

Pediatric Fulminant Leptospirosis Complicated by Pericardial Tamponade, Macrophage Activation Syndrome and Sclerosing Cholangitis

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Background: Leptospirosis is a zoonotic infectious disease caused by pathogenic spirochetes of the genus *Leptospira*. Although it is usually asymptomatic and self-limited, severe potentially fatal illness accompanied by multi-organ failure may occur.

Case Report: Here we report an unusual case of severe leptospirosis successfully treated with continuous venovenous hemofiltration (CVVHF) and therapeutic plasma exchange (TPE). The patient presented with pericardial tamponade, renal failure and macrophage activation syndrome, and later suffered prolonged jaun-

dice and sclerosing cholangitis during hospitalization in the pediatric intensive care unit (PICU). To the best of our knowledge, sclerosing cholangitis due to leptospirosis has not been reported in the literature.

Conclusion: Leptospirosis should be kept in mind in the differential diagnosis of sepsis and septic shock with fever, thrombocytopenia, jaundice and renal failure. TPE and CVVHF should start early after the diagnosis of leptospirosis with multiorgan failure.

Keywords: Leptospirosis, macrophage activation syndrome, pericardial tamponade, sclerosing cholangitis

Leptospirosis is an infectious disease with numerous clinical manifestations characterized by vasculitis. Although it is usually asymptomatic and self-limited, life-threatening multiorgan failure may occur. Weil syndrome is a severe form of leptospirosis, which is caused by *Leptospira icterohemorrhagiae*, which is typically transmitted via contact with urine from infected animals. It is characterized by impaired renal and hepatic function, jaundice, hemorrhagic pneumonitis, thrombocytopenia, cardiac arrhythmias and circulatory collapse (1).

Herein, we report a case of fulminant leptospirosis successfully treated with continuous venovenous hemofiltration (CVVHF) and therapeutic plasma exchange (TPE). She presented with pericardial tamponade, renal failure and macrophage activation syndrome, and later she had prolonged jaundice and sclerosing cholangitis during hospitalization.

CASE PRESENTATION

A 15-year-old girl admitted to a hospital with a fever of 40°C, widespread maculopapular rash, and weakness. She was hospitalized in another hospital because of a preliminary diagnosis of measles. Measles serology resulted negative, and she had persistent fever. After three days, she developed acute renal failure with hematuria, mild pericardial and pleural effusion.

Rheumatological diseases, especially systemic lupus erythematosus, were considered because of fever, pancytopenia, maculopapular rash, renal failure and polyserositis. She was treated with steroid pulse therapy for systemic rheumatic diseases. On the second day of methylprednisolone pulse therapy, she was referred to our pediatric intensive care unit (PICU) due to a loss of unconsciousness, total anuria and hypotension, which was not responding to adequate fluid resuscitation, and severe diarrhea.

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Her physical examination was as follows; she was unconscious (Glasgow coma scale 6), intubated, her pupils were bilaterally miotic and reactive to light, and fever was 39°C. There were diffuse petechiae and edema on her body. Her oxygen saturation was 94% (FiO₂: 60%), breath sounds were equal with wide crackles. She was tachycardic (160/minutes), hypotensive (95/63 mmHg, mean: 73 mmHg) despite 0.1 mcg/kg/min of adrenaline infusion, capillary refill time was prolonged (5 seconds), and her heart sounds were rhythmic and deep. She had 5 cm hepatomegaly and 2 cm splenomegaly on abdominal examination. She developed cardiac arrest within the first hour after admission to PICU and cardiopulmonary resuscitation was performed for about 15 minutes. Echocardiography showed massive pericardial effusion and diastolic collapse of the right ventricle which was consistent with pericardial tamponade. Approximately 150 mL of serous fluid was drained by pericardiocentesis and a pericardial tube was inserted into the pericardial cavity.

Laboratory findings showed metabolic acidosis (pH: 7.24, pCO₂ 24 mmHg, bicarbonate 12.7 mmol/L) with a high level of lactate (6.1 mmol/L, normal range 0.4-2.2 mmol/L). A complete blood count with differential revealed a WBC level of 3820/mm³, a hemoglobin level of 9.3 g/dL, a hematocrit level of 29.2%, and a platelet level of 14000/mm³. Prothrombin time was 17.2 seconds, aPTT was 40.2 seconds and fibrinogen level was 45 mg/dL (180-400 mg/dL). Liver function tests resulted as follows; AST 1132 U/L (0-35), ALT 458 IU/L (0-35), GGT 74 U/L (0-38), LDH 951 U/L (125-247), ALP 39 IU/L (30-120), total bilirubin 8 mg/dL (0.2-1.2), direct bilirubin 5.5 mg/dL (0-0.2), total protein 3.5 g/dL (6.6-8.3) and albumin 1.6 g/dL (3.5-5.2). Serum electrolyte levels were normal except hypokalemia (2.2 mmol/L). Biochemical analysis of pericardial fluid was compatible with exudate. There were 100/mm³ WBC (90% lymphocyte, 10% neutrophil) and 8800/mm³ red blood cells in the analysis of pericardial fluid cell-count. A culture of the pericardial fluid was positive for *Pseudomonas aeruginosa*. There was right lower lobe infiltrate on the chest radiograph. Bilateral grade 2 renal parenchymal disease, hepatosplenomegaly and minimal peritoneal fluid were observed in abdominal ultrasonography. Macrophage activation syndrome was diagnosed because of persistent fever for seven days, pancytopenia, high levels of liver function tests, hyperferritinemia (95860 ng/mL), hypertriglyceridemia (319 mg/dL) and hypofibrinogenemia (45 mg/dL). Bone marrow aspiration revealed hypocellularity with no obvious leukemic cells and hemophagocytosis.

Vancomycin, meropenem and adrenaline infusion (0.3 mcg/kg/min) treatments continued. Continuous venovenous hemofiltration (Prismaflex®, M 100 filter; Gambro Lundia AB, Sweden) and TPE (Prismaflex®, TPE 2000 filter; Gambro Lundia AB, Sweden) treatment were started for anuria, macrophage activation syndrome, and thrombocytopenia-associated multiple organ failure (TAMOF). Fresh frozen plasma was

used as replacement fluid for TPE. Plasma exchange volume was calculated as follows $0.065 \times \text{kg} \times (1 - \text{Htc})$. Pulse steroid therapy continued for macrophage activation syndrome.

Crimean-Congo hemorrhagic fever, BK virus, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, herpes simplex virus, parvovirus B19 serology, salmonella and Brucella agglutination tests were negative. Anti-nuclear antibody, anti-dsDNA, ENA panel, P-ANCA, lupus anticoagulant, anticardiolipin, antiphospholipid, and anti-glomerular basement membrane antibodies were negative. Serum C3 was low and C-ANCA was positive. Leptospirosis investigated because of fever, rash, jaundice, renal failure and severe thrombocytopenia. Leptospira IgM and IgG resulted positive. After spirochetes were viewed under dark field microscopy directly, diagnosis of leptospirosis was confirmed. Ampicillin was added to the patient's current treatment. During the inpatient period, she stated to us that she had contact with a stray cat one week ago before admission to the hospital.

Oliguria, thrombocytopenia (1000-30,000/mm³) and jaundice (total bilirubin and direct bilirubin values increased to 40.5 and 19 mg/dL, respectively) persisted for one month. Viral serologies, liver autoantibodies, ceruloplasmin, and α 1-antitrypsin were normal for etiology of the jaundice. Magnetic resonance cholangiopancreatography resulted as intrahepatic bile ducts stenosis and enlargement were observed in some places. Liver biopsy showed nonspecific intrahepatic cholestasis and bilirubin plugs. On the fortieth day, endoscopic retrograde cholangiopancreatography (ERCP) resulted as intrahepatic bile ducts stenosis like the pruned tree view consistent with sclerosing cholangitis. Stents were placed in proximal, right, and common bile ducts during ERCP. Her stent was removed after 10 days because she did not benefit from stenting. Therapeutic plasma exchange (Prismaflex®, TPE 2000 filter; Gambro Lundia AB, Sweden) was performed with 4% albumin every other day for hyperbilirubinemia. Oliguria, thrombocytopenia and jaundice began to improve after fifty-five days.

A percutaneous endoscopic gastrostomy was inserted prior to discharge due to malnutrition and inadequate oral intake. She was transferred to the pediatric ward sixty-two days after hospitalization in PICU.

DISCUSSION

Leptospirosis is an infectious vasculitis which can occur with very different features. Spirochetes live in renal tubular cells of wild and domestic animals. Through the urine of these animals, the pathogen infects water and soil. The transmission to humans occurs via exposure of the mucosa and/or broken skin to contaminated water or soil, or direct contact with the tissues of infected animals (1). Our patient had a history of contact with a stray cat. There was no other significant history.

Acute renal failure due to Weil's disease occurs at the frequency of 10 to 60%. The most characteristic and frequent involvement is acute interstitial nephritis. Glomerular involvement is quite varied. Mesangial proliferation, infiltration of mononuclear cells, IgM, and C3 depositions may observe. In some patients, anti-cardiolipin IgG, ANCA, and anti-platelet antibodies were found. The role of antineutrophil cytoplasmic antibodies in the vasculitis of Weil's disease is not yet understood (2). Our patient had long-term renal failure. As consistent with the literature, C-ANCA was positive and C3 was low. Renal biopsy was performed, tubulointerstitial nephritis determined while there was no glomerular pathology.

Increased permeability and edema formation occur due to vascular damage in the early stage of the Weil's disease. Hepatic injury, mild decrease in enzyme activity, and jaundice occur due to edema. After two weeks, jaundice increases as a result of centrilobular cholestasis and the toxic effects of bilirubin (3). Jaundice was seen in the course of our patient, as is consistent with the literature. Sclerosing cholangitis in our patient due to leptospirosis has not been reported in the current literature.

Cardiac involvement due to leptospirosis may occur non-specific ECG findings, arrhythmias, myocarditis, pericarditis and endocarditis (4). In a prospective study, myocarditis and arrhythmias were seen in 18% of leptospirosis patients; pericarditis was seen in 6% (4). Pericarditis related pericardial tamponade was observed in our patient.

Hemophagocytic syndrome is very rare in leptospirosis. It is thought that it is secondary to abnormal immune response triggered by infection (5). In the literature, one adult (6) and two pediatric (5, 7) cases have been reported. Our patient with secondary hemophagocytic syndrome due to leptospirosis is one of the rare cases in the literature.

Thrombocytopenia is common with Weil's disease. In a study, thrombocytopenia was present at the time of admission in 200 cases (53.5%), and it developed during the hospital stay in 150 cases (40.3%) in the total 374 number of leptospirosis patients (8). Thrombocytopenia-associated multiple organ failure which is a thrombotic microangiopathic syndrome an independent risk factor for poor outcome in critical illness. Therapeutic plasma exchange has been successfully used as a treatment for microangiopathy (9). In our previous observational study, we found that TPE had reduced the mortality about 40% in patients with TAMOF (10). Our patient was diagnosed TAMOF due to leptospirosis and successfully treated with TPE. The main reason of multiorgan failure and severe clinical course is increased releasing of endotoxins after antibiotics administration in leptospirosis. The aim of TPE treatment in leptospirosis is removal of endotoxins and inflammatory mediators as in sepsis. We have used this treatment successfully in our patient.

In conclusion, leptospirosis should be kept in mind in differential diagnosis of sepsis and septic shock with fever, thrombocytopenia, jaundice, and renal failure. Therapeutic plasma exchange and CVVHF should be start early after the diagnosis of leptospirosis with multiorgan failure.

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