

Syphilitic Hepatitis in HIV-Infected Patients: A Report of 7 Cases and Review of the Literature

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Background. A recent resurgence of primary and secondary syphilis has been observed in certain population groups, particularly among persons infected with human immunodeficiency virus (HIV). Liver involvement is an infrequently recognized complication of early syphilis, with no previous reports among HIV-infected patients.

Methods. We describe 7 cases of syphilitic hepatitis in HIV-positive individuals and review the literature.

Results. At our institutions, all patients presented with a rash consistent with secondary syphilis. Each case was characterized by a conspicuous increase in serum alkaline phosphatase level (mean level \pm standard deviation, 905 ± 523.6 IU/L) and milder elevations in serum transaminase levels. The mean CD4⁺ absolute T cell count was 317 cells/mm³, and the median rapid plasma reagin (RPR) titer was 1:128. There was a significant correlation between higher CD4⁺ cell counts and the RPR titers ($R = 0.93$; $P = .002$). Symptomatic resolution and biochemical improvement, particularly a significant decrease in serum alkaline phosphatase levels ($P = .02$), occurred following antibiotic therapy.

Conclusions. Hepatic dysfunction is not uncommon in HIV-infected persons and is attributable to multiple causes. In the appropriate clinical setting, syphilitic hepatitis is an easily diagnosed and reversible etiology of liver dysfunction. The recognition of this entity will prevent unnecessary evaluation of abnormal liver enzyme levels in HIV-positive patients.

Liver enzyme abnormalities in HIV-positive individuals frequently pose a diagnostic challenge. Elevation of liver enzyme levels may be due to opportunistic infections such as infection with *Mycobacterium avium* complex (MAC), cytomegalovirus (CMV), or *Cryptosporidium* species [1]. High rates of coinfection with hepatotropic viruses, hepatitis B virus and hepatitis C virus, are of increasing concern. Neoplastic diseases, such as non-Hodgkin lymphoma and Kaposi sarcoma, can also be associated with liver involvement. Alcohol abuse and use of potentially hepatotoxic medications, including many antiretroviral agents, can further contribute to liver damage [2, 3].

Treponema pallidum, the etiologic agent of syphilis, is known to cause disease in virtually every organ in the human body, including the liver. The incidence of

primary and secondary syphilis has increased substantially over the past several years in populations engaged in high-risk behavior [4–6]. Despite sharing a common mode of transmission, there have been no reported cases in the literature of hepatitis attributed to syphilis in HIV-infected individuals.

At our institutions (George Washington University Medical Center and Veterans Affairs Medical Center; Washington, D.C.), we have identified 7 cases of hepatitis due to secondary syphilis in HIV-infected patients. Elevation of liver enzyme levels resolved with antibiotic therapy in all patients. Given the variety of infectious and toxic hepatic complications encountered by patients with underlying HIV infection, recognizing this reversible cause of hepatitis may not only assist in determining the course of therapy but also defray the costs of unnecessary medical testing.

CASE REPORT

A 39-year-old homosexual man with HIV infection presented to the Infectious Diseases clinic of George Washington University Medical Center in February 2001 with a 3-week history of dull, intermittent abdominal

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pain located in the right upper quadrant. The patient denied fever, chills, nausea, and vomiting. There was no associated melena or change in bowel habits. There was no history of alcohol abuse or recent consumption of acetaminophen or any other over-the-counter medication. The patient denied unprotected sexual exposure.

HIV infection had been diagnosed in this patient in 1986 with no history of opportunistic infection. Six months prior to presentation, the patient's antiretroviral regimen consisted of lamivudine, stavudine, and indinavir, and the absolute CD4⁺ T cell count was 455 cells/mm³. The patient's plasma HIV RNA level was 1145 copies/mL as determined by the Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostic Systems).

Physical examination findings were notable for the presence of scleral icterus and a generalized papular rash. Abdominal examination revealed mild right upper quadrant tenderness not associated with rebound, guarding, or Murphy sign. The findings of a genitourinary and rectal examination were unremarkable. The complete blood cell count and the differential blood cell count were within normal limits. The alkaline phosphatase level was 727 IU/L (normal level, 20–125 IU/L), the total bilirubin level was 4.1 mg/dL, and urinalysis revealed 2+ bilirubin. The results of serum albumin and coagulation studies were normal. Serological test results were negative for acute hepatitis A and chronic hepatitis B and C infections. The abdominal ultrasound was unrevealing for hepatobiliary pathology. The serum rapid plasma regain (RPR) titer was 1:4096, and the results of a fluorescent treponemal antibody absorption test (FTA-Abs) were reactive.

Treatment for secondary syphilis was initiated with aqueous penicillin G at a dosage of 5 million units intravenously every 6 h. Two weeks of antibiotic therapy were completed with complete resolution of rash, abdominal pain, and icterus. After therapy, there was normalization of the serum alkaline phosphatase level (139 IU/L) and total bilirubin level (0.8 mg/dL). RPR test results were nonreactive 12 months after treatment.

METHODS

Case definition. Following the recognition of syphilitic hepatitis in the patient described above, we subsequently collected data on 6 additional cases in HIV-infected patients at our institutions during the period 2001–2003. The diagnosis of syphilitic hepatitis was made on the basis of the following criteria: (1) abnormal liver enzyme levels indicating hepatic involvement; (2) serological evidence for syphilis, with a positive RPR titer and a reactive FTA-Abs result or microhemagglutination assay result positive for *T. pallidum* (MHA-TP) in conjunction with an acute clinical presentation consistent with secondary syphilis; (3) exclusion of alternative causes of hepatic damage, such as acute viral hepatitis, use of medication, malignancy, or

opportunistic infection; and (4) improvements in liver enzyme levels following appropriate antimicrobial therapy.

Data on age and on clinical manifestations of early syphilis (i.e., presence of genital ulcers, fever, or generalized rash consistent with syphilis) were collected for each patient. Laboratory tests included measurement of liver-related enzyme levels (i.e., alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase levels), measurement of total bilirubin level, RPR titer, FTA-Abs, or MHA-TP, and CD4⁺ and CD8⁺ T lymphocyte counts at the time of diagnosis and after therapy. Historical liver enzyme levels recorded prior to presentation with hepatitis were retrieved from patient charts. Plasma quantitative HIV RNA levels were measured at the George Washington University Medical Center using the Amplicor HIV-1 Monitor Test, version 1.5, and at the Veterans Affairs Medical Center using the Versant HIV-1 RNA 3.0 assay (bDNA) (Bayer Diagnostics). The presence of comorbid conditions, including viral hepatitis, active alcohol consumption, injection drug use, and concurrent HAART, was documented.

Literature review. A search of the MEDLINE database (from January 1966 through 31 April 2004) was conducted utilizing the keywords “syphilis,” “HIV,” “AIDS,” “immunodeficiency,” “hepatitis,” “hepatic,” “liver,” and “jaundice” to identify case reports, series of cases, and descriptions of syphilitic hepatitis published in the English-language literature.

Statistical analyses. Laboratory data obtained before and after therapy were analyzed with a 2-tailed Student's *t* test. A Pearson correlation analysis for CD4⁺ and CD8⁺ T lymphocyte counts and RPR titer (log₂) were performed using the SPSS statistical package, software version 11.0 (SPSS).

RESULTS

All 7 patients with syphilitic hepatitis were male, with a mean age (\pm SD) of 39.9 \pm 8.4 years. The mean absolute CD4⁺ and CD8⁺ T lymphocyte counts, HIV RNA level (log₁₀ copies/mL) at or within 6 months of diagnosis, and the RPR titer (log₂) at the time of presentation with secondary syphilis are shown in table 1. Although 1 patient met the criteria for AIDS (CD4⁺ cell count, <200 cells/mm³), none of the patients were severely immunocompromised with advanced disease.

Four of the 7 patients were outpatients when they received a diagnosis, and 3 patients had been hospitalized because of the severity of presenting symptoms before receiving a diagnosis (table 2). Only 2 patients were prescribed HAART at the time of diagnosis. None of the patients had a prior history or documentation of syphilis. Liver enzyme data preceding the presentation of hepatitis was available for 5 patients, and these values were within the normal range. For all patients, a detailed history failed to reveal a change in either usage of routine prescription medications or use of over-the-counter antipyretics prior to presentation. In 6 of the 7 patients, the initial

Table 1. Laboratory data for 7 HIV-infected patients with syphilitic hepatitis at the time of diagnosis and selected hepatobiliary parameters after antibiotic therapy of 2–6 weeks duration for 5 patients with available data.

Variable	Laboratory value			P ^a
	Mean ± SE	Range	Normal range	
RPR titer (log ₂)	6.71 ± 3.68	1–12		
T cell count ^b , cells/mm ³				
CD4 ⁺	317.3 ± 108.1	183–455	490–1740	
CD8 ⁺	838.1 ± 208.8	371–1982	180–1170	
HIV RNA level, log ₁₀ copies/mL	3.99 ± 0.88	2.79–4.87		
Alkaline phosphatase level, IU/L			20–125	
At diagnosis	905.9 ± 523.6	234–1870		
After therapy ^c	295.2 ± 51.8	109–409		.02
Alanine aminotransferase level, IU/L			2–60	
At diagnosis	183.3 ± 91.7	95–332		
After therapy ^c	116 ± 43	45–284		NS
Aspartate aminotransferase level, IU/L			2–50	
At diagnosis	159.6 ± 71.2	76–276		
After therapy ^c	90 ± 37	35–234		NS
Total bilirubin level, mg/dL			0.3–1.3	
At diagnosis	4.1 ± 5.1	0.2–13.6		
After therapy ^c	1.0 ± 0.3	0.2–2.0		NS

NOTE. NS, not significant; RPR, rapid plasma reagin.

^a Determined with paired 2-tailed Student's *t* test.

^b Mean T cell percentages were as follows: CD4⁺ cells, 22%; CD8⁺ cells, 52%.

^c Data are for 5 patients with values available for the period 2–6 weeks after completion of antibiotic therapy.

evaluation included abdominal imaging studies to rule out intrahepatic lesions, obstructive extrahepatic masses, and cholelithiasis. The results of serological tests for hepatitis B infection were negative in all patients; however, chronic hepatitis C infection had been diagnosed in 1 of the patients (patient 6) 4 years prior to presentation. Patient 3 was an active injection drug user; none of the patients reported current alcohol abuse.

All patients presented with a rash consistent with secondary syphilis, and skin involvement was the only notable physical finding in 2 patients. Although there were no documented genital or rectal ulcers, other symptoms included fever, jaundice, and right upper quadrant abdominal pain (table 2). The RPR titer ranged from 1:2 to 1:4096, with a median value of 1:128. Patient 1, whose RPR titer was only 1:2, had a convincing clinical presentation for secondary syphilis that met our case definition. His diagnosis was also supported by a positive MHA-TP result (4+) at the time of this diagnosis and a negative RPR result documented 8 weeks earlier.

Only 1 patient had a CD4⁺ cell count of <200 cells/mm³ at the time of diagnosis of syphilitic hepatitis, and all patients had a detectable HIV RNA level (table 2). A correlation analysis revealed that there was a significant relationship between higher absolute CD4⁺ cell counts and the RPR titer (log₂) (*R* = 0.93; *P* = .002) (figure 1). This relationship was not evident between RPR titer and absolute CD8⁺ cell count.

The most prominent laboratory abnormality at the time of presentation was a marked elevation of alkaline phosphatase levels in all patients. Milder elevations in liver transaminase levels were noted in all patients, and modest hyperbilirubinemia occurred in 3 individuals (table 1).

Treatment consisted of a 14-day course of intravenous β-lactam antibiotics. Patient 6, who had known coinfection with hepatitis C virus prior to presentation, had the highest liver enzyme levels after treatment. After antibiotic therapy, there was a significant reduction in the mean (±SD) alkaline phosphatase level (905 ± 523.6 vs. 295.2 ± 51.8 IU/L; *P* = .02), and the other liver-associated enzyme levels trended towards normal in all patients (table 1).

DISCUSSION

Following a remarkably low incidence over several years, the prevalence of primary and secondary syphilis has increased in the United States since 2001, particularly among individuals at risk for HIV infection [4]. Sexual transmission of *T. pallidum* classically results in localized ulcerative disease, with subsequent dissemination resulting in mucocutaneous and visceral involvement. HIV-infected patients who engage in unsafe sexual practices are at an increased risk for coinfection with syphilis. Recognition of syphilitic hepatitis as a reversible cause of liver

Table 2. Clinical and demographic features at the time of presentation and antibiotic treatment received for 7 HIV-infected patients with syphilitic hepatitis.

Patient	Age, years	Symptoms and physical findings	RPR titer	CD4 ⁺ cell count, cells/mm ³	HIV RNA level, copies/mL	Antibiotic treatment
1	40	Rash, right upper quadrant abdominal pain, and fever	1:2	183	46,021	Penicillin G
2 ^a	33	Rash	1:16	260	75,000	Ceftriaxone
3 ^a	35	Rash, jaundice, and fever	1:32	214	40,000	Penicillin G
4 ^a	50	Rash	1:128	298	2525	Penicillin G
5 ^b	30	Rash, jaundice, and fever	1:512	365	617	Penicillin G
6	52	Rash and fever	1:512	446	38,876	Penicillin G
7 ^b	39	Rash, jaundice, and right upper quadrant abdominal pain	1:4096	455	1145	Penicillin G

NOTE. RPR, rapid plasma reagin.

^a Hospitalized at time of diagnosis.

^b Previously prescribed HAART.

dysfunction highlights the importance of considering the diagnosis in persons with HIV infection.

Despite the recognition of hepatic involvement with syphilis in 1585 by Paracelsus, nearly 30 years have elapsed since a series of patients with syphilitic hepatitis has been described. An extensive search of the MEDLINE database identified 48 cases of syphilitic hepatitis reported since 1966 [7–33]. Secondary syphilis in immunocompromised, HIV-infected individuals accompanied by liver involvement has never previously been reported.

The largest review to date, performed by Feher et al. [14] in 1975, identified 17 cases of early (i.e., primary and secondary) syphilis with hepatic abnormalities. Although hepatomegaly was a common clinical finding, elevation of alkaline phosphatase levels was not a prominent feature in this early study. Since 1975, isolated case reports have described hepatic abnormalities in individuals with clinical and serological evidence of secondary syphilis. In contrast to the early case series of Feher et al. [14], these published reports highlighted the presence of accompanying generalized rash, a marked elevation of serum alkaline phosphatase levels, and a modest increase in bilirubin and hepatic transaminase levels [15–33].

The key histological findings in cases of syphilitic hepatitis include a nonspecific periportal hepatocyte necrosis, pericholangiolar inflammation, and an inconsistent demonstration of spirochetes. Several investigators have attributed the cholestasis and elevation of serum alkaline phosphatase levels to an intense pericholangiolar inflammation [9–11, 17, 22].

Despite the extent of biochemical and histological derangement in cases of syphilitic hepatitis, as well as the high vascularity of the liver, treponemes have been demonstrated in liver biopsy specimens in only 15 of the reported cases. Feher et al. [14], who reported 7 of these cases, did not comment on any factors that may predispose to higher levels of spiroche-

temia. Of 8 patients who were described more recently, 1 patient was receiving immunosuppressive therapy after liver transplantation [29], 2 patients were found to have rectal condylomas at the time of diagnosis of hepatic disease [10, 23], 3 patients were men who had sex with men [10, 23, 25], and 4 patients had no apparent predisposing factors [13, 27]. The HIV status of these individuals was not described. The failure to demonstrate spirochetes in liver biopsy samples may be due to technical factors during storage and staining of specimens or be the result of effective phagocytosis by the Kupfer cells.

The clinical manifestations of syphilitic hepatitis are thus attributable to the periportal inflammatory response accompanying treponemal invasion. It is postulated that the dissemination of spirochetes from sites of primary lesion during the secondary stage of infection results from poor host immune response, whereas the spontaneous resolution of lesions of secondary syphilis result from subsequent development of cell-mediated immunity [34, 35]. In the HIV-infected host, there

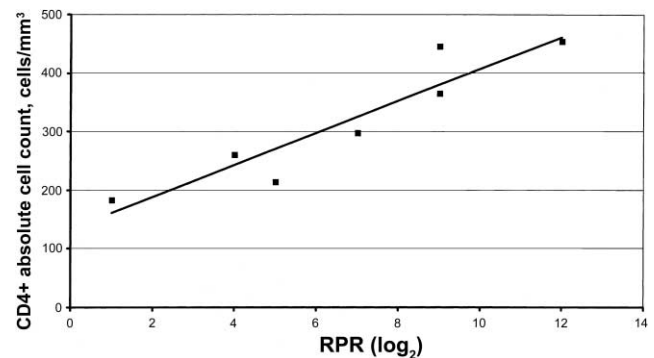


Figure 1. Rapid plasma reagin (RPR) titer (log₂) and CD4⁺ T lymphocyte count for 7 HIV-positive patients with syphilitic hepatitis (Pearson correlation coefficient: $R = 0.93$; $P = .002$)

is aberrant cellular immune activation, as well as dysregulation of B lymphocyte function [36, 37]. These factors may contribute to the ineffective host defense and containment of spirochetes during the primary stage of infection and to the persistence of the secondary stage of infection.

In a finding similar to prior observations of syphilitic hepatitis, the 7 HIV-positive patients in our institution presented with generalized rash characteristic of secondary syphilis and disproportionate elevation of serum alkaline phosphatase levels. At presentation, the level of underlying immune suppression did not warrant testing for either MAC- or CMV-related hepatitis in the initial diagnostic evaluation of these patients. No other causes of acute hepatitis were identified by imaging or laboratory testing, including acute viral hepatitis. Liver biopsy was performed in the 1 patient with a history of chronic hepatitis C virus infection, but examination of the biopsy specimens failed to reveal spirochetes by Warthin-Starry stain. None of the patients had evidence of extrahepatic visceral involvement.

The mean CD4⁺ absolute T cell count in our patients was 317 cells/mm³ (normal range, 490–1740 cells/mm³) and had a range of 183–455 cells/mm³, reflecting a relatively intact immune system in these patients. One can speculate that the periportal inflammation responsible for the clinical and laboratory manifestations of this infection is more likely to be evident in patients with a preserved host immune response. It may also be true that patients with higher CD4⁺ cell counts are less likely to experience the debilitating medical complications of HIV infection. Healthier patients may engage in high-risk sexual behaviors, increasing their likelihood of acquiring syphilis. However, we found that there was a relationship between the RPR titer and the absolute CD4⁺ T lymphocyte count at the time of diagnosis, which was not related to therapy with HAART. Higher titers correlated with higher CD4⁺ T lymphocyte counts and suggest that the host inflammatory response is indeed a factor in the development of the clinical manifestations of syphilitic hepatitis.

The most convincing evidence for the etiologic role of syphilis in promoting hepatocellular injury is the rapid remission of clinical and biochemical abnormalities following treatment. Posttreatment histological findings among the group of subjects reported in Feher et al. [14] showed resolution of inflammation in all 14 patients and absence of spirochetes in the 7 patients who had demonstrable organisms before initiation of therapy. In our series, additional liver biochemistry studies that were performed after completion of treatment with β -lactam antibiotics revealed a decrease towards baseline values in all the patients. A Jarish-Herxheimer reaction with worsening of skin rash and transient increase in liver enzyme levels after administration of penicillin has been described [32, 33], but neither of these posttherapy effects were noted in our patients.

In HIV-infected individuals, hepatic involvement can present

together with the cutaneous manifestations of secondary syphilis. Patients with higher CD4⁺ cell counts may be more likely than others to manifest clinical hepatitis as a result of a more robust inflammatory response in the periportal region. The recognition of this relatively infrequent manifestation of syphilis is not only important therapeutically but may assist in reducing unnecessary medical costs that might otherwise be incurred in evaluating elevated liver enzyme levels in HIV-infected patients. The diagnosis should be entertained as a potential etiology of abnormal liver enzyme levels in the proper clinical setting, and the condition is reversible with appropriate antimicrobial therapy.

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