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Efficacy of Plasmapheresis in Severe Leptospirosis Case

Ciddi Leptospiroz Olgusunda Plazmaferez Etkinliği

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Abstract

This study highlighted the efficacy of therapeutic plasma exchange and hemodialysis in a case of leptospirosis presenting with severe acute kidney injury. Leptospirosis is a zoonosis caused by spirochetes; it is more common in the tropics. It can be asymptomatic or present across a broad clinical spectrum, which may lead to mortality. A physically active 84-year-old male patient with a history of hypertension and prostate cancer, was admitted to our hospital with complaints of decreased oral intake for a week, weakness in the lower extremities, and subsequently developed a cough, fever, and jaundice. The patient was conscious, less cooperative than usual or expected, and appeared unwell on physical examination. His blood pressure was 155/94 mmHg, and he had tachycardia (111/min). The sclerae were icteric, and the conjunctivae were pale. Except for the presence of rales at lung bases, other systemic examinations were normal. Laboratory evaluation revealed anemia, thrombocytopenia, hyperbilirubinemia, and increased creatinine levels. Detection of risk factors for leptospirosis transmission in the patient's history, recreational activities such as long forest walks and consumption of contaminated raw vegetables, and compatible clinical findings suggested Weil's disease as the preliminary diagnosis. Leptospira polymerase chain reaction positivity in the urine confirmed the diagnosis. The patient developed oliguria during the course, and we started renal replacement therapy. The emergence of alveolar hemorrhage prompted us to apply plasmapheresis as rescue therapy. We achieved a dramatic renal recovery after ensuring diuresis with two sessions of plasmapheresis. Plasmapheresis as a rescue therapy successfully manages leptospirosis cases that present with multi-organ involvement, with high mortality.

Keywords: Leptospirosis, therapeutic plasma exchange, acute kidney injury, alveolar hemorrhage, hemodialysis

Öz

Bu çalışma ciddi akut böbrek hasarı ve alveoler hemoraji ile başvuran ciddi bir leptospiroz olgusunda plazmaferez etkinliğini vurgulamaktadır. Leptospiroz, spiroketlerin neden olduğu, tropik bölgelerde daha yaygın görülen bir zoonozdur. Asemptomatik olabileceği gibi mortaliteye neden olabilecek geniş bir klinik spektrumda gözlenebilir. Hipertansiyon ve prostat kanseri öyküsü olan, fiziksel olarak aktif 84 yaşında erkek hasta; bir haftadır oral alımda azalma, alt ekstremitede güçsüzlük ve sonrasında gelişen öksürük, ateş, sarılık yakınmaları ile hastanemize başvurdu. Başvuru muayenesinde hastanın şuuru açık, kooperasyon zayıf ve düşkün durumdaydı. Kan basıncı 155/94 mmHg, nabız dakika sayısı 111/dk, skleralar ikterik ve konjuktivaları soluktu. Akciğer bazallerinde raller dışında sistemik bakıları olağandı. Laboratuvar verilerinde anemi, trombositopeni, hiperbilirubinemi ve kreatinin yüksekliği saptandı. Hastanın öyküsünde leptospirosis bulaşına ilişkin risk faktörlerinin saptanması (uzun orman yürüyüşleri gibi rekreasyonel aktiviteler ve kontamine çiğ sebze tüketimi) ve uyumlu klinik bulgular ön tanıda Weil hastalığını düşündürdü. Tanı idrarda Leptospira polimeraz zincir reaksiyonu pozitifliği ile doğrulandı. Hastalığın seyrinde oligüri gelişmesi üzerine renal replasman tedavisi başlandı. Alveolar hemoraji başlaması üzerine hastaya son çare tedavi olarak plazmaferez uygulandı. Hastada iki seans plazmaferez tedavisi sonrası idrar çıkışı başlaması ve diyaliz ihtiyacının ortadan kalkması ile dramatik bir renal düzelme sağlandı. Yüksek mortalite riski olan çoklu organ tutulumlu leptospiroz olgularında plazmaferez tedavisi başarılı bir yönetim sağlamaktadır.

Anahtar Kelimeler: Leptospiroz, terapötik plazma değişimi, akut böbrek hasarı, alveolar kanama, hemodiyaliz

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Introduction

Leptospira is a spirochete that causes disease in humans. Although Leptospira is more common in tropical and temperate climates, it is in fact a common zoonotic agent throughout the world[1]. Rodents are the most important reservoir. However, many mammals can serve as primary reservoirs for Leptospira. It remains viable in the renal tubules of infected mammals, from where it is shed into the environment through urine[2]. Transmission to humans occurs through skin abrasions, mucous membrane, or conjunctival contact with soil or water contaminated with rodent urine, or oral ingestion of contaminated food and water. The bacteria can survive for months in soil and fresh water contaminated with urine, and even longer in temperate climates[3].

It is thought that the septicemic and immune responses may play a role in the development of clinical signs after the incubation period. Leptospirosis is usually an asymptomatic or self-limiting infection. In some cases, it can lead to multiple organ failure and even death[4]. Leptospirosis has two different clinical forms, anicteric and icteric forms. The rarer and more severe form is icteric leptospirosis, also known as Weil's disease[2]. Icteric leptospirosis is a disease characterized by acute kidney injury (AKI), jaundice, and fever. Thrombocytopenia, anemia, and neurological findings may also be observed. Rarely, it can lead to atypical presentations such as pulmonary hemorrhage, thrombotic thrombocytopenic purpura, and Guillain-Barré syndrome (GBS)[5]. We report a case of leptospirosis in which direct hyperbilirubinemia, anemia, thrombocytopenia, AKI, and pulmonary hemorrhage were at the forefront.

Case Report

A socially and physically active 84-year-old man with a history of hypertension and previous surgery for prostate cancer was admitted to our tertiary care hospital with complaints of decreased oral intake, lower extremity weakness, and subsequent cough, hemoptysis, fever, myalgia and yellowing of the skin for one week. The patient had no known allergy, history of antibiotic use, or hospitalization in the last three months. He had only used non-steroidal anti-inflammatory drugs (NSAIDs) for the same complaints. On the physical examination, the patient was conscious, fully oriented, and capable of cooperation, although collapsed. The vital signs were as follows: blood pressure 155/94 mmHg, respiratory rate 18/min, pulse rate 111/min, body temperature 36.4 °C. The sclerae were icteric and the conjunctivae were pale. Lung auscultation revealed bilateral basilar rales. Other systems were normal.

The laboratory results during hospitalization and outpatient follow-up are shown in Table 1. On admission, the leukocyte count was normal; however, there was an increased neutrophil percentage and the patient was anaemic and thrombocytopenic. The patient had hyperbilirubinemia with predominant direct bilirubin. The urea and creatinine levels of the patient were consistent with AKI. There were hyponatremia and transaminase levels that were slightly above the upper limit of normal. There was a 2+ result in the direct Coombs polyspecific, and IgG tests. The peripheral smear showed neutrophilia and sporadic echinocytes. No schistocytes were observed. The patient was evaluated for thrombotic microangiopathy. Thrombotic microangiopathy or haemolytic anaemia were not considered. In viral hepatitis serology, no significant feature was found.

Radiological examination revealed bilateral minimal pleural effusion on thoracic computed tomography (CT) and lesions compatible with dependent atelectasis or ground-glass opacities in the basal regions. The infiltrates in the lungs were not interpreted as alveolar hemorrhage. No biliary pathology was found on abdominal CT. Linear density increases in the bilateral perirenal regions were reported. With the diagnosis of pyelonephritis, a urine culture was performed and meropenem antibiotherapy was started.

On the third day of treatment with meropenem, the urine culture was negative. There was no response with regard to the AKI parameters and infectious parameters. The patient described intermittent bloody sputum, and ascending progression of lower extremity weakness. The patient was found to take long walks in the woods every day and consume raw roots of various vegetables and herbs such as ginger. Leptospirosis was considered in the differential diagnosis on the basis of medical history, clinical, and laboratory data. In the second week of symptoms, whole blood and urine samples were taken for a Leptospira polymerase chain reaction (PCR) test. Real-time PCR for Leptospira was performed with these samples using an in-house method at the Public Health Institute of Türkiye.

The treatment was changed to intravenous ceftriaxone 1x2 g for leptospirosis, while awaiting the results of the test. The ataxia that was present on neurological examination was considered secondary to the general condition. The patient was started on hemodialysis due to anuria, pulmonary hemorrhage, and severe AKI. Plasmapheresis was performed in two sessions on the 3rd and 4th day of hospitalization. After plasmapheresis, diuresis was achieved and renal function improved rapidly. The need for hemodialysis was

Table 1. Laboratory findings of the patient during hospitalisation and after discharge

	Day 0	Day 3	Day 4	Day 6	Day 12 (discharge)	Month 1 after discharge
Leukocyte (4.2-10.6 ×10³/mm³)	7.9	8.5	8.0	14.4	6.3	5.6
Neutrophil (37-80%)	94%	86%	85%	80%	70%	62%
Platelet (140-400×10³/mm³)	47	76	80	116	490	251
Haemoglobin (12.2-16.2 gr/dL)	10.9	10.8	12	12.2	10.9	10.9
CRP (0-5 mg/L)	233	193	63	28	25	
Procalcitonin (0.04-0.1 mcg/L)	2.17	54.9	19.37		0.07	
Total bilirubin (0.3-1.2 mg/dL)	7.14	9.82	8.69	5.12	1.51	
Direct bilirubin (0.0-0.2 mg/dL)	5.1	6.68	5.43	3	0.73	
Creatinine (0.8-1.3 mg/dL)	6	7.3	5.8	5.6	2.9	1.86
Urea (17-43 mg/dL)	144	191	174	190	145	55
Sodium (136-146 mmol/L)	126			124	138	143
ALT (0-50 U/L)	51	40	36	32	27	
AST (0-50 U/L)	58	32	44	35	25	
aPTT (21-36 sn)	32.3			24.2		
INR (0.8-1.2)	1.11			0.91		
Fibrinogen (170-420 mg/dL)	765			351		

Urinalysis: Leukocyte negative, Erythrocyte 3+, Protein 1+, Urobilinogen normal, Nitrite negative

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

eliminated after the second plasmapheresis treatment. The follow-up laboratory course of the patient whose laboratory parameters rapidly recovered is given in Table 1. On the 10th day of hospitalization, the diagnosis of leptospirosis was confirmed when Leptospira PCR was negative in the whole blood sample but positive in the urine. Ceftriaxone treatment was completed for ten days, and the patient had a creatinine level of 2.9 mg/dL, and was scheduled for outpatient follow-up. The creatinine level was 1.86 mg/dL at the end of month one. By the end of the first year of long-term follow-up, the creatinine level was 1.6 mg/dL. Written informed consent was obtained from the patient.

Discussion

This case report highlights the rapid urine output and clinical improvement achieved with plasmapheresis treatment in a case of leptospirosis with a high risk of mortality, that was followed by pulmonary hemorrhage, hematological involvement, and anuric renal damage. In the literature review, there were two successfully managed cases with meropenem antibiotherapy from Türkiye[6]. In some in vitro studies, carbapenems have been reported to have excellent activity against Leptospira[7]. However, renal and biliary parameters continued to deteriorate, and due to poor clinical/laboratory response, and no clear evidence of *in vivo* efficacy found in the literature, it was decided to replace antibiotherapy with ceftriaxone, as it is the recommended first-choice parenteral agent against Leptospira. In view of pulmonary hemorrhage, hematological, and possible neurological involvement, plasmapheresis treatment was started as a last resort.

Leptospirosis is a zoonotic disease that can lead to multi-organ involvement, and, in the presence of pulmonary hemorrhage, to a high mortality rate. Specific treatment options are very limited, especially in the presence of

alveolar hemorrhage, and the treatment options' efficacy has not been proven in large case series. In the literature, success with therapeutic plasma exchange (TPE) and/or extracorporeal membrane oxygenation has been reported in very few cases of severe leptospirosis[8-10].

In many infections such as coronavirus disease-2019 (COVID-19) and influenza, which "progresses with lung damage and multiple organ failure" similar to leptospirosis, TPE has proven to be beneficial in controlling hyperinflammation and cytokine storm, and the clinical course[11,12]. Based on the COVID-19 experience, TPE may be beneficial in preventing endothelial and end-organ damage through many mechanisms[13]. Leptospirosis is an infection with vasculitic consequences through immunological mechanisms. The first possible mechanism of action of TPE in leptospirosis is the removal of inflammatory cytokines, thereby stabilizing the endothelial membrane. Another mechanism is the removal of antigens that trigger the immune response against Leptospira and antibodies that are produced against them, which damage host cells due to molecular similarities.

Leptospira are 0.15 µm in diameter and 10 to 20 µm in length[14]. It may be technically feasible to remove the microorganism from micropores during processing due to the microorganism's diameter being larger than the micropores. Another possible mechanism of action is to reduce the infectious load: in this way. Turgutkaya et al.[15] claim that the viral load can be cleared by a similar mechanism and may have a beneficial effect on survival.

On the other hand, TPE is an invasive procedure involving the potential for complications and adverse effects. There are common but mild adverse effects such as temporary increases in body temperature, nausea, and vomiting. Serious complications, including hypotension, electrolyte imbalances and arrhythmias, have also been reported[13,16]. The removal of antibodies is not merely a therapeutic mechanism, but can also lead to a decline in immunity and predispose to infectious complications[16]. Another major limitation of TPE is that it requires specialised equipment and experienced medical staff[13].

Our patient's involvement in "recreational activities" (forest walks) and consumption of uncooked vegetables/plants are risk factors for transmission[17]. In addition to clinical and laboratory findings consistent with leptospirosis, the detection of the pathogen in the urine sample by Leptospira PCR confirmed the diagnosis. The fact that PCR was negative in the whole blood sample, but positive in urine was consistent with the natural course of leptospirosis, considering the timing of the patient's hospital presentation and investigations. In the patient who presented at least one week after the onset of symptoms, the bacteremia period (first week) ended and the urinary shedding period started in the second week[3].

Pulmonary hemorrhage is a complication that can occur in Weil's disease[10]. In the literature, the mortality rate in cases of alveolar hemorrhage is reported to be 50-70%[2]. Although the pulmonary infiltrates in the thorax imaging of our patient were not considered a sign of hemorrhage, pulmonary involvement was assessed clinically due to marked hemoptysis. This was decisive in the rapid decision to initiate plasmapheresis.

Similar to our patient who presented with AKI and regressed bilirubin levels after TPE, cases with diffuse pulmonary infiltrates on lung imaging that were not interpreted as hemorrhage have been reported[18]. There have been case series in which improvement has been achieved with plasma exchange using a continuous veno-venous haemofiltration pattern as well[19].

Although our patient had a history of GBS-like ascending progression of lower extremity weakness and trunk ataxia, this could not be confirmed by neurological conduction studies. A variant of GBS associated with leptospirosis has been described in the literature on the basis of case reports and confirmed by electroneurophysiological studies. Complete or partial response to plasmapheresis treatment has also been reported in cases of GBS secondary to leptospirosis[9]. Peripheral nerve involvement is rare in leptospirosis. However, there are cases of transient lower limb weakness and "GBS-like" findings during or after Leptospira interrogans infection[20]. Thus, ataxia can be considered a neurological involvement of leptospirosis, although the diagnosis of GBS was excluded in our case.

Few cases of success with plasmapheresis in leptospirosis complicated by multiple organ involvement have been reported in the literature[9,10]. The dramatic clinical response after the simultaneous initiation of ceftriaxone and plasmapheresis was thought to be a benefit of plasmapheresis.

Conclusion

Leptospirosis has a wide variety of clinical manifestations. Patients may present with signs and symptoms that

mimic a wide range of hematological, neurological, and rheumatological conditions. In addition to antibiotic therapy, it should be kept in mind that plasmapheresis may be a rescue treatment, especially in cases with high mortality risk.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., S.E., G.M., D.Ç., Concept: S.S., S.E., G.M., D.Ç., Design: S.S., S.E., G.M., Data Collection or Processing: S.S., S.E., Analysis or Interpretation: S.S., S.E., Literature Search: S.S., S.E., Writing: S.S., S.E., D.Ç.

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