the risk of neurosyphilis is increased 3- to 4-fold when the CD4\(^+\) cell count is below 350/\(\mu\)L and by 19-fold if the serum VDRL titer is above 1:32.\(^1\)\(^5\) The most common CNS manifestations are cranial nerve palsy, including visual disturbances, hearing loss, tinnitus, and facial weakness.\(^1\)\(^3\) Syphilitic paraplegia (Erb paralysis) and meningomyelitis can also occur.\(^1\)\(^3\) Anterior uveitis occurs in 5% to 10% of patients with secondary syphilis, especially in HIV-infected persons.\(^1\)\(^1\) In a case series of early neurosyphilis in HIV-positive MSM, approximately 75% presented with visual problems or headache.\(^1\)\(^7\)

Eventually, there is remission of symptoms and progression to the latent period of disease, during which serological test results remain positive and relapses are possible. Latency is divided into 2 categories:

- Early latent (within the first year of disease) during which 75% of relapses occur.
- Late latent (after the first year of disease), in which relapses are uncommon.\(^1\)\(^3\)

In most patients, the infection is controlled and does not progress to late disease. Tertiary, or late, syphilis is a slowly progressive disease that occurs in 15% to 40% of untreated patients. As noted, it can affect any organ system, and well-recognized forms include neurosyphilis, cardiovascular syphilis, and gummatous syphilis.\(^1\)\(^,1\)\(^3\) Spirochetal pathogenesis and host factors can
affect the course of disease progression. Cardiovascular complications, such as aortitis, are the most common and occur 10 to 30 years after the initial infection. After the original inoculation with T pallidum, infection can recur. For example, meningeovascular syphilis may recur 5 to 10 years after initial infection; general paresis, 15 to 20 years after; and tabes doralis, 25 to 30 years after.\textsuperscript{13}

**DIAGNOSIS**

Dark-field examinations of lesion exudate or tissue with confirmation by direct fluorescent antibody tests are definitive methods for diagnosing early syphilis. Unfortunately, dark-field microscopy requires special equipment and training and is unsuitable for oral or rectal samples because of the potential presence of nonpathogenic spirochetes in such specimens.\textsuperscript{1,7} Diagnosis can also be made with histological examination of biopsy specimens of suspicious lesions and by specific immunofluorescent or immunoperoxidase antibody staining of biopsy samples. Silver stain can be nonspecific.\textsuperscript{1,13}

The diagnosis can also be made by serological testing in most infected persons. There are 2 types of tests:

- Nonreponemal tests (VDRL and RPR).
- Treponemal tests (FTA-ABS and T pallidum particle agglutination).\textsuperscript{13}

Nonreponemal test antibody titers usually correlate with disease activity and are reported quantitatively. Results may be false-positive or they may inaccurately reveal increasing reaginic titers despite adequate therapy—especially with early HIV infection when there is the greatest polyclonal B-cell stimulation.\textsuperscript{13} Also, nonreponemal tests may fail to elicit a response because of an overwhelming antigen load or severe immune dysfunction that occurs late in the disease.\textsuperscript{13}

Therefore, 2 different serological tests are needed to confirm a diagnosis of syphilis. Chancres are associated with positive nonreponemal serology in approximately 70% of patients.\textsuperscript{16} A 4-fold change in titer is considered necessary to demonstrate a clinically significant difference, either as a new or relapsing infection when the titer rises or as a response to treatment when it falls.

Current CDC guidelines recommend examination of cerebrospinal fluid (CSF) in asymptomatic HIV-infected persons with late latent syphilis or with syphilis of unknown duration as well as in HIV-infected persons in whom therapy for early or late syphilis fails or who have neurological signs and symptoms.\textsuperscript{18} Lumbar puncture is not routinely recommended for neurologically asymptomatic HIV-infected patients with early syphilis. However, some studies have shown that a nonreponemal serological titer of 1:32 or higher was associated with abnormal CSF findings suggestive of neurosyphilis in HIV-coinfected persons.\textsuperscript{19,20} The serum RPR titer was significantly associated with increased odds of neurosyphilis; for every 2-fold increase in titer, the odds of neurosyphilis increased 1.4-fold.\textsuperscript{19} CD4\textsuperscript{+} cell counts below 350/µL were also associated with CSF abnormalities of neurosyphilis.\textsuperscript{20}

Based on these studies, some researchers recommend that neurologically asymptomatic HIV-infected patients whose serum RPR titer is 1:32 or higher should undergo lumbar puncture—regardless of syphilis stage. Some experts still do not recommend CSF examinations for HIV-infected patients who present with primary, secondary, or early latent syphilis with no neurological symptoms, regardless of the RPR titer or CD4\textsuperscript{+} cell count.\textsuperscript{7}

Indications for CSF examination include such clinical findings as cranial nerve palsies and otological or ophthalmological signs or symptoms, tertiary syphilis, treatment failure (defined by recurrence or persistence of symptoms), and lack of serological response (4-fold decrease in RPR titers at 12 months for early syphilis).\textsuperscript{7}

Any patient who undergoes lumbar puncture and is found to have an elevated CSF leukocyte count (WBC count greater than 5/µL) should be considered to have neurosyphilis.\textsuperscript{18} However, given that many HIV-infected patients have some degree of pleocytosis at baseline, many experts recommend using a WBC threshold of 20/µL to diagnose neurosyphilis in HIV-coinfected patients to account for underlying CSF pleocytosis.\textsuperscript{1,16} A normal CSF WBC count rules out neurosyphilis. The CSF-VDRL test is very specific but insensitive, and the CSF FTA-ABS test is not recommended, since it can yield false-positive results; however, a negative CSF FTA-ABS test result can be helpful in ruling out neurosyphilis.\textsuperscript{13}

**TREATMENT**

Treatment of primary and secondary syphilis and early latent syphilis in HIV-infected persons is similar to that in persons without HIV infection: benzathine penicillin G, 2.4 million units intramuscularly in a single dose.\textsuperscript{18} Some specialists recommend additional treatments (eg, benzathine penicillin G administered at 1-week intervals for 3 weeks, as recommended for late syphilis); however, there is no evidence to support better outcome or improved serological response with additional therapy.
Doxycycline (100 mg orally twice daily for 14 days) or tetracycline (500 mg orally 4 times daily for 14 days) is an alternative therapy for those who are allergic to penicillin. Patients with late latent syphilis or syphilis of unknown duration and normal findings on CSF examination can be treated with benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks. HIV-infected patients who have either late latent syphilis or syphilis of unknown duration should have a CSF examination before treatment. Patients in whom CSF findings are consistent with neurosyphilis should be treated with parenteral penicillin G 18 to 24 million units per day, administered as 3 to 4 million units intravenously every 4 hours or by continuous infusion, for 10 to 14 days. Alternative therapy is procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg orally 4 times a day, both for 10 to 14 days.

For those with penicillin allergy and no cross-reactivity to cephalosporins, ceftriaxone 2 g daily either intramuscularly or intravenously for 10 to 14 days is the treatment of choice. Desensitization to penicillin can also be performed. Ceftriaxone has been compared with intravenous benzathine penicillin G for the treatment of neurosyphilis in 30 HIV-infected patients. There were similar improvements in CSF parameters—including VDRL titer, WBC count, and protein concentration. In HIV-infected persons with syphilis, serological titers declined more slowly than in HIV-negative persons. Another study showed that CSF-VDRL reactivity was 2.5 times less likely to normalize in HIV-infected persons as in those without HIV infection. Also, CSF-VDRL was 3.7 times less likely to normalize in HIV-infected persons with CD4+ cell counts of 200/µL or less. Since most HIV-infected persons are also at risk for subsequent reinfection, it is difficult to determine whether lack of decline is a consequence of reinfection, immunosuppression, or relapse of disease from hidden reservoirs (such as the eye).

Generally, a 4-fold decrease in nontreponemal titers (from 1:64 to 1:16) by 6 to 12 months of follow-up is considered an appropriate response to therapy. Close clinical monitoring is important, and the CSF examination should be repeated every 6 months. Re-treatment should be considered if CSF findings are unchanged.

The CDC recommends that because of the long incubation period for syphilis, any of a syphilis patient's sexual contacts who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis should be treated presumptively, even if that contact is seronegative. The CDC currently recommends that all HIV-infected patients be screened for syphilis and other sexually transmitted disease every 3 to 6 months.

The case presented here highlights the varied clinical manifestations of syphilis, especially during the secondary stage in an HIV-infected person. The acute presentation of bulky and diffuse lymphadenopathy resembles lymphoma. Our patient's HIV RNA level was still undetectable during the time of acute illness, and despite his high titers, he responded well to treatment with clinical resolution of his lymphadenopathy and appropriate decrease in serological titers. This patient's case was included in a recent retrospective study of 118 cases of syphilis diagnosed at this institution over 7 years. Patients presented with a wide range of symptoms, sometimes including only nonspecific complaints (such as sore throat, mouth ulcers, or cervical lymphadenopathy). The vagueness of these clinical presentations can lead to a lengthy delay in diagnosis.

In summary, there is no truly typical presentation of syphilis, since any organ system may be involved. It is important to maintain a high level of clinical suspicion, not only to prevent disease complications and to avoid unnecessary tests and procedures but also to prevent outbreaks and potential transmission of HIV.

References:

A "Usual" Case of Syphilis
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