□ CASE REPORT □

Weil's Disease in a Patient with Chronic Viral Hepatitis and History of Alcohol Abuse

Leonidas Christou, Georgios Kalambokis and Epameinondas V Tsianos

Abstract

Clinical and laboratory diagnosis of severe leptospirosis (Weil's disease) may be difficult when other pathological processes that may cause similar clinical syndromes or affect immune response to infections co-exist. In addition, the optimal management of the disease remains to be defined. We report on a case of Weil's disease, in which concurrent chronic hepatitis B virus infection and alcohol abuse caused diagnostic and therapeutic difficulties.

Key words: leptospirosis, Weil's disease, chronic hepatitis B, alcohol abuse

Introduction

Leptospirosis is a re-emerging zoonosis caused by spirochetes from the genus leptospira and is typically associated with rural settings. Transmission occurs via contact with urine from infected animals; incubation period ranges from 4 days to 4 weeks. The clinical spectrum of leptospirosis may be mild and self-limited or fulminant with jaundice, renal failure, and bleeding manifestations (Weil's disease) (1). Mortality in severe forms remains high even when optimal treatment is provided (2). Early clinical suspicion and laboratory confirmation of leptospirosis is essential, since delays in diagnosis may increase mortality (3).

Alcohol-related toxicity and chronic hepatitis B virus (HBV) infection are common pathological processes (4), which can occasionally produce clinical syndromes similar to leptospirosis (5-8). There are no data regarding the clinical course of leptospirosis in chronic alcoholics, while there is only one report of concurrent leptospirosis and HBV infection (9). Here, we describe a patient with Weil's disease, in whom concomitant chronic HBV infection and alcohol abuse caused diagnostic and therapeutic difficulties.

Case Report

A 54-year-old man was evaluated at another hospital for a 4-day history of myalgia and abdominal pain. Two weeks previously, he had been at a rural area and gardened with bare hands. Past history included a 20-year of HBsAg carriage and alcohol abuse, for which he did not receive regular medical attention; he was drinking alcohol until the time of admission. He reported moderately increased transaminase levels during periods of heavy alcohol consumption to decrease when he abstained from alcohol, but no hospital admission was required; HBV DNA was never measured. Physical examination was remarkable for jaundice and mild non-tender hepatomegaly; his spleen was not palpable. Significant laboratory values were: haemoglobin 12 g/dl, white blood cell count 11,350 cells/mm^3 (neutrophils 85%), platelet count 164,000 cells/mm^3, serum creatinine 1.3 mg/dl (0.6-1.2), serum urea 67 mg/dl (11-54), aspartate aminotransferase 65 IU/l (10-35), alanine aminotransferase 59 IU/l (10-35), total/direct bilirubin 5.1/3.2 mg/dl (0.1-1/0.01-0.2), and C-reactive protein 31 mg/l (<6). Chest radiography and echocardiography on admission were normal; abdominal ultrasound and tomography showed mild hepatomegaly with normal echogenicity of liver parenchyma and normal spleen (Fig. 1). A hepatitis virus panel investigation confirmed chronic HBV infection with negative antibodies against HBeAg; superinfection with hepatitis D, hepatitis A, or hepatitis C viruses was excluded. Enzyme-linked immunosorbent assay (ELISA) for IgM antibodies against *leptospira*, performed on admission, was negative. There was
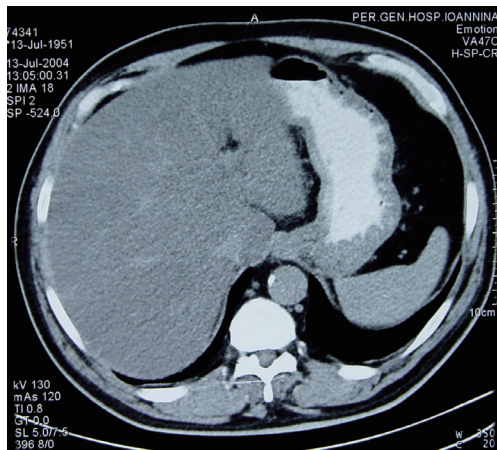
Figure 1. Abdominal tomography on day 1 showing a marginal increase in liver size and normal echogenicity of liver parenchyma. No splenomegaly was detected.

no laboratory evidence of infection with malaria, Hantaan virus, Epstein-Barr virus, herpes simplex virus, or cytomegalovirus. On day 3, he presented fever and non-bloody diarrheas. Several sets of blood and urine cultures were negative. Ceftriaxone 2 g daily was started but his condition was not improved. Renal and liver function continued to deteriorate (Fig. 2) while a second abdominal ultrasound on day 4 showed mild ascitic fluid collection, which became clinically significant over the following days. On day 10, the patient was referred to our hospital for further investigation.

On admission to our department, heart rate was 100 beats/min, blood pressure 88/45 mmHg, and temperature 38℃. He was deeply jaundiced with tense ascites. Blood results showed haemoglobin 8.5 g/dl, white blood cell count 19,970 cells/mm^3 (neutrophils 83%), platelet count 114,000 cells/mm^3, international normalized ratio 1.39 (<1.2), serum creatinine 5 mg/dl, serum urea 155 mg/dl, aspartate aminotransferase 65 IU/l, alanine aminotransferase 62 IU/l, total/direct bilirubin 26.8/18 mg/dl, and C-reactive protein 52 mg/l (1-7); diuresis and serum potassium levels remained normal. Urinalysis showed microhematuria and pyuria. Stool examination for occult blood was positive. Diagnostic abdominal paracentesis showed exudative ascites with no evidence of infection (white cell count 190/mm^3; monocytes 85%). Serum drawn on day 10 remained negative for leptospirosis. Immunologic investigation, including rheumatoid factor, antinuclear, anti-double stranded DNA, and antineutrophil cytoplasmic antibodies, was normal.

Initial management consisted of intravenous administration of fluids and human albumin, and blood transfusions. Large volume paracentesis was performed and antibiotic treatment changed to cefotaxime 2 g daily with the clinical suspicion of alcoholic hepatitis. Steroids were not used, as active HBV infection was also considered, and blood samples were withdrawn for measurement of HBV DNA.

On day 12, the patient presented melena, with upper endoscopy showing three non-actively bleeding duodenal ulcers, and somnolence and disorientation. Neurological ex-

amination did not reveal any focal neurological deficits; lumbar puncture was not performed due to coagulopathy. On day 14, short-term haemodialysis was instituted for acute renal failure concurrently with the vasopressin analogue terlipressin 2 mg, six hourly, due to persistent haemodynamic instability and possible alcoholic hepatitis-related renal failure. Following terlipressin administration for 5 days, a steady increase in arterial pressure and a decrease in heart rate were noted. Renal function steadily improved, and from day 16, no further renal support was needed. The third week of illness, jaundice started to resolve, whereas liver enzymes continued to increase; his fever, cerebral symptoms, ascites, and low platelets, also persisted. Eventually, serum samples obtained on days 16 and 22 were reported positive for leptospira, while increased HBV DNA levels (>2×10^5 copies/ml) were reported on day 24. Antibiotic therapy switched to intravenous penicillin 6 million units per day and lamivudine, 100 mg daily, was administered.

With this management, his clinical condition gradually improved, and on day 45, the patient was discharged well. Liver function abnormalities and anemia resolved slowly within the next 3 months, up to which time HBVDNA became undetectable.

Discussion

The present patient developed a fulminant febrile illness with jaundice, acute renal failure, ascites, impaired conscience, and gastrointestinal bleeding. Considering the patient's former history and initial infection work-up, alcohol and HBV-related complications were put first in our differential diagnosis. Alcoholic hepatitis has been well associated with the development of the above-mentioned clinical manifestations. Fever and/or neutrophilia are also commonly observed prompting antibiotic treatment due to increased infection risk. Cefotaxime has been suggested to be the drug of choice (8), and on this account, it was preferred over ceftriaxone in our patient. Steroids seem to improve prognosis, while terlipressin may be useful in alcoholic hepatitis-related renal failure (8). Active HBV replication in our patient might represent reactivation or exacerbation of chronic HBV infection. Both conditions could have been triggered by alcohol abuse (4), and are known to produce acute liver damage accompanied by a clinical syndrome similar to that described in our patient (5-7); IgM anti-HBcAg may not be detected (7). Decompensated liver cirrhosis could be considered in the present case. However, there was no evidence to support such a possibility.

Leptospirosis was strongly suspected in the present case despite initial negative serology. Of note, co-infection with leptospira and HBV has been reported only once (9), while there is no data for leptospirosis in patients with concurrent alcohol abuse. The presentation of Weil's disease is often atypical and organ failures may occur 4 to 9 days after the onset of symptoms (10). Serum bilirubin is frequently high and may persist for several weeks but transaminases and al-
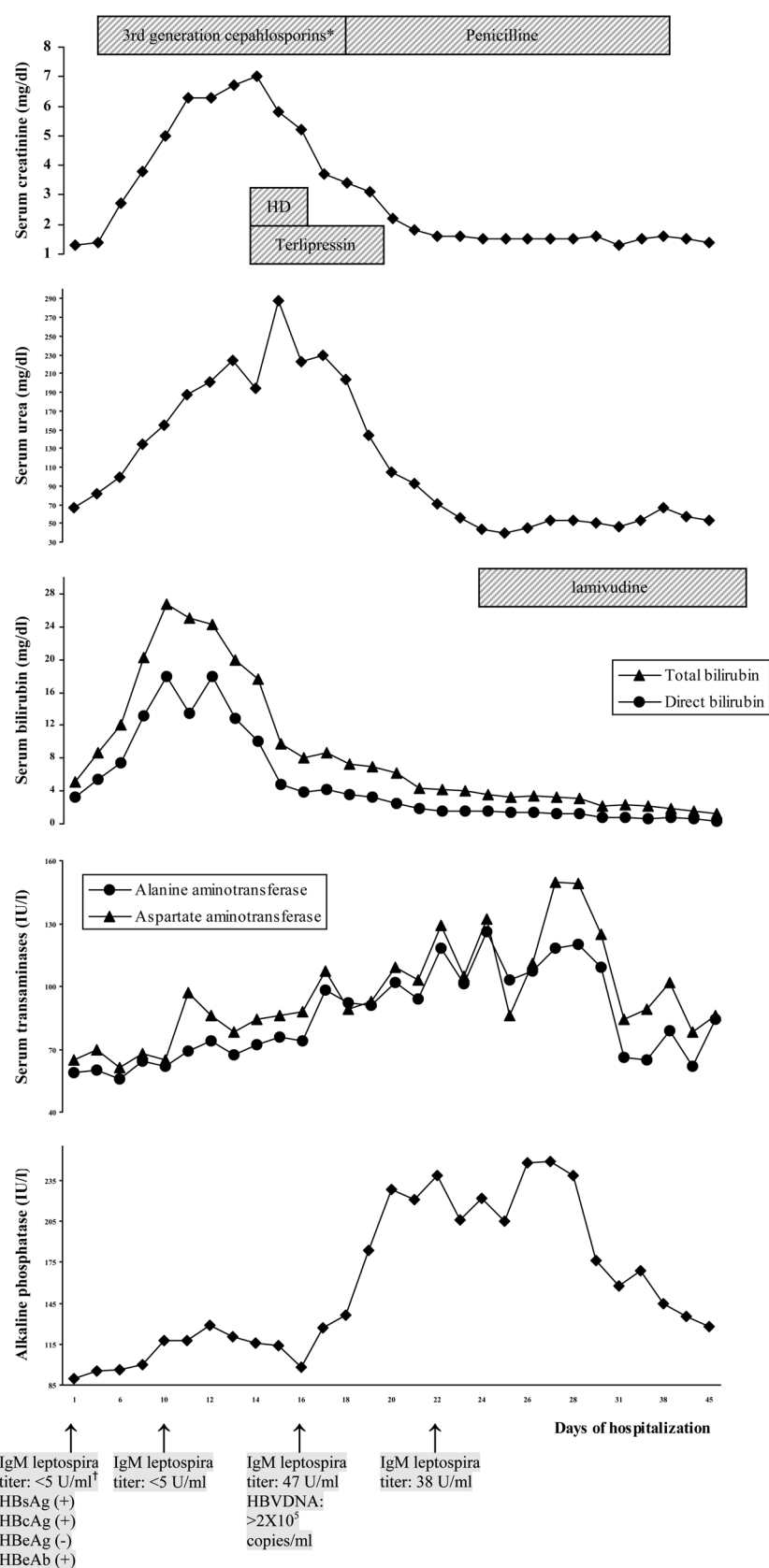
Figure 2. Evolution of renal and liver function parameters during hospitalization at another hospital (day 1 to day 9) and after referral to our department (day 10). HD: haemodialysis, Ab: antibodies, HBV: hepatitis B virus

*Ceftriaxone, day 1 to day 9; cefotaxime, day 10 to day 18.

† IgM concentrations for negative, borderline, and positive results were: <15 U/ml, 15-20 U/ml, and >20 U/ml, respectively.

kaline phosphatase are usually moderately elevated (1). The serum levels of transaminases and alkaline phosphatase remained elevated despite the resolution of jaundice in our patient, however, this particular pattern of liver dysfunction is difficult to explain. Significant renal impairment is seen in 50-75% of patients, commonly with normal diuresis and preserved potassium balance; hemodialysis in needed in 30% of patients (10). Haemodynamic derangement has been involved in the development of acute renal failure (11). Altered sensorium, lasting 1 to 8 days, is the most common neurological presentation of leptospirosis (12), while haemorrhagic manifestations are observed in 30-50% (10). Ascites has been rarely reported in Weil's disease, though less severe than that reported in the present case (10, 13); its pathogenesis may involve leptospiral or immune complex-related vasculitis. Thrombocytopenia occurs frequently, and is associated with poor prognosis (1), whereas significant anemia, possibly related to marrow suppression, is fairly uncommon (14). Whether active HBV replication in our patient was triggered by *leptospira* infection is unknown. Nevertheless, it is likely that HBV infection or/and alcohol abuse affected the progress of the clinical and laboratory abnormalities, predisposing to more severe or unusual clinical course of leptospirosis. Moreover, alcohol may favor leptospiral vasculitis by causing endothelial dysfunction (15), while a previous report suggested an association between more severe malaria and HBV carriage (16).

ELISA is the method of choice for the diagnosis of leptospirosis allowing serologic confirmation during the first week of the disease (1) and initiation of treatment while it is likely to be more effective (17). By contrast, development of antibodies against *leptospira* in the present patient occurred over the third week after onset of symptoms. This could be related with the immunosuppressive effects of alcohol abuse (15). Chronic HBV infection could also impair immune response, as shown by the significantly reduced levels of antibodies against *P. falciparum* ring-infected erythrocyte surface antigen in HBV carriers compared to those who cleared HBV (18). We can also speculate that immunodeficient responses, both against HBV, leading to chronic infection, and leptospirosis, take place in some patients.

Early antibiotic treatment of leptospirosis has been associated with a better prognosis (3). Penicillin has long been considered the drug of choice, though ceftriaxone and cefotaxime are emerging as acceptable agents (19). However, neither cephalosporin showed clinical benefit in our patient, supporting the recent view that the optimal treatment for severe leptospirosis remains to be defined (19). Vasoconstrictor agents have been shown to improve systemic hemodynamics and renal function in patients with leptospirosis (20). Terlipressin facilitated recovery of renal function in our patient, obviating the need for longer-term hemodialysis. To our knowledge, terlipressin has not previously been employed in leptospiral nephropathy.

Weil's disease is likely to be misdiagnosed or overlooked in patients with history of alcohol abuse or chronic HBV infection, due to potentially overlapping clinical features. The need to carry out a series of serologies is to be insisted upon, particularly when impaired immune response to infections is a concern, since development of antibodies against *leptospira* may then be unusually delayed. Optimal antibiotic treatment has not yet been defined while vasoconstrictor agents, such as terlipressin, may facilitate the recovery of renal function.

References

1. Levett PN. Leptospirosis. Clin Microbiol Rev **14**: 296-326, 2001.
2. McBride AJ, Athanazio DA, Reis MG, Ko AI. Leptospirosis. Curr Opin Infect Dis **18**: 376-386, 2005.
3. Kobayashi Y. Human leptospirosis: management and prognosis. J Postgrad Med **51**: 201-204, 2005.
4. Gao B. Interaction of alcohol and hepatitis viral proteins: implication in synergistic effect of alcohol drinking and viral hepatitis on liver injury. Alcohol **27**: 69-72, 2002.
5. Meyer RA, Duffy MC. Spontaneous reactivation of chronic hepatitis B infection leading to fulminant hepatic failure. Report of two cases and review of the literature. J Clin Gastroenterol **17**: 231-234, 1993.
6. Davis GL, Hoofnagle JH, Waggoner JG. Spontaneous reactivation of chronic hepatitis B virus infection. Gastroenterology **86**: 230-235, 1984.
7. Kanno A, Suzuki H, Miyazaki Y, et al. Severe acute exacerbation in chronic hepatitis B virus infection in Sendai, Japan. Tokohu J Exp Med **155**: 363-371, 1988.
8. O'Beirne J, Patch D, Holt S, Hamilton M, Burroughs AK. Alcoholic hepatitis-the case for intensive management. Postgrad Med J **76**: 504-507, 2000.
9. Kaushik SP, Yim HB, Tan CC. Weil's syndrome and concomitant hepatitis B infection. Singapore Med J **40**: 104-105, 1999.
10. Gerke P, Rump LC. Leptospirosis-3 cases and a review. Clin Nephrol **60**: 42-48, 2003.
11. Sitprija V, Losuwanrak K, Kanjanabuch T. Leptospiral nephropathy. Semin Nephrol **23**: 42-48, 2003.
12. Mathew T, Satishchandra P, Mahadevan A, et al. Neuroleptospirosis-revisited: experience from a tertiary care neurological centre from south India. Indian J Med Res **124**: 155-162, 2006.
13. Wang SC, Wang YM. Leptospirosis: report of one case. J Microbiol Immunol Infect **32**: 129-132, 1999.
14. Bal AM. Unusual clinical manifestations of leptospirosis. J Postgrad Med **51**: 179-183, 2005.
15. Watson RR, Borgs P, Witte M, et al. Alcohol, immunomodulation, and disease. Alcohol Alcohol **29**: 131-139, 1994.
16. Thursz MR, Kwiatkowski D, Torok ME, et al. Association of hepatitis B surface antigen carriage with severe malaria in Gambian children. Nature Medicine **1**: 374-375, 1995.
17. Katz AR, Ansdell VE, Effler PV, Middleton CR, Sasaki DM. Assessment of the clinical presentation and treatment of 353 cases of laboratory confirmed leptospirosis in Hawaii, 1974-1998. Clin Infect Dis **33**: 1834-1841, 2001.
18. Souto FJ, Fontes CJ, Gaspar AM. Relation between hepatitis B carrier status and antibody against synthetic plasmodium falciparum erythrocyte surface (pf155-RESA) antigen. Mem Inst Oswaldo Cruz **97**: 197-198, 2002.
19. Griffith ME, Hospenthal DR, Murray CK. Antimicrobial therapy of leptospirosis. Curr Opin Infect Dis **19**: 533-537, 2006.

20. Niwattayakul K, Sitprija V. Leptospiral acute renal failure: effects of dopamine and furosemide. Ren Fail **29**: 159-162, 2007.