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CLINICAL VIGNETTE

Neurosyphilis and the Jarisch-Herxheimer Reaction in a Patient with HIV

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Case Presentation

A 38-year-old male with a past medical history of HIV presented with five months of body aches and profound fatigue. The patient also had a history of generalized anxiety disorder and recurrent herpes simplex virus (HSV) meningitis, currently on valacyclovir prophylaxis. He identified as gay and reported not having any new sexual partners since his long-term partner died a year prior. He was afebrile on presentation. His exam was notable for cervical lymphadenopathy and a diffuse maculopapular rash, clearly seen on his chest, abdomen, palms and soles. His labs showed a CD4 count of 547 cells/mm³, with a viral load of almost 36,000. His RPR titer was reactive at 1:64, and he had a positive confirmatory treponemal TP-PA test. Outside records showed the patient had a non-reactive RPR titer six months prior, confirming his current presentation and labs were consistent with secondary syphilis.

The patient was scheduled for administration of penicillin via intramuscular (IM) injection. During this visit, he provided additional history, including having a new sexual partner in the past six months and decreased daily adherence to his highly active antiretroviral therapy (HAART). He also mentioned new bilateral blurry peripheral vision for a couple of months, along with slow gait and difficulty remembering details. Patient's neurological exam was normal. However, in the setting of new neurological symptoms with the possibility of neurosyphilis, he was referred for urgent ophthalmologic evaluation.

Within eight hours of administration of IM penicillin, the patient experienced significant worsening of his symptoms. He developed high fever, shaking chills, malaise, nausea, emesis, and episodes of confusion which he described as feeling "delirious." With the use of antipyretics and an antiemetic, his symptoms significantly improved after 24 hours. Following recovery in his symptoms, the patient underwent ophthalmologic evaluation which did not reveal any abnormalities. He was seen in follow up and informed of the need for a lumbar puncture to confirm the diagnosis of neurosyphilis given his symptoms. The patient has prior lumbar punctures for recurrent HSV meningitis and did not want the procedure. Given his symptoms and a high RPR titer making neurosyphilis more likely, he was scheduled for empiric treatment with intravenous (IV) penicillin for 10 days through home health.

Following completion of empiric treatment for neurosyphilis, the patient reported significant improvement at follow-up. Specifically, the profound fatigue, the body aches and rash re-

solved. However, he felt his memory was not yet fully recovered and he still felt slow to remember usual details. His memory symptoms continued to improve, however, were not yet completely resolved at two-month follow-up.

Discussion

Syphilis is an infection caused by the spirochete *Treponema pallidum*, with most cases sexually transmitted.¹ In the United States, men who have sex with men (MSM) account for almost half of all cases of primary and secondary syphilis. In 2018, the rate of primary and secondary syphilis was 10.8 cases per 100,000 population. This was a 14.9% increase from the prior year. In addition, in 2018, 41.6% of cases of primary and secondary syphilis in MSM were in patients with HIV.² In 2015, of the 48,045 cases of syphilis reported in the U.S., 0.8% were classified as neurosyphilis.³ Early symptomatic neurosyphilis is also more common in patients with HIV.⁴⁻⁶ In addition, syphilis may increase the rate of HIV transmission, and by causing immunosuppression and decreased immune response by the host, can lead to higher rates of HIV disease.⁵ To prevent increases in coinfection and further complications, screening and prompt treatment is necessary. Primary care providers should be familiar with differing presentations for patients with and without HIV.

Syphilis has multiple stages characterized by typical presentations. Early syphilis, within the first twelve months of infection, can be separated into three clinical manifestations. The first is primary syphilis with a typical presentation of a painless ulcer or chancre. This ulcer is often missed by patients. Secondary syphilis often presents as a systemic illness. Similar to the initial symptoms described in the case, patients often present with a disseminated rash, which often involves the palms and soles, fever, headache and malaise. It is important to note that some patients may be asymptomatic, and this is referred to as early latent syphilis if it is within the first year of infection or late latent if thereafter.¹ In patients with HIV, multiple studies have noted secondary syphilis may present with hepatitis.⁷⁻⁸ A study of 62 patients with HIV diagnosed with early syphilis, reported almost 20% of participants developed hepatitis.⁷ Others have reported higher incidence up to 38%, with liver enzymes normalizing after treatment for syphilis.⁸ Rarely, co-infection may also present with pneumonitis in secondary syphilis.⁹

The late syphilis stage is characterized by either latent or tertiary syphilis. Tertiary syphilis is when patients develop cardiovascular or gummatous manifestations from the disease. About 15-40% of untreated people will develop tertiary syphilis. Neurosyphilis does not fit within a defined timeline, as it may present at any stage of the infection. Patients may present with meningitis, cranial nerve dysfunction, altered mental status, loss of vibration sense, or ocular symptoms.^{1,10} In a Johns Hopkins study of a cohort of 41 HIV patients with and neurosyphilis, a CD4 count less than 350 cells/mm³ and a RPR titer greater than 1:128 vs. less than 1:32 at the time of syphilis diagnosis were predictors of developing neurosyphilis. About 60% of patients diagnosed with neurosyphilis were symptomatic, and uveitis, confusion, headaches, and gait abnormalities were the most common presentations. For those asymptomatic, a lumbar puncture was performed in the absence of serologic response after treatment or high baseline RPR titer defined as greater than 1:32. At one-year follow-up, 38% of patients had persistence of their major symptom at diagnosis even after appropriate treatment.⁴ Other presentations of neurosyphilis in patients with HIV may be stroke without prodromal symptoms.¹¹ Therefore, screening to prevent such complications is key. In addition, a RPR titer of 1:32 or higher in a patient with HIV has been predictive of possible neurosyphilis.^{8,12} It has also been reported that in patients with HIV, neurosyphilis often presents in earlier stages, commonly concomitant with secondary syphilis.¹³

The treatment of syphilis varies based on stage and does not differ among patients with or without HIV. Typical treatment of early syphilis is one injection of Benzathine penicillin G 2.4 million units administered intramuscularly. Three doses are required seven days apart for either late latent syphilis or latent syphilis of unknown duration. The treatment recommended for neurosyphilis is IV penicillin 18–24 million units per day for 10-14 days.^{10,14} A reaction that can occur in the first 24 hours after administration of penicillin is the Jarisch-Herxheimer reaction (JHR), seen in the case reviewed. This reaction is characterized by fever, malaise, headache, exacerbation of rashes and myalgias. It can occur with treatment of other spirochetal infections such as Lyme disease and leptospirosis, but it presents most often after syphilis treatment.^{10,15} The pathophysiology of this reaction is thought to be secondary to activation of the cytokine cascade upon destruction of spirochetes.¹⁶ The most common antibiotic culprits include tetracycline and penicillin.¹⁵ For patients with neurosyphilis, prescribing a steroid course before the treatment may reduce the severity, although not the incidence, of JHR.⁵

Our patient showed typical signs of neurosyphilis with predominantly memory impairment. His predominant neurological symptom was persistent in follow-up after adequate treatment, which has been reported in a few prior cases. In patients with HIV, case reports have shown different presentations of this reaction. A 45-year-old male with HIV and neurosyphilis developed rigorous chills, tachycardia, and tachypnea after IV administration of penicillin. This presentation was initially confused with a drug allergy and upon further review deter-

mined to be JHR. The patient tolerated the rest of the IV course of penicillin.¹⁶ Other case studies have shown patients with HIV who develop JHR may also have a worsen flare of hepatitis resembling cholangitis.⁹

Conclusion

Syphilis can have multiple clinical manifestations. A high level of suspicion and familiarity with varying possible presentations are needed to test and treat accordingly. Prompt diagnosis and treatment is important to prevent complications. In patients with HIV, immunosuppression often characterized by a low CD4 count and the presence of a high viral load can predispose to development of neurosyphilis. When a patient with HIV develops any neurological symptoms, there should be a high suspicion for neurosyphilis. Similarly, given the synergistic relationship between HIV and syphilis, the presence of neurosyphilis should trigger immediate testing for HIV. In addition, patients may develop JHR after anti-treponemal treatment. It is important to counsel patients on the possibility of this reaction and treat empirically with antipyretics to lessen the immune response. Primary care physicians are at the forefront of patient care and should be familiar with the different presentations of syphilis for all sexually active patients, including those with HIV.

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