A Case of Syphilis Presenting with Initial Syphilitic Hepatitis and Serological Recurrence with Cerebrospinal Abnormality

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Abstract

We present the case of an immunocompetent 50-year-old Japanese man with a cerebrospinal fluid (CSF) abnormality relevant to syphilis; his original presentation was liver dysfunction, the etiology of which was uncertain until positive serology for syphilis was identified. Liver dysfunction was promptly resolved after oral penicillin therapy; however, serological recurrence developed. CSF abnormality associated with syphilis was confirmed by subsequent lumbar puncture. Syphilis should be included in the differential diagnosis of patients with liver dysfunction of unknown etiology, and possible neurosyphilis should be considered when the treatment becomes refractory, even when there is no evidence of neurological manifestations.

Key words: syphilitic hepatitis, cerebrospinal fluid abnormality, neurosyphilis

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Introduction

The incidence of syphilis, a sexually transmitted disease, has increased substantially over recent years in Japan, especially in populations involved in high-risk sexual behavior (1). Syphilis is a systemic disease caused by the bacterium Treponema pallidum (T. pallidum), and a wide variety of organs are recognized to be involved, including the liver. The incidence of distinctive liver dysfunction, termed syphilitic hepatitis, is uncommon in early syphilis; however, this complication can occasionally occur, and several reports on syphilitic hepatitis have been published to date (2). Syphilitic hepatitis is a reversible condition, which responds well to antibiotics, therefore early recognition of the disease is important to facilitate early treatment as well as prevention of further spread of syphilis. When encountering cases of unexplained liver dysfunction, syphilitic hepatitis should be included in the differential diagnosis.

Penicillin-based regimens are the first-line treatment of syphilis, and usually serological improvement occurs in parallel with the therapy. Otherwise, we should consider the possible involvement of the central nervous system (CNS), even when there is no evidence of neurosyphilis.

We describe herein a patient with subclinical cerebrospinal fluid (CSF) abnormalities associated with syphilis whose initial presentation was syphilitic hepatitis, and who achieved complete remission after serological flare by intravenous penicillin therapy.

Case Report

In mid-May, 2008, a 50-year-old Japanese man was referred to the Social Insurance Central General Hospital for assessment of abnormal liver function tests identified at an annual general health checkup. His initial laboratory findings were as follows: white blood cell (WBC) count, 6,010/microL (normal value, 4,000-9,000); red blood cell (RBC) count, 419×10⁴/microL (normal value, 410-530×10⁴); hemoglobin (Hb), 12.7 g/dL (normal value, 14-18); platelet count (Plate), 34.6×10⁴/mL (normal value, 12-36×10⁴); total serum protein (TP), 8.0 g/dL (normal value, 6.5-8.0); serum albu-

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Figure 1. Physical examination on admission revealed a non-pruritic macular erythematous skin rash was found all over his body.

Figure 2. Histological examination obtained by liver biopsy performed in June 2008. The portal area was edematous with infiltration of a few inflammatory cells, resulting in intralobular bile duct degeneration. Mild interface hepatitis accompanied by periportal hepatocyte necrosis was also demonstrated (Hematoxylin and Eosin staining).

min (Alb) 3.5 g/dL (normal value, 4.1-5.1); aspartate aminotransferase (AST), 102 IU/L (normal value, 10-33); alanine aminotransferase (ALT), 110 IU/L (normal value, 4-30); alkaline phosphatase (ALP), 634 IU/L (normal value, 167-345); γ-glutamyl transpeptidase (γ-GTP), 225 IU/L (normal value, 10-75); serum total bilirubin (TB), 0.5 mg/dL (normal value, 0.2-1.2); amylase 81 IU/L (normal value, 30-120); serum creatine (Cr), 0.7 mg/dL (normal value, 0.6-1.1); fasting blood glucose (FBG), 103 mg/dL (normal value, 70-107). He seemed to be generally asymptomatic. His antecedent medical records, including the liver function test, were unremarkable. In addition, there was no history of alcohol abuse, toxic drug use or smoking. Further close evaluation revealed serum hypergammaglobulinemia: IgG, 2,455 mg/dL; IgA 435 mg/dL; IgM, 204 mg/dL. Serology for hepatitis A, B and C was negative, as was anti-mitochondrial antibody; however, antinuclear antibody (ANA) was positive at 1:40 (homogeneous and speckled pattern). Abdominal ultrasonography showed a normal liver appearance without chronic change.

Hepatic injury associated with the autoimmune mechanism was initially suspected from the positive ANA serology and high level of serum IgG; however, laboratory data did not fulfill the criteria proposed by the international autoimmune hepatitis group (3). Since the etiology of his hepatic dysfunction was unclear and the levels of ALP and γ-GTP were gradually elevated to 1,584 IU/L and 389 IU/L, respectively, a month later, liver biopsy was scheduled to clarify the cause of his liver function abnormality.

On admission, he was 168 cm tall and weighed 56 kg, blood pressure was 109/63 mmHg and temperature was 36.2 °C. The general physical examination was basically normal; however, there was generalized non-pruritic macular eruption all over his body (Fig. 1), and palpable and painless bilateral inguinal lymph nodes measuring over a centimeter were noted. A routine qualitative serological test for syphilis on hospitalization was found to be positive, which led us to consider the presence of underlying syphilitic disease. As suspected, subsequent quantitative rapid plasma reagin (RPR) and Treponema pallidum latex agglutination (TPLA) tests were significantly elevated to 2,157 R.U (normal value, 0-1) and 1,411 T.U (normal value, 0-9), respectively. Repeat physical examination showed no genital ulcers or induration or neurological abnormalities. He denied homosexuality but confessed to intercourse with several casual partners several weeks to months prior to admission. According to the positive serology for syphilis together with the clinical manifestation, including an indicative skin rash, bilateral inguinal lymph node enlargement, and a history of promiscuous behavior, syphilitic hepatitis was highly suspected.

Histological examination of a liver specimen taken on June 17 revealed the following features by light microscopy. The lobular architecture (portal tracts-centrilobular relationship) was preserved. The portal area was found to be edematous with infiltration by a mild number of inflammatory cells, resulting in the degeneration of bile ducts (Fig. 2). Mild interface hepatitis was also seen. Around the central area, there was mild inflammation caused by increased histiocytic cells. In the hepatic lobule, a lesion infiltrated by histiocytes was revealed. No spirochetes were demonstrated in his liver biopsy specimens.

Since these findings in the liver histology were also consistent with those previously reported in syphilitic hepatitis, oral therapy with 2 g/day amoxicillin hydrate (AMPC) was initiated on June 19. A Jarisch-Herxheimer reaction did not develop. Subsequent to the therapy, both the skin rash and enlarged lymph nodes regressed, and abnormal liver function tests all promptly returned to normal: AST 26 IU/L, ALT 22 IU/L, ALP 180 IU/L, γ-GTP 37 IU/L, together with a decrease in the levels of serological tests for syphilis: RPR 3 R.U, TPLA 194 T.U within 8 weeks, and then AMPC was discontinued (Fig. 3). Sixteen weeks after the cessation of AMPC, at the end of January, 2009, however, the levels of RPR and TPLA were found to have re-increased to 211 R.U and 21,354 T.U, respectively. Despite immediate reinstitu-
Figure 3. Once AMPC therapy was initiated, the abnormally elevated levels of ALT and ALP decreased promptly, suggesting that the liver enzyme abnormalities in the present case were closely associated with syphilis. Even when serological recurrence occurred, liver function tests remained normal and no elevation of ALT or ALP levels was seen thereafter.

Figure 4. Eight-week therapy with oral AMPC provided excellent efficacy to decrease the levels in the serological test for syphilis; however, 16 weeks after the cessation of AMPC, the levels of RPR and TPLA were markedly flared. Despite immediate restart of the same therapy with oral AMPC, the response was slower than the first-round treatment. Due to abnormal findings in CSF associated with syphilis, intravenous PCG administration was introduced for 14 days, resulting in the complete reduction and maintenance in the levels of RPR and TPLA.
cells/μL, 17 mg/dL protein, and 67 mg/dL sugar. RPR in his CSF was nonreactive; however, TPLA was 17 T.U and the fluorescent treponemal antibody-absorption (FTA-ABS) test was reactive, suggesting the possibility of CSF involvement of syphilis. He was therefore given 4 million units of benzylpenicillin potassium (PCG) intravenously every 6 hours for 14 days, resulting in complete restoration. No serological recurrence or liver dysfunction is seen at present.

**Discussion**

This case report raises important clinical points when dealing with patients with syphilis; first, *T. pallidum* infection can initially manifest as hepatic injury without any other symptom; therefore, syphilitic hepatitis should be kept in mind as a differential diagnosis in liver enzyme abnormality of uncertain etiology; second, the possibility of CNS involvement should be considered when the serological test for syphilis is exacerbated and the efficacy of the initial antitubercular therapy becomes refractory.

The prevalence of syphilis had shown a gradual decline until 2004; however, it is currently resurging and has been recognized as an important public health problem in Japan (1). Syphilis is a systemic disease and is known to affect a wide variety of organs, including the liver; however, overt distinctive hepatic involvement, referred to as syphilitic hepatitis, is relatively uncommon. The precise incidence of syphilitic hepatitis is difficult to estimate because published reports are sparse. The largest review to date, by Feher et al in 1975, showed the frequency of hepatitis to be 9.7% (17 syphilitic hepatitis out of 175 syphilis patients) (4); however, the presence of hepatitis C could not be ruled out at that time; hence, the exact frequency was unclear. By an extensive search of the MEDLINE database from 1966 to 2004, only 48 cases of syphilitic hepatitis were published in the English-language literature (2).

The liver enzyme pattern in the majority of syphilitic hepatitis cases is characterized by a disproportionate increase in the ALP level in comparison with a modest elevation of aminotransferases and bilirubin levels; however, some cases have shown predominant hepatocellular damage (5), and others have presented with severe cholestasis (6) or fulminant hepatic failure (7). The diagnostic criteria for syphilitic hepatitis are as follows: abnormal liver enzyme levels, serological evidence of syphilis in conjunction with acute clinical presentation consistent with secondary syphilis; the exclusion of alternative causes of hepatic damage; prompt liver function recovery after antimicrobial therapy (8). The case presented here met all of these criteria. In addition, histological features, including nonspecific portal inflammatory infiltrates, periportal hepatocyte necrosis, and pericholangiolar inflammation, were also consistent with syphilitic hepatitis reported previously (6, 8). As in the present case, identification of spirochetes in liver biopsy specimens failed in the majority of published cases (5-7, 9). There are various pathogeneses, such as direct portal venous inoculation and immune complex-mediated disease (6); however, given the rarity of detecting spirochetes in liver specimens, direct hepatotoxicity of the microorganism seems to be unlikely.

Eight-week therapy with oral AMPC seemed to be effective and resulted in the complete recovery of liver function tests and satisfactory decline of serological titers; however, 16 weeks after the cessation of AMPC, the levels of RPR and TPLA flared (Figs. 5, 6). As he denied the possibility of re-infection from unsafe sexual intercourse, recurrence of the primary infection, previously controlled by AMPC, was thought to be likely. Despite prompt restarting of oral AMPC, the serological response to antibiotics was undoubtedly slower than in the initial therapy (Fig. 6). It has been reported that the reduction in the titer of serological tests after treatment among HIV-co-infected patients may be slower (10); however, HIV infection in the present case was reconfirmed to be negative at that time, and so we postulated the presence of some obstinate focus. Because CNS involvement can occur during any stage of syphilis (11), and CSF evaluation is recommended in those who experience treatment failure (12), we performed lumbar puncture, considering the possibility that *T. pallidum* had already invaded his CSF before the first therapy with AMPC, and that the pathogen was not eradicated by the therapy might lie hidden in CSF and resurge gradually. Because AMPC cannot reach the CSF at a sufficient concentration to eradicate all *T. pallidum*, AMPC alone was thought to be insufficient to treat neurosyphilis.

RPR was negative and WBC counts and protein level were not elevated; however, TPLA as well as FTA-ABS was reactive in his CSF, indicating intrathecal anti-treponemal antibody production. RPR in CSF is highly specific and is the most reliable test for neurosyphilis; however, because it is also known to be insensitive, the presence of neurosyphilis cannot be excluded by nonreactive RPR in CSF (13). For this reason, the above findings were not inconsistent with those in neurosyphilis, although disease activity was thought to be quite low. We thought that this was because AMPC administration reintroduced 8 weeks prior to CSF analysis had provided a certain level of antibiotic effect, and disease activity had been calmed considerably. Optimal therapeutic strategies for syphilitic patients with CSF abnormalities have not been established because it is not possible to predict which case will or will not progress to overt neurosyphilis.

In our case, serological recurrence as well as resistance to the initial therapy led us to consider administering a more intensified regimen in order to prevent the patient progressing to a more severe condition of the disease.

In conclusion, we present a case of CSF abnormality relevant to syphilis, the first manifestation of which was incidentally found liver dysfunction of unknown etiology. Although syphilitic hepatitis has been thought to be a relatively rare condition, clinical awareness of the disease is mandatory to diagnose it correctly and treat it appropriately. In addition, the possibility of neurosyphilis should be con-
sidered when a favorable response to therapy is reduced.

References


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