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Case Report

Weil's Disease Associated With Epstein-Barr Virus

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Abstract

Weil's disease caused by *Leptospira* species is characterized by impaired hepatic and renal function. We report a 71-year-old man with Weil's disease associated with Epstein-Barr Virus (EBV). The patient was admitted because of progressive jaundice for 1 week. EBV infection and leptospirosis were determined by serologic tests. After treatment with intravenous penicillin and minocycline, the jaundice subsided. Immunosuppression during active EBV infection has been reported previously, and therefore, this could have caused the severe symptoms after *Leptospira* infection in our case. [*Tzu Chi Med J* 2010;22(1):47–49]

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1. Introduction

Leptospirosis is a zoonotic disease caused by *Leptospira*, which comprises 24 serogroups and 250 serovars, and is transmitted to humans by direct or indirect exposure to urine or other body fluids of infected animals [1,2]. Although considered to be the most geographically widespread zoonosis, it is restricted to some occupational groups with a high exposure risk such as farmers, miners, abattoir workers and sewer workers [1,2]. The clinical presentation in humans ranges from a mild flu-like illness to a severe illness with jaundice, meningitis, renal failure, pulmonary hemorrhage and, occasionally, death.

Weil's disease caused by *Leptospira* species is characterized by impaired hepatic and renal function. Mortality rates range from 5% to 40% [1–4]. More than 60% of serologically identified infections are asymptomatic [5,6]. Epstein-Barr virus (EBV) can induce complex humoral and cell-mediated immune responses in humans, which impair liver function [7,8]. Weil's disease associated with active EBV infection has not been reported previously.

2. Case report

A 71-year-old man was admitted because of a 1-week history of general malaise. The patient was a farmer who had a 35-year history of consumption of 100–200 mL rice wine, once or twice per week. He had been in good health until 1 week prior to admission. Examination at admission revealed tea-colored urine in addition to general malaise. The patient had no history of travel and had not taken any medicine in the previous year.

The patient's body temperature was 36°C, blood pressure was 137/92 mmHg, heart rate was 71 beats

per minute and respiratory rate was 18 cycles per minute. Physical examination showed that his skin and sclera were icteric, but there were no infected throat, lymphadenopathy, splenomegaly, edema or Kayser-Fleischer rings. A hemogram showed a leukocyte count of 17,310/mL with 93% segmented neutrophils, a hemoglobin level of 11.8 g/dL, and a platelet count of 34,000/mL. Prothrombin and activated partial thromboplastin times were 10.9 and 32.6 seconds, respectively (reference values, 10 and 10.9 seconds, respectively). Electrolyte levels were within normal limits. Serum aspartate aminotransferase level was 332 IU/L, alanine aminotransferase level was 188 IU/L, total bilirubin was 33 mg/dL, direct bilirubin was 21.6 mg/dL, lactate dehydrogenase was 641 IU/L, total protein was 6.6 g/dL, albumin was 2.68 g/dL, alkaline phosphatase was 242 IU/L, γ-glutamyl transpeptidase was 200 IU/L, urea nitrogen was 66 mg/dL, creatine was 1.0 mg/dL and C-reactive protein was 27.22 mg/dL. Abdominal sonography and computed tomography showed mild splenomegaly without other specific findings.

The patient was treated with parenteral ceftriaxone (2 g every 12 hours). Bilirubin levels increased despite treatment (total bilirubin was 55.7 mg/dL; direct bilirubin was 38 mg/dL). Serum antibodies against hepatitis A and serum surface antigen of hepatitis B were negative. Serum antibodies against hepatitis C were positive but hepatitis C RNA was undetectable with polymerase chain reaction. EBV serum immunoglobin G and M were positive, while serum immunoglobin against EBV nuclear antigen was negative. Two blood cultures were negative.

Despite ceftriaxone treatment, leukocytosis and jaundice persisted. The antibiotic regimen was changed to parenteral penicillin G (3 MU every 6 hours) and parenteral minocycline (100 mg every 12 hours) on day 5 of hospitalization. A microscopic agglutination test using serum antibodies against *Leptospira santarosai* serovar *shermani*, *L. borgpetersenii* serovar *poi*, and *L. tarassovi* performed at the Taiwan Center for Disease Control revealed a greater than four-fold increase in paired serum samples (Table 1). Jaundice and leukocytosis progressively subsided and the patient was discharged after 3 weeks. During the subsequent 11 months, mild jaundice in the absence of specific discomfort was observed.

Table 1 — Change in serum antibody titers against *Leptospira* species in paired serum samples

Leptospira species	Day 4	Day 18
Leptospira santarosai serovar *shermani*	1:400	1:6400
L. borgpetersenii serovar *poi*	1:200	1:6400
L. tarassovi	1:200	1:3200

3. Discussion

Seroprevalence studies support the view that subclinical leptospirosis infections are common worldwide. More active surveillance leads to an increased detection of human cases [9]. In general, the diagnosis is initially based on clinical suspicion, and is confirmed later by laboratory results, usually by the detection of specific antibodies using the microscopic agglutination test. In our case, EBV infection and leptospirosis were confirmed by serologic methods. Cross-reactivity between these serologic tests does not occur [10]. EBV infection is typically acquired during the childhood or teenage years; over the age of 40, the infection rate is 2–10% [11]. The frequency with which adults older than 40 years old develop clinically overt disease is unknown because of the low rate of susceptibility in this age group. However, many elderly patients with acute EBV have been reported [12–15]. In the present case, acute EBV infection was likely, given the absence of serum immunoglobin to EBV nuclear antigen. Unfortunately, the possibility of a false negative could not be excluded because of the lack of paired serum. The results of EBV serological testing indicated that reactivation of EBV was still possible.

The pathogenesis of leptospirosis involves diffuse vasculitis. The clinical presentation in most patients is mild and self-limited, but uncommonly severe Weil's disease characterized by hepatic impairment is manifest. The pathogenesis of jaundice is disorganized and can involved *Leptospira*-mediated obliteration of the sinusoids [16]. In patients infected with EBV, the major hepatic manifestation is a self-limited elevation in hepatocellular enzyme levels [8]. Minimal swelling and vacuolization of hepatocytes, pleomorphic lymphocytic and monocytic portal infiltrations and minimal swelling of the bile ducts are evident, and biliary stasis is rare [17]. Less commonly, those over 40 years old can develop peripheral lymphadenopathy, pharyngitis, and splenomegaly and, unlike young adults, have a more prolonged fever, liver involvement and jaundice [11–15].

Disease determinants for leptospirosis are presumably related to exposure that influences the inoculum size during infection and host factors [5,18]. An important epidemiological question is as follows: why do certain exposed individuals develop mild symptomatic infections, while others progress to develop Weil's disease? In patients with self-limited leptospirosis, a spirochetemic phase is generally followed by an immune phase. During the immune phase, organisms disappear from the blood [19]. Immunity for leptospirosis may be antibody-mediated since *Leptospira* are extracellular pathogens and protection can be passively transferred in hamsters [20]. When monocytes are stimulated with lipopolysaccharide or phorbolmyristate acetate, two strong inducers of tumor necrosis factor-α expression, EBV inhibits stimulus-induced liberation of

70–90% of tumor necrosis factor-α, which participates in regulation, maturation, activation and proliferation of B and T lymphocytes [21–23]. These EBV immunosuppressive effects may delay antibody-mediated immunity to *Leptospira*, and prolonged survival of *Leptospira* increases the chances of sinusoid obliteration. Weil's disease caused by *Leptospira* may be attributable to immunosuppression caused by active EBV infection.

Although immunosuppression occurs in patients with active EBV infection, coinfection with other pathogens has seldom been reported. *Chlamydophila pneumoniae* coinfection with EBV has been described [24]. Rickettsioses and malaria coinfection with *Leptospira* have been demonstrated with similar epidemiological profiles and clinical presentations [25,26]. In clinical practice, EBV serology is typically carried out when a patient presents with infectious mononucleosis. However, elderly patients with active EBV rarely display the classical triad of acute EBV infection. Active EBV infection is rarely considered when a patient presents with jaundice or other symptoms that are considered to be caused by another pathogen. EBV infection in elderly patients may thus be underestimated or even ignored. Clinical studies are needed to clarify whether EBV-mediated immunosuppression influences the severity of other infectious diseases.

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