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Fever and Rash in a Patient With Hepatitis

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Figure. Left, Pigmented, macular rash on palmar surface of left hand. Right, Pigmented, macular rash on plantar surface of left foot.

A 56-year-old man with longstanding human immunodeficiency virus (HIV) infection presented for evaluation of new-onset fatigue and malaise. He was adherent to his antiretroviral therapy (ART) regimen (tenofovir/emtricitabine, raltegravir), with a recent CD4 lymphocyte count of 382 cells/mm³ (18%) and HIV RNA below the level of assay detection. Initial evaluation was unremarkable except for new abnormalities in hepatic laboratory results (alanine aminotransferase, 217 U/L (3.6 μ kat/L); aspartate aminotransferase, 149 U/L (2.5 μ kat/L); alkaline phosphatase, 610 U/L (10.2 μ kat/L); total bilirubin, 2.2 mg/dL (37.6 μ mol/L); and albumin, 3.1 g/dL). He denied having jaundice, pruritus, abdominal pain, or other gastrointestinal symptoms and reported no alcohol intake or recent use of new medications. He reported taking atorvastatin for dyslipidemia and testosterone gel for hypogonadism. Test results for hepatitis A, B, and C were negative, as were results for anti-smooth muscle and antimitochondrial antibodies. Results of a serum antinuclear antibody test were positive, with a titer of 1:640. Liver biopsy demonstrated moderately active interface and lobular hepatitis with plasma cells and periportal cholestasis, findings suggestive of autoimmune hepatitis. The patient was started on prednisone and azathioprine. Shortly thereafter he developed fever to 38.9°C and a macular rash that involved his palms and soles (Figure). Physical examination was otherwise normal.



Quiz at jama.com

WHAT WOULD YOU DO NEXT?

- A. Stop atorvastatin secondary to statin-associated hepatitis
- B. Continue prednisone and azathioprine for autoimmune hepatitis
- C. Check a rapid plasma reagin (RPR) test
- D. Biopsy the skin lesions

Diagnosis**Secondary syphilis with syphilitic hepatitis****What to Do Next**

C. Check a rapid plasma reagin (RPR) test.

Discussion

The key clinical features are malaise, fever, and a macular rash involving the palms and soles, findings highly suggestive of secondary syphilis. A wide range of other systemic manifestations may occur, including glomerulonephritis, periostitis, neurologic symptoms, and hepatitis. Syphilitic hepatitis in this patient is suggested by a disproportionate elevation of serum alkaline phosphatase accompanied by modest increases in bilirubin and hepatic transaminase levels.¹ Idiosyncratic liver injury associated with statins can present with a cholestatic or hepatocellular injury pattern, although it is a relatively rare condition and is not associated with a rash involving the palms and soles.² Biopsy of skin lesions is 74% to 94% sensitive for the diagnosis of syphilis when combined with immunohistochemistry³ but is not usually necessary in secondary syphilis, which is diagnosed with a reactive RPR confirmed by a treponemal-specific serologic test.

Whereas liver disease associated with late syphilis (eg, liver gummas) was described long ago, hepatitis as part of early syphilis is a relatively recently recognized phenomenon. In 1975, Fehér et al published a case series of 17 patients with untreated early syphilis in whom liver tests indicated hepatic injury. Examination of liver tissue demonstrated the presence of treponemes in 7 of these patients.⁴ Hepatic inflammation attributable to *Treponema pallidum* involves a neutrophil-predominant infiltrate localized around the portal triad and bile ductules.⁵ Necrosis of hepatocytes is usually focal and concentrated around the portal vessels. Significant cholestasis is not a prominent feature, although mild elevation in serum bilirubin level can be present owing to biliary congestion related to pericholangiolar inflammation. The disproportionate elevation of serum alkaline phosphatase is thought to be a consequence of the inflammatory response around the bile ductules. Syphilis-induced inflammation is characterized by plasma cell–predominant infiltrates in a variety of or-

gan systems, although not typically in syphilitic hepatitis. Plasma cell infiltrates, however, are often seen in autoimmune hepatitis.⁶ Autoimmune disease, perhaps counterintuitively, can occur in HIV-infected persons. Autoimmune hepatitis is more often seen when CD4 count is high (>500 cells/mm³), presumably because the response is mediated by CD4⁺ T cells.⁷

Syphilis, in keeping with its reputation as the “great imitator,” can present with myriad clinical syndromes, challenging the acumen of diagnosticians. The reemergence of syphilis has become a public health concern over the past 15 years.⁸ During this time, the rate of infection has more than doubled, from 2.1 to 5.3 cases per 100 000 US population.⁹ This reemergence, especially in men who have sex with men, including those who are HIV-infected, should prompt clinicians to consider syphilis as a possible diagnosis for a wide range of clinical presentations in this group.

The diagnosis of secondary syphilis implies recent unprotected sexual exposure and should prompt a thorough sexual history. Early (primary and secondary) syphilis is far more transmissible than latent or late syphilis, and the diagnosis mandates a discussion of safer sexual behaviors. Effective antiretroviral therapy has substantially reduced the risk of HIV transmission, prompting some to suggest that the use of barrier protection during sex is no longer required for patients with well-controlled HIV infection.¹⁰ It is important to emphasize, however, that antiretroviral therapy has no effect on transmission of other sexually transmitted infections, including syphilis.

Patient Outcome

The RPR was reactive at a titer of 1:256. A *T pallidum* IgG enzyme immunoassay was also reactive, confirming the diagnosis of syphilis. Immunohistochemical staining of the liver biopsy specimen demonstrated spirochetes to be present. The patient was prescribed 2.4 MU of intramuscular benzathine penicillin G. His fever and rash resolved promptly, as did his abnormal hepatic laboratory values. Azathioprine and prednisone were discontinued. At follow-up 4 months later, his liver panel remained within normal limits, and his RPR titer had decreased to 1:8.

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Submissions: We encourage authors to submit papers for consideration as a JAMA Clinical Challenge. Please contact Dr McDermott at mdm608@northwestern.edu.

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