The Trouble with Treponemes

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Asking about a patient's sexual history can mean the difference between a long, costly evaluation and a quick diagnosis when syphilis may be the etiology of the patient's symptoms.

A 43-year-old, black man with a history of hepatitis B presents to a primary care clinic with an enlarged lymph node in his left groin. He reports that this swollen lymph node has been present for several weeks. He says he has had no fever, chills, weight loss, rash, penile lesions or discharge, or previous episodes of a swollen lymph node in the groin area. He does not use tobacco or alcohol and has not been taking any medications.

Physical examination reveals a soft, 1- to 2-cm, nontender lymphadenopathy in the left groin without overlying skin changes. No genital lesions are apparent. Results of the patient's complete blood count and serum chemistries are normal. His provider prescribes levofloxacin PO 500 mg/day for suspected reactive lymphadenopathy.

When, after one month, his lymphadenopathy fails to resolve, he is given another two-week course of levofloxacin and is referred to an oncologist for evaluation of possible lymphoma. Computed tomography and positron emission tomography scans show cervical, axillary, hilar, abdominal, pelvic, and inguinal lymphadenopathy. Lymph node biopsy reveals reactive lymphocytosis. Bone marrow biopsy shows no sign of malignancy.

Based on these findings, his physicians explore infectious etiologies. They order an HIV antibody test and Lyme disease, Epstein-Barr virus, and cytomegalovirus titers—all of which are negative.

The patient is referred to the infectious disease clinic. Toxoplasmosis titers conducted there come back negative. A rapid plasma reagin (RPR) test, however, is reactive at 1:64, and this result is confirmed by a reactive fluorescent treponemal antibody.

After treatment with a total of 7.2 million U of benzathine penicillin IM for late latent syphilis, the patient's RPR titer decreases fourfold and his lymphadenopathy resolves.

CAN YOU IDENTIFY THE ERRORS?

The error in this case was the provider's failure to address the patient's sexual history and then consider sexually transmitted diseases (STDs) in the differential diagnosis of inguinal lymphadenopathy.

Obtaining a sexual history entails a discussion of how many sexual partners the patient has had, current sexual activity, condom use, and any history of genital ulcer disease. If the patient reports previous ulcer disease, the provider should ask about the nature of the disease, including whether the lesions were painful or recurrent. In addition, providers should not assume that a patient participates in heterosexual activity exclusively. Men who have sex with men have an increased risk of infection with a quinolone resistant STD. The practitioner in this case did appropriately discuss constitutional symptoms such as rash, fever, and weight loss, all of which can be associated with infectious etiologies as well as with malignancy.

Any patient with a history of a potential STD—hepatitis B in this patient's case—should be screened for other STDs, such as syphilis and HIV. This screening is particularly important with the increasing frequency of HIV and syphilis coinfection.[1] In this case, completing a more thorough history and STD investigation could have avoided a prolonged, expensive, and invasive workup.

GETTING TO THE ROOT OF THE PROBLEM

Syphilis has long been known as "the great imitator" because of its protean manifestations and diagnostic dilemmas. It is an STD caused by infection with the spirochete *Treponema pallidum*, which often passes through three overlapping clinical stages.

Primary syphilis

Patients with primary syphilis typically present with a chancre (a painless, small, round ulcer located at the site of infection) an average of 21 days after exposure (range, 10 to 90

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days). This stage is often associated with inguinal lymphadenopathy.

Secondary syphilis

Symptoms of secondary syphilis typically develop four to 10 weeks after the initial chancre. A rash occurs most often during this stage, usually described as macular or maculopapular. This rash commonly is found on the patient's trunk, arms, palms of the hands, or soles of the feet—but also may affect the face. The papules of secondary syphilis can coalesce in intertriginous areas, causing highly infectious lesions known as condyloma lata. The lesions may be accompanied by constitutional symptoms, such as low-grade fever, arthralgias, and generalized lymphadenopathy.

Another manifestation of secondary syphilis is the appearance of superficial, painless, mucosal erosions in the mouth or genital regions. Central nervous system (CNS) involvement during this stage can manifest as aseptic meningitis, cranial neuropathy, or anterior uveitis.

Latent syphilis

Latent syphilis is defined as the period after the manifestations of secondary syphilis resolve. Patients become asymptomatic at this time, which can be divided further into early and late stages.

About one third of individuals with untreated latent syphilis develop tertiary syphilis, characterized by gumma—which are inflammatory lesions of the skin, the CNS, or bone. General pareses from cerebral involvement and tabes dorsalis from posterior column demyelination characterize CNS involvement in tertiary syphilis.

Diagnosis

To make a syphilis diagnosis, mucocutaneous lesions, such as chancre or condyloma lata, can be scraped and examined under a dark-field microscope. This test is particularly important for patients with primary syphilis, in whom an antibody response may not yet be positive. The spirochete has a classic corkscrew or folding motion that is detectable using this method of examination—provided the slides are examined immediately. In addition, the examination's sensitivity varies with the skill of the technician.

Scrapings should be examined on three different days before a lesion is determined to be free of *T. pallidum*.[2] Direct fluorescent antibody assays, such as the fluorescent treponemal antibody-absorbed (FTA-abs) test, can be used to detect treponemal antigens from scrapings. These tests are advantageous because they can be performed on dried specimens and, therefore, do not require immediate evaluation by a specially trained microscopist.

Patients suspected of having syphilis are evaluated initially with a nontreponemal serology test, such as RPR or venereal disease research laboratory tests, both of which measure antibody response to lipoidal antigen.

Positive nontreponemal tests are confirmed with a treponemal test, such as the FTA-abs, that measures treponemal-specific antibodies by immunofluorescence. False-positive nontreponemal results may be seen with various conditions, including autoimmune diseases, tuberculosis, pregnancy, infectious mononucleosis, HIV, rickettsial infections, and other spirochete infections (such as leptospirosis).[3] Nontreponemal serology tests are 78% to 86% sensitive during the primary syphilis stage, 100% sensitive in secondary syphilis, and 95% to 98% sensitive in latent syphilis.[4] FTA-abs is 84% sensitive in primary syphilis and 100% sensitive in secondary and latent syphilis.[4]

GOOD NEWS IN TREATMENT

Fortunately, syphilis has not yet demonstrated any clinically significant resistance to penicillin—its therapeutic mainstay[3] and drug of choice for treatment. Primary, secondary, or early latent syphilis can be treated with benzathine penicillin G 2.4 million U IM in a one-time dose. Patients with late latent syphilis, syphilis of unknown duration, or tertiary syphilis should be treated with benzathine penicillin G 2.4 million U IM each week for three weeks.[5] Neurosyphilis should be treated with benzathine penicillin 3 to 4 million U IV every four hours or as a continuous infusion for 10 to 14 days.[5]

Second-line agents, such as doxycycline, can be used in penicillin-allergic patients who are not pregnant and do not have neurosyphilis. Penicillin-allergic patients who are pregnant or have neurosyphilis, however, should undergo penicillin desensitization.[5]

Follow-up with a nontreponemal serology test (such as RPR) at six months and 12 months is recommended. Treatment failure is defined as either the failure of titers to decline fourfold within six months or a fourfold increase in titers after treatment is completed.[5]

The RPR may not be available as a primary diagnostic modality in some settings with limited resources, where targeted test-and-treat eradication strategies are performed, because cold storage is required for reagents and electricity is needed to operate a rotator. To alleviate these drawbacks, new RPRs that are stable at room temperature are becoming more readily available, as are solar powered rotators.[6]

Similarly, confirmatory assays usually are not available outside of reference laboratories in these limited settings, but the availability of confir-

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matory testing platforms that do not require electricity also is increasing.[6] New platforms for predicting clinical phenotypes of infected strains of *T. pallidum* are under development. These may help identify patients who are at risk for developing neurosyphilis and, therefore, would benefit from more extensive evaluations, such as lumbar puncture or empiric therapy targeted at the CNS.[7]

The case presented here emphasizes the importance of primary care providers obtaining a thorough patient history and performing a complete physical examination in order to prevent unnecessary, time consuming, and costly evaluations. It also demonstrates the consequences of failing to obtain a comprehensive sexual history, as the patient's previous hepatitis B infection represents a history of a potential STD. ●

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