CASE REPORT

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Icterohaemorrhagic leptospirosis in patients with history of alcohol abuse – report of two cases

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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 severe with jaundice, renal failure, and bleeding manifestations (icterohaemorrhagic leptospirosis, so called Weil's disease). Mortality in severe forms remains high even when optimal treatment is provided. Early clinical suspicion and laboratory confirmation of leptospirosis is essential since delays in diagnosis may increase mortality. Alcohol-related toxicity and alcoholic hepatitis are common pathological processes, which can occasionally produce clinical syndromes similar to leptospirosis. There are few reports regarding the clinical course of leptospirosis in chronic alcoholics. Here, we describe two patients with Weil's disease, in whom alcohol abuse caused therapeutic difficulties. One of the cases was with lethal outcome.

Key words: Leptospirosis, Weil's disease, alcoholic hepatitis, alcohol abuse

Alkol suistimali olan iki hastada görülen ikterohemorajik leptosiroz

Leptospiroz, spiroketlerin neden olduğu genellikle kırsal yaşamla ilişkili olan ve son dönemde sıklığında artış görülen zoonoz bir enfeksiyondur. Bulaş, enfekte hayavanların idrarına temas ile olur, inkübasyon süresi 4 gün ile 4 hafta arasındadır. Klinik tablo kendini sınırlayan hafif leptospirozdan, sarılık, böbrek yetmezliği ve kanama ile karakterize ikterohemorajik leptospiroz, Weil hastalığı'na kadar değişebilir. Optimal tedaviye rağman ağır seyreden formlarında mortalite yüksektir. Tanı için erken klinik şüphe ve labaratuvar ile doğrulama gereklidir ve tanının gecikmesi halinde mortalite artar. Alkole bağlı toksisite ve alkolik hepatit sık görülen sorunlardır ve nadiren leptospiroz benzeri tabloya neden olabilirler. Kronik alkoliklerde leptospirozun klinik seyri hakkında az sayıda yayın bulunmaktadır. Burada, alkol kullanımı nedeni ile tedavide güçlük çekilen iki Weil hastası sunulmuştur. Hastalardan birinde seyrin sonunda ölüm gerçekleşmiştir.

Anahtar kelimeler: Leptospirozis, Weil hastalığı, alkolik hepatit, alkol bağımlılığı

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, acute renal failure (ARF), 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, 6). There is only one report regarding the clinical course of lep-

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tospirosis in chronic alcoholics (7). Here, we describe two patients with Weil's disease and history of chronic alcohol abuse, treated in the Clinic of Infectious Diseases at the University Hospital "Dr Georgi Stranski" – Pleven. One of the cases was with lethal outcome.

CASE REPORT

Case 1

A 46-year-old man was evaluated in the Emergency Ward of University Hospital – Pleven for a 7-day history of fever, generalized myalgia (strongest in calf muscles), headache, adynamia, diarrhea (without vomiting), bloated abdomen, and decreased urine output (since 3 days). Treatment with amoxiclav and ibuprofen was prescribed from general practitioner, but was not performed. The patient waded in the river Iskar with bare feet two weeks previously. He reported presence of rats in his house. Past history included a 20-year period of alcohol abuse. He had drunk big volumes of alcohol until the time of admission. Previous diagnosis in the Emergency Ward was alcohol hepatitis and differential diagnosis was hepatic cirrhosis. Physical examination was remarkable for jaundice and large tender hepatomegaly. The spleen also was palpable. Cardiac examination revealed tachycardia and hypotension. Laboratory findings in the Emergency Ward were: hemoglobin 127 g/L, white blood cells count (WBC) 12.7 x 10^9 cells/L (neutrophils 85%), platelet count 40 x 10^9 cells/L, aspartate aminotransferase (AST) 123 IU/L, alanine aminotransferase (ALT) 100 IU/L, total/direct bilirubin 107/64 µmol/L. Chest radiography and electrocardiography on admission were normal. Abdominal ultrasound revealed severe hepatomegaly with steatotic transformation of liver parenchyma without intra-hepatic cholestasis, normal gallbladder and spleen, hyperechogenic pancreas, kidneys with normal total and parenchymal measures. Ascitic fluid collection was not observed. Hepatitis A, hepatitis B, and hepatitis C viruses were excluded by hepatitis-virus-panel investigation. There were no laboratory evidences of infection with *Hantaan virus, Epstein-Barr virus, or Cytomegalovirus.*

On admission to the Clinic of Infectious Diseases at the University Hospital (3 hours later), heart rate was 58 beats/min, blood pressure 75/60 mm Hg, and temperature 36.8° C. The patient was with intense jaundice and tender abdomen. Blood investigations (in Table 1) showed hemoglobin 125 g/L, WBC count 24.3 x 10^9 cells/L (neutrophils 92%), platelet count 65 x 10^9 cells/L, serum creatinine 382 µmol/L, blood urea nitrogen 18.6 mmol/L, AST 69 IU/L, ALT 49 IU/L, total/direct bilirubin 302/235 µmol/L, fibrinogen 7.4 g/L, C-reactive protein 258 mg/L, as well as normal serum potassium and sodium levels. Oligo/anuria (50 mL/8 h) persisted. The investigation of urine showed albuminuria and pyuria. Based on history and typical laboratory findings, icterohaemorrhagic leptospirosis (Weil' disease) was suspected. Micro-agglutination test (MAT) for IgM antibodies against *Leptospira,* performed in the Reference Laboratory for Leptospirosis (National Center of Infectious and Parasitic Diseases – Sofia), was positive for *L. icterohaemorrhagiae* (titer 1 : 3200; reference value ≤ 1 : 100) and confirmed clinical diagnosis. The consultation with nephrologists concluded that the patient did not need dialysis.

The initial management consisted of intravenous administration of fluids and human albumin, and plasma transfusions. Penicillin (16 million U per day) was started, together with steroid (dexamethazone initial dose 28 mg per day), ranitidine gastro-protection, dopamine perfusion, furosemide, and hepato-protection (L-ornithine, ademethionine). Transfusion of thrombocytes concentrate was performed because of thrombocytopenia. Sedatives were administered 16 hours after admission because of severe generalized convulsion, and lumbar puncture was performed. Cerebrospinal fluid (CSF) was clear with WBC count of 124 x 10^6 cells/L (neutrophils 68%), CSF-protein - 0.89 g/L (reference <0.45), and normal glucose. Latex test and culture were negative. Mannitol 10% 300 mL was infused because of aseptic meningitis, suspected by signs of meningeal irritation (confirmed by the above-mentioned CSF investigation). There were no focal neurological deficits. Neurological examination gradually became normal, but the patient was somnolent and disoriented. Cardiac abnormalities developed such as decreased heart tones, instable blood pressure, and electrocardiographic signs of myocardial dysfunction (rhythm and conductive abnormalities). The abdomen was bloated and the peristalsis was slow. Serum amylase level increased, suggesting pancreatic involvement. The jaundice increased. Renal functions were critical – after short increasing of urine output (to 5 L/24 h) since the fourth day, it decreased. Dialysis was initiated on the fifth day because of elevation of blood nitrogen parameters. Dyna-

Table 1. Laboratory findings of reported cases with leptospirosis after admission in Clinic of Infectious Diseases

Test	First investigation		Last investigation		Reference value
	1st case	2nd case	1st case	2nd case	
Hemoglobin (g/L)	125	149	75	70	120-188
Leucocytes (cells x 10^9/L)	24	17	26	11	4.0-11.0
Neutrophils (%)	92	92	92	87	50-80
Platelets (cells x 10^9/L)	65	162	665	432	150-400
Urea (mmol/L)	19	10	42	18	1.7-8.3
Creatinine (μmol/L)	382	270	512	112	44.2-134
K+ (mmol/L)	3.6	4.2	4.8	4.5	3.5-5.6
Na+ (mmol/L)	131	136	137	134	130-151
Total bilirubin (μmol/L)	302	206	541	231	3.4-21
Direct bilirubin (μmol/L)	235	157	416	162	0.8-8.5
Aspartate aminotransferase (IU/L)	69	32	59	54	≤37
Alanine aminotransferase (IU/L)	49	30	25	73	≤40
Glutamiltransferase (IU/L)	37	472	147	304	15-28
Alkaline phosphatase (IU/L)	31	70	70	396	50-260
Serum amylase (IU/L)	282	78	1749	171	30-300
Lactate dehydrogenase (IU/L)	1380	287	2591	370	100-360
Total protein (g/L)	55	59	52	54	58-80
Albumins (g/L)	27	28	21	21	35-55
Fibrinogen (g/L)	7.4	8.7	7.6	4.8	2.0-4.5
Prothrombin index (%)	113	89	28	100	80-110
Creatine kinase (IU/L)	271	278	346	260	80-190
C-reactive protein (g/L)	258	291	46	14	0-5

mic of serum bilirubin and creatinine is shown on figure 1. Petechial rash on the trunk appeared on the sixth day followed by melena. Extremely decreased hemoglobin level and erythrocyte count required transfusions of erythrocytes concentrate. Despite the intensive treatment, the patient was critically ill, in stupor, with severe hypotension unresponsive to permanent dopamine perfusion. The fifth dialysis séance (on the tenth day) was interrupted because of critically worsening of vital functions, and the patient died with acute cardiocirculatory and respiratory failure.

Acute inflammatory perivasal and interstitial changes were observed on autopsy in the myocardium, liver, kidneys, gastrointestinal tract, spleen, adrenals, leptomeninges, and encephalon. Histological investigation revealed centrilobular necrosis of hepatocytes, erosions in the stomach and intestines (reason for gastrointestinal bleeding), focal bleeding in the lungs, tubular necrosis and cholaemic nephrosis in the kidneys (due to ARF), severe haemorrhagic-necrotic pancreatitis (a reason for diffuse sero-fibrinous peritonitis). In the central nervous system (CNS), acute aseptic leptomeningitis and perivasal inflammation (typical for encephalitis) were observed. Co-morbidity included exacerbated catarrhal bronchitis and acute catarrhal-desquamative bronchiolitis.

Case 2

A 61-year-old man was found in severe condition from his neighbors and was evaluated in the Emergency Ward of the University Hospital – Pleven for a 4-day history of myalgia in calf muscles and decreasing to complete lack of urine output. He denied fever, headache, nausea and vomiting, diarrhea, abdominal pain. Previous treatment was not performed. The patient fished in the river Iskar and waded with bare foots three weeks before the clinical onset. He reported presence of rats in his house. The past history included a 30-year alcohol abuse. He had drunk big volumes of alcohol until the time of admission. The physical examina-

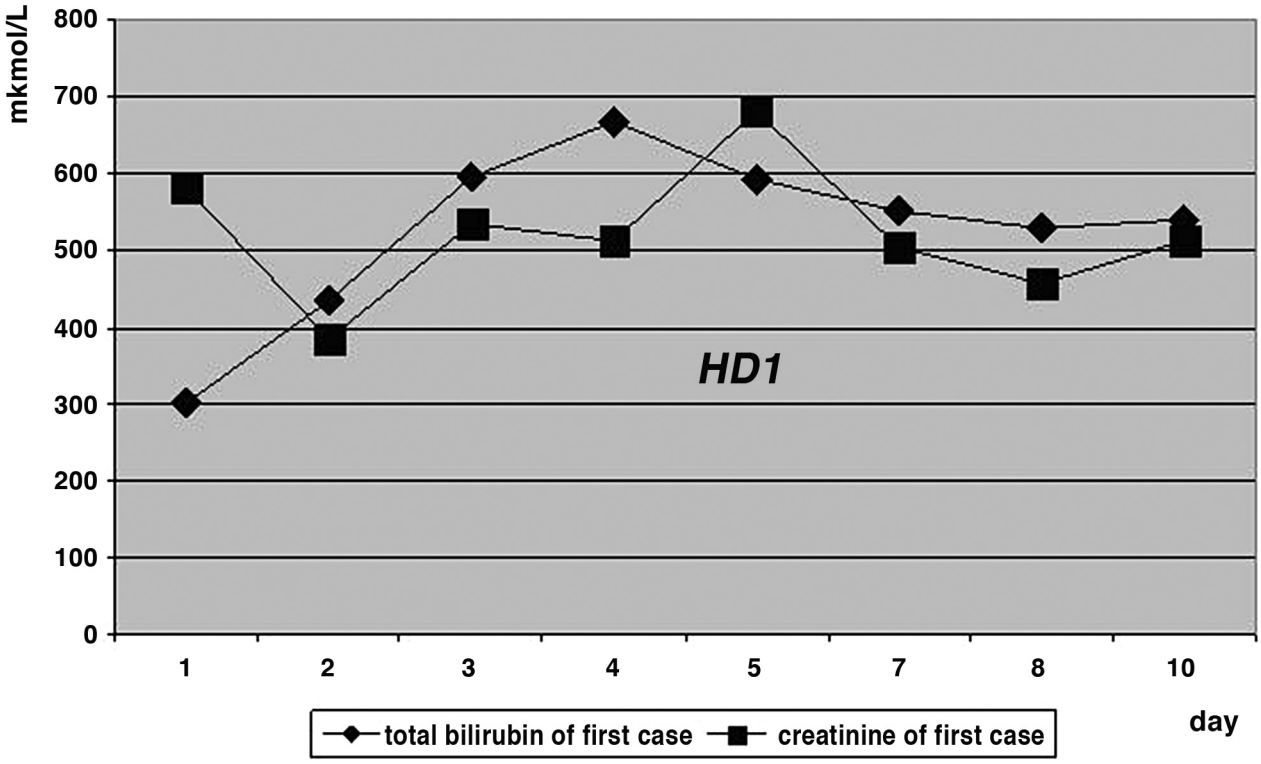

Figure 1. Total bilirubin and creatinine levels of the first case after admission in the Clinic of Infectious Diseases.
HD1 – initial dialysis of the first case (on the 5th day).

tion revealed petechial rash on the trunk, intense jaundice, and large tender hepatomegaly. The spleen also was enlarged. The cardiac examination revealed tachycardia and hypotension – the heart rate was 88 beats/min and blood pressure was 84/50 mm Hg. The temperature was normal. Laboratory findings (in Table 1) were: hemoglobin 149 g/L, WBC 16,9 x 10^9 cells/L (neutrophils 92%), platelet count 162 x 10^9 cells/L, serum creatinine 382 μmol/L, blood urea nitrogen 18,6 mmol/L, total/direct bilirubin 206/157 μmol/L, AST 32 IU/L, ALT 30 IU/L, and C-reactive protein 291 mg/L. The investigation of urine revealed albuminuria and macrohaematuria. The chest radiography and electrocardiography on admission were normal. Abdominal ultrasonography demonstrated severe hepatomegaly with steatotic transformation of liver parenchyma without intra-hepatic cholestasis. The gallbladder was with tick wall without concrements. The spleen was normal, but the pancreas was hyperechogenic. The kidneys were with normal total and parenchymal measures. A mild ascitic fluid collection in perihepatic and perisplenic spaces was manifested. Hepatitis A, hepatitis B, and hepatitis C viruses were excluded by hepatitis-virus-panel investigation. There were no laboratory evidences of infection with *Hantaan virus, Epstein-Barr virus,* or *Cytomegalovirus.* Based on the history and typical laboratory findings, severe leptospirosis was suspected. The consultation with nephrologists concluded that the patient did not needed dialysis.

The initial management consisted of intravenous administration of fluids and human albumin, and plasma transfusions. Penicillin (10 million U per day) was started and after eight days was followed by sulperazone (2g/24 h) for twelve days. Steroid was used (methylprednizolone 160 mg per day initial dose), together with ranitidine gastro-protection, furosemide, and hepato-protection (L-ornithine, ademethionine). Dialysis was initiated on the second day because of ineffective conservative treatment of ARF, and totally eight séances were performed. An epistaxis occurred followed by thrombocytopenia, and transfusions of thrombocytes concentrate were performed. The jaundice increased and correlated with serum bilirubin levels (Figure 2). There were no signs of myocardial and respiratory dysfunctions. The CNS was not affected. Laboratory and ultrasound evidences for pancreatic involvement were found.

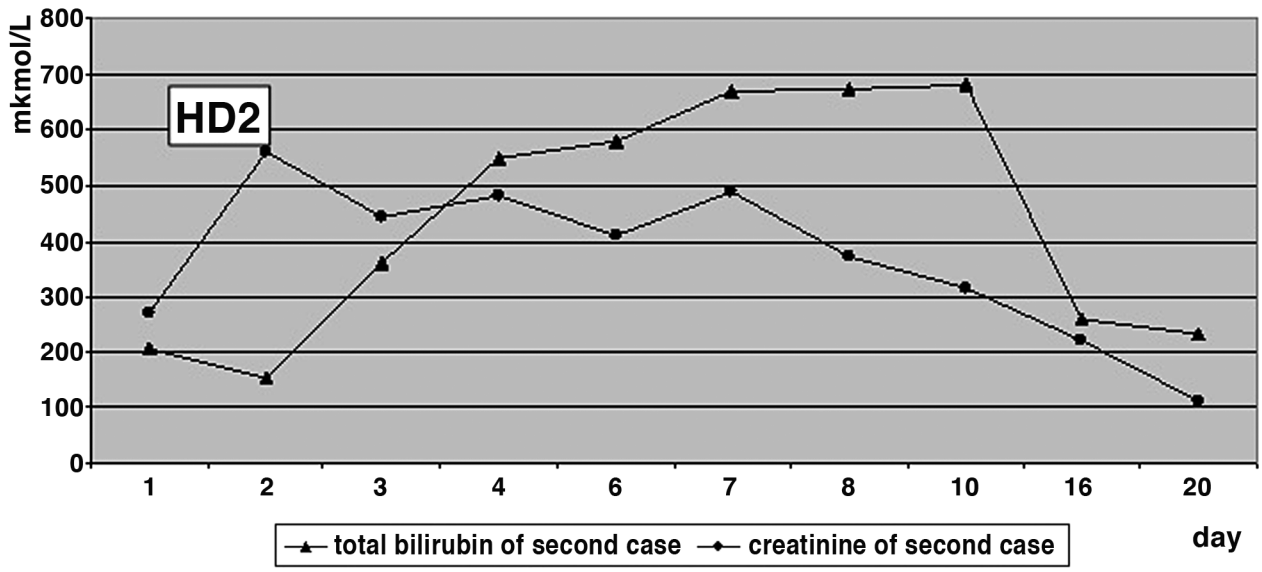

Figure 2. Total bilirubin and creatinine levels of the second case after admission in the Clinic of Infectious Diseases.
HD2 – initial dialysis of the second case (on the 2nd day).

In the following days, the patient's condition gradually improved, the hemorrhagic diathesis contracted, jaundice decreased, renal functions improved (urine output increased and creatinine level decreased to normal – Figure 2). On the twentieth day, the patient was discharged. The abnormalities of liver function and anaemia resolved slowly within the next month, up to which time, the bilirubin level became normal. MAT for IgM antibodies against leptospira, performed in the Reference Laboratory for Leptospirosis (mentioned above), was positive for *L. icterohaemorrhagiae* (titer 1 : 6400) and confirmed the clinical diagnosis.

DISCUSSION

Icteric leptospirosis is a severe disease in which the clinical course is often rapidly progressive. Severe cases often present late in the course of the disease, and this contributes to the high mortality rate, which ranges between 5 and 15%. The icteric form of leptospirosis occurs in 5 to 15% of all patients (1). The complications of severe leptospirosis emphasize the multisystemic nature of the disease. Leptospirosis is a common cause of ARF, which occurs in 16 to 40% of cases (10, 15). In patients with ARF, oliguria is a significant predictor of death. Serum amylase levels are often raised significantly in association with ARF, but clinical symptoms of pancreatitis are not a common finding. Necrotizing pancreatitis has been detected at autopsy. Cardiac and CNS involvement are common in severe cases and contribute to unfavorable outcome (1).

The first patient developed a fulminant febrile illness with jaundice, ARF, ascites, impaired consciousness, and gastrointestinal bleeding. Considering the patient's history, leptospirosis, alcoholic hepatitis, or hepatic cirrhosis were discussed in the differential diagnosis. The onset of the second case was not sudden and without reporting of fever. Alcoholic hepatitis has been well associated with the development of the above-mentioned clinical manifestations. Fever and/or neutrophilia are also commonly observed. Cefotaxime has been suggested to be the drug of choice in alcoholic hepatitis (6), but because of suspected leptospirosis penicillin was preferred over cefotaxime in the reported patients. Steroids seem to improve prognosis, while terlipressin may be useful in alcoholic hepatitis-related renal failure (6). Acute HBV replication or reactivation of chronic HBV infection was excluded in our patients. 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 the reported patients (5). Decompensated liver cirrhosis could be considered in the present cases. However, there was no evidence supporting such a possibility. Leptospirosis was strongly suspected in the cases and was confirmed serologically (by MAT). Of note, leptospirosis in patients

with concurrent alcohol abuse has been reported only once (7). The presentation of Weil's disease is often atypical and organ failures may occur 4 to 9 days after the onset of symptoms (8). Serum bilirubin is frequently high and may persist for several weeks, but transaminases and alkaline phosphatase are usually moderately elevated (1). That constellation was observed in the reported cases – serum levels of transaminases were slightly elevated and contrasted to severe jaundice. Both slightly elevated alkaline phosphatase levels and abdominal ultrasonography confirmed the lack of cholestasis.

Significant renal impairment is seen in 50-75% of patients, commonly with normal diuresis and preserved potassium balance. Hemodialysis is needed in 30% of patients (9). Hemodynamic derangement has been involved in the development of ARF (10). Altered sensorium, lasting 1 to 8 days, is the most common neurological presentation of leptospirosis (11), while hemorrhagic manifestations are observed in 30-50% (9). Ascites has been rarely reported in Weil's disease (9, 12), usually mild, such as that reported in the present cases; its pathogenesis may involve leptospiral or immune complex-related vasculitis (7).

Thrombocytopenia occurs frequently and is associated with poor prognosis (1), whereas significant anaemia, possibly related to marrow suppression, is fairly uncommon (13). It is likely that alcohol abuse affects the progress of the clinical and laboratory abnormalities, predisposing to more severe clinical course of leptospirosis. Moreover, alcohol may favor leptospiral vasculitis by causing endothelial dysfunction (14). We consider that independent of chronic alcohol abuse in both reported cases, the delayed dialysis in the first case is the most important reason for his lethal outcome. The cardiac involvement, aseptic meningoencephalitis, and haemorrhagic-necrotic pancreatitis (a reason for diffuse sero-fibrinous peritonitis) also provoked therapeutic difficulties and contributed to the unfavorable prognosis.

MAT is the method of choice for the diagnosis of leptospirosis allowing serologic confirmation after the first week of the disease (1). However, the initiation of treatment is likely to be more effective during the first week (before serological confirmation) and usually begins empirically (15). The development of antibodies against *Leptospira* in the reported patients occurred in the second week after the onset of the symptoms. This could be related with the immunosuppressive effects of alcohol abuse (16). Some authorities speculate that immunodeficient responses against leptospirosis take place in some patients (14).

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 (16). In the second case, sulperazone showed clinical benefit, supporting the recent view that the optimal treatment for severe leptospirosis remains to be defined (16). Vasoconstrictor agents have been shown to improve the systemic hemodynamics and renal function in patients with leptospirosis (16). We used dopamine perfusion to reduce hypotension and consequently 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 serological tests 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 dopamin, may facilitate the recovery of renal function.

CONCLUSION

Alcohol abuse together with other pathogenic factors worsens the prognosis of severe leptospirosis. The early initiation of both intensive therapy and dialysis contribute to favorable outcome.

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