Syphilis-Related Hepatitis in a Liver Transplant Patient

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We herein describe a case of secondary syphilis hepatitis in a liver transplant patient. This homosexual man presented 15 years after an orthotopic liver transplant with nonsquamous papillomacular rash, mild cytolysis, and anicteric cholestasis. Laboratory tests showed syphilis seroconversion with a VDRL test titer of 1/256, a *Treponema pallidum* hemagglutination assay of 1/5120, and a positive immunoglobulin M fluorescent *Treponemal* antibody absorbance. A liver biopsy performed 13 months after the diagnosis showed low-grade hepatitis with a METAVIR score of A1F1; it also showed moderate, nonspecific portal inflammation consisting primarily of neutrophils, with no evidence of cholestasis. The patient was given benzathine-penicillin (2 400 000 IU) with a transient increase in prednisolone dosages. Cytolysis rapidly, and cholestasis progressively, disappeared. Results of an immunoglobulin M fluorescent *Treponemal* antibody absorbance test became negative, whereas the VDRL test and the *Treponema pallidum* hemagglutination assay titers decreased slightly over time.

Key words: *Tissue transplantation, Hepatitis virus, Treponema pallidum, TPHA, VDRL*

Treponema pallidum, the etiologic agent of syphilis, is known to cause disease in virtually every organ in the human body, including the liver. Recently, there has been a resurgence of primary and secondary syphilis in persons infected with human immunodeficiency virus (HIV), where hepatic dysfunction is not uncommon. The manifestations include a conspicuous increase in the patient's alkaline phosphatase level and milder elevations in serum transaminase levels (1). Conversely, in recipients of organ transplants, hepatic syphilis has been reported only 3 times, that is, in 2 patients in the context of secondary syphilis and another in the context of late syphilis (2-4). The first case that described a liver transplant patient receiving azathioprine/steroid immunosuppression was in 1983, but no liver biopsy was performed. Here, we describe a likely case of secondary syphilis hepatitis in a liver transplant patient, in a homosexual man 15 years after receiving a transplant.

Case

A 53-year-old homosexual man underwent an orthotopic liver transplant in August 1989 because of end-stage liver disease related to hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) cirrhosis. Immunosuppression was accomplished with cyclosporine, steroids, and azathioprine with antithymocyte globulin induction. The results of his liver function tests were normal at month 1 and remained so until the end of 2003. He had no recurrence of HBV, HCV, or HDV infections. In March 2004, he presented at the outpatient clinic with a nonsquamous papillomacular rash on the trunk, arms, and thighs, without fever of 1 month's duration. The results of a genitourinary examination were unremarkable. He had neither hepatosplenomegaly nor lymphadenopathy. There was neither pruritus nor icterus. Medications included azathioprine (50 mg b.i.d.), cyclosporine (60 mg b.i.d.), atenolol (50 mg q.d.), and ursodeoxycholic acid (200 mg q.d.). His cyclosporine C2 level was 249.6 nmol/L. His liver function tests showed mild cytolysis (aspartate aminotransferase, 1.65 μkat/L; alanine aminotransferase, 2.28 μkat/L) associated with anicteric cholestasis (gamma glutamyl

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transpeptidase, 2.55 μkat/L; alkaline phosphatase, 2.55 μkat/L; total bilirubin, 14 μmol/L). Results of a liver ultrasonography were normal. Polymerase chain reaction results for serum HBV, HDV, HCV, hepatitis E virus, human herpesvirus 6, and parvovirus B19 were negative. HIV1 and HIV2 serologies were negative. Liver autoantibodies were also negative. Other laboratory results included leucocytes, 6.1×10^9/L; hypereosinophilia, 0.53×10^9/L; mild thrombopenia (platelets, 149×10^9/L); and hemoglobin level, 152 g/L. The CD4 count was 0.55×10^9/L and the CD4/CD8 ratio was 1. His serum creatinine level was 100 μmol/L; there was no proteinuria. Conversely, the syphilis serology was strongly positive (see Table). The VDRL titer was 1/256, the *Treponema pallidum* hemagglutination assay (TPHA) was positive at 1/5120, and the IgM fluorescent *Treponemal* antibody absorbance was positive.

At this point, we retrospectively assessed the patient's serum for syphilis, which had been collected 1 year before signs of syphilis appeared; the results were negative. After a thorough discussion with the patient, he acknowledged that he had had many same-sex partners within the previous months. A liver biopsy was performed, but unfortunately, no hepatic tissue was recovered. Thus, the patient was diagnosed as having secondary syphilis that involved the liver allograft. He was given benzathine-penicillin at a dose of 2 400 000 IU, and prednisolone was transiently increased to 40 mg/day for 3 weeks in case there was syphilis-related portal inflammation. There was no Jarisch-Herxheimer reaction. Treatment was associated with a slow decrease in cholestasis and VDRL titers (see Table). IgM fluorescent *Treponemal* antibody absorbance remained positive for 13 months and then became negative. Thirteen months after the initial diagnosis of secondary syphilis, the patient underwent a liver biopsy: this showed low-grade hepatitis with a METAVIR score of A1F1; it also showed nonspecific, moderate, portal inflammation primarily including neutrophils, with no evidence of cholestasis. No Treponema spirochetes were found with a Warthin-Starry silver stain. Finally, there were no signs of acute or chronic rejection; in particular, there was no ductopenia.

Discussion

Treponema pallidum, the etiologic agent of syphilis, is known to cause disease in virtually every organ of the human body, including the liver. Recognition of hepatic involvement with syphilis, and the avocation of treating syphilis with mercury, was made in the

Table Laboratory data of the liver transplant patient with secondary syphilis

Tests	May 2003	Feb 2004	April 2004	Sept 2004	Oct 2004	April 2005	Oct 2005	March 2006
VDRL	Negative	ND	1/256	1/64	1/32	1/8	1/8	1/16
TPHA	Negative	ND	1/5120	1/40960	1/40960	1/40960	1/20480	1/40960
IgM FTA ABS	ND	ND	++++	++	++	++	+/-	+/-
AST (normal range, 0.05-0.5 μkat/L)	0.45	1.65	0.75	0.67	ND	0.43	0.43	0.43
ALT (normal range, 0.08 -0.57 μkat/L)	0.42	2.28	0.63	0.63	ND	0.35	0.35	0.62
AP (normal range, 1.67-4.67 μkat/L)	1.28	2.55	3.07	5.52	5.66	4.25	3.37	1.13
GGT (normal range, 0.11-0.63 μkat/L)	0.92	2.52	1.65	2.32	2.58	1.33	1.45	1.18
Bilirubin (μmol/L)	15	14	28	16	24	8	22	17
Creatinine (μmol/L)	104	96	94	97	99	113	99	81
LDH (normal range, 3.51-6.35 μkat/L)	1.75	9.38	7.4	7.93	ND	6.91	6.48	6.29

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; FTA-ABS, fluorescent *Treponemal* antibody absorbance; GGT, gamma glutamyl transpeptidase; Igm, immunoglobulin M; LDH, lactate dehydrogenase; ND, not determined; TPHA, *Treponema pallidum* hemagglutination assay

mid 1500s by Paracelsus (5). However, the first case reported in the literature was in 1967 (6). The incidence of primary and secondary syphilis has substantially increased over the past several years in populations engaged in high-risk sexual behavior (7). Secondary syphilis is one of the causes of hepatitis in HIV-infected patients (1).

Syphilis should be considered in patients with acute liver dysfunction, especially if they are homosexual men, because it is easily treatable at this stage. Syphilis hepatitis may be mild to severe. The first and largest study, published in 1975, identified 15 cases of early syphilis with liver dysfunction. Hepatomegaly was a common clinical finding, whereas elevation of alkaline phosphatase was not (8). Since then, many hepatic syphilis cases have shown a marked elevation of serum alkaline phosphatase, and a modest increase in bilirubin and hepatic transaminases (1). The key histologic findings in cases of syphilitic hepatitis include nonspecific periportal hepatocyte necrosis, pericholangiolar inflammation, and an inconsistent presence of spirochetes (9).

To the best of our knowledge, this is the second case of suspected hepatic syphilis in a liver transplant patient. Secondary syphilis has only been reported, so far, in 3 organ transplant patients. The first case (2) was reported in 1983, in a 48-year-old homosexual man who was a recipient of a liver transplant for HBV-related cirrhosis. His clinical and biological presentation included diffuse pain, low-grade fever, skin rash, cholestasis, and thrombopenia. No liver biopsy was performed. He recovered after a course of penicillin. The second case is that of a 24-year-old heterosexual black patient who, at 16 months after receiving a renal transplant, presented with a fever (38.2°C), a small erythematous ulcer on the foreskin surrounding the glans penis, and scleral icterus. A biological examination found hepatic cytolysis with icteric cholestasis; the liver biopsy stained positive for *T. pallidum*, and an unfixed section of the liver showed spirochetes. Liver-function test results returned to normal after benzathine-penicillin treatment (3). The third case report involved a cardiac transplant patient (4). This was a 45-year-old man who had undergone orthotopic heart transplant 7 years earlier. He presented with late syphilis with cutaneous lesions, an increase in alkaline phosphatase levels, and neurologic symptoms, that is, altered mental status and gait instability. A Warthin-Starry silver stain on a skin biopsy taken from one of the palmar collarettes demonstrated numerous spirochetes. This patient had contracted syphilis 20 years earlier and probably had not received sufficient treatment. Pretransplant VDRL test serology was not available. After benzathine-penicillin therapy, his skin lesions resolved and alkaline phosphatase levels normalized.

HIV-infected patients have been found to have high titers of rapid plasma regain and high CD4+ T lymphocyte counts (1). This suggests that the host inflammatory response is a factor in the development of clinical manifestations of syphilis-related hepatitis. Indeed, our patient had a normal CD4 count. The most convincing evidence for the etiologic role of syphilis in promoting hepatocellular injury is the absence of histologic signs of acute or chronic rejection, and the remission of clinical and biochemical abnormalities following treatment.

To date, there have been no reports of syphilis transmission through organ procurement. However, there are 2 reports of brain-dead syphilitic donors who had received penicillin G (10) or ceftriaxone (11) before organ procurement; there was no subsequent transmission to the recipient.

Our report highlights the fact that in immunocompromised patients, such as organ transplant patients with high-risk sexual behavior, safe sex instruction is a necessary part of pretransplant counseling. Moreover, one must consider secondary syphilis when the patient presents with skin rash and liver dysfunction. Rapid initiation of treatment with penicillin results in a cure.

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