Leptospirosis: a six-case report from west black sea, Turkey

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SUMMARY

Leptospirosis is a ubiquitous acute bacterial zoonosis. This report describes six cases presenting to our hospital with symptoms such as fever and muscle pain and diagnosed as leptospirosis. All cases presented with fever, muscle pain, and lethargy and were engaged in activities such as farming, hunting, and fishing. Thrombocytopenia and impaired liver function tests were found in all patients, increased creatine-kinase in five, and increased creatinine in four. Leptospirosis was diagnosed using polymerase chain reaction (PCR). The course of the disease resulted in cure in three cases, chronic kidney disease sequelae in one, and death in two. In conclusion, the possibility of leptospirosis should be considered in patients presenting with non-specific symptoms such as fever and muscle pain and developing thrombocytopenia, and liver and kidney function disorder. Risk factors should also be investigated when taking histories. Early diagnosis and antibiotic therapy being started as quickly as possible are important in terms of the course of the disease.

Keywords: Leptospirosis, Weil's disease, Black sea region, Turkey.

INTRODUCTION

Leptospirosis is regarded as a global public health problem due to growing incidence rates in both developing and developed countries. It is an acute bacterial zoonosis caused by pathogenic *Leptospira* species. It exhibits a wide geographical distribution and is endemic in rainy tropical and subtropical regions in particular [1].

Various animals including both wild animals in nature and domestic pets can acts as hosts to *Leptospira* spp. These can survive for extended periods in the environment in urine spread by these carrier animals. The disease is transmitted to humans either by direct contact with infected animal urine, or by means of urine-contaminated water, soil or foodstuffs. The individual's occupation and place of residence are therefore significant in the transmission of the disease [2].

The clinical manifestation in leptospirosis may vary from mild, non-specific flu-like infection to Weil's disease involving severe complications such as multiorgan failure. There is no diagnostic criterion in the early period of the disease. Weil's disease, the most severe form of leptospirosis is seen in 5-10% of cases and represents a manifestation involving multiorgan failure progressing with liver failure, acute kidney failure, bleeding disorder and fever, and is capable of resulting in mortality [3, 4]. Mortality rates between 3% and 54%, depending on the organ system affected, have been reported in different publications [5, 6].

Our region of Turkey, the Black Sea region, receives plentiful rainfall all four seasons of the year, and rodents capable of acting as a reserve for *Leptospira* spp. are frequently seen, especially in rural areas. The incidence of leptospirosis has

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increased in our region in recent years. We report six cases of leptospirosis from Düzce in 2017-2019.

PATIENTS AND METHODS

The demographic characteristics, symptoms, and clinical findings of all cases are summarized in Table 1, while laboratory findings are given in Table 2. Diagnosis was based on polymerase chain reaction (PCR) in serum specimens sent to the Public Health General Directorate (PHGD) Microbiology Reference Laboratory. The written consents of patients were obtained for this report.

Case 1: A 77-year-old man presented to our hospital's emergency department due to fever, headache, and articular pain. Lethargy and headache had begun five days previously, while muscular and articular pain and fever had commenced two days previously. The patient was engaged in farming and drank village water. He had a known history of hypertension and coronary artery disease. He did not smoke or consume alcohol. At physical examination his general condition was average, and he was lucid and cooperative. Body temperature was 36.8° C, heart rate 80 beats/min, blood pressure 110/80 mmHg, and respiration rate 20/min. Physical examination was unremarkable. Leukopenia and thrombocytopenia were determined in the emergency department, and the patient was admitted to the infectious diseases ward to investigate the etiology of the fever. C-reactive protein (CRP), blood culture, stool culture, peripheral smear, the Wright agglutination test, anti-HIV, anti-HAV-IgM, HbsAg, anti-HCV, and echocardiography were requested. Complete urine analysis was unremarkable. HSGM tests for leptospirosis and hantavirus infection due to the history of drinking village water were sent to the Microbiology Reference Laboratory. The patient was started on intravenous (iv) ceftriaxone 1x2 g and levofloxacin therapy. No atypical cells were observed at peripheral smear, while the platelet count was 150,000/mm^3. The internal diseases department was consulted due to creatinine elevation. No additional suggestion was made. No growth occurred in blood or stool culture, and brucella tube agglutination, hepatitis markers, and anti-HIV were negative. No vegetation was determined at echocardiography. Fever, symptoms, and laboratory findings resolved over three-

Table 1 - Demographic characteristics, symptoms, and clinical findings of leptospirosis patients.

Demographic characteristics	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*
Age/Sex	*77/M*	*69/M*	*34/M*	*56/M*	*46/M*	*62/M*
Occupation	*Farmer*	*Farmer*	*Clerical*	*Farmer*	*Farmer*	*Clerical*
Symptoms and findings						
Durations (days)	5	7	4	4	3	4-5
Fever	+	+	+	+	+	+
Icterus	+	+	+	-	+	+
Nausea-vomiting	-	-	+	-	+	+
Myalgia	+	+	+	+	+	+
Conjunctival hyperemia	-	-	-	+	-	+
Eruption	-	+	-	-	-	-
Shortness of breath	-	+	+	-	+	-
Epistaxis	-	-	+	-	-	-
Headache	+	+	+	+	+	+
Renal failure	+	+	+	+	+	+
Hepatomegaly	-	+	-	+	-	-
Splenomegaly	-	+	-	+	-	-
ARDS*	-	+	+	-	+	-

*Acute respiratory distress syndrome.

Table 2 - Laboratory findings of patients.

Laboratory findings	*Normal values*	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*
Leukocyte (/mm^3)	4500-11,000	1800	18,700	8900	15,200	10,100	10,200
Hemoglobin (gr/dl)	12-16	13,9	11,8	13,9	13	12,6	11,9
Platelet (/mm^3)	130,000-400,000	109,000	14,000	23,000	96,000	96,000	16,500
CRP (mg/dL)	0-6	29	41	41	47	38	96
ESH (mm/hour)	0-20	77	65	90	65	94	77
Urea (mg/dl)	7-25	45	208	146	76	86	161
Creatinine (mg/dl)	0.3-14	1.36	5	5.1	1.1	2.9	5.9
AST (IU/lt)	10-42	195	72	67	49	111	61
ALT (IU/lt)	10-60	123	45	43	38	67	45
Total bilirubin (mg/dl)	0.4-1.35	1.8	13.8	9.6	1	11.9	20
Direct bilirubin (mg/dl)	0.1-0.5	0.8	8.7	6.5	0.4	7.3	14
CK (IU/lt)	22-200	316	560	977	60	2483	460
LDH (IU/lt)	100-240	396	588	302	463	373	380
ALP (IU/lt)	25-100	217	185	64	132	114	110
GGT (IU/lt)	7-60	145	77	121	68	88	86
PTT (sec)	11-15	12,6	13,1	12	14,3	13	14,2
Leptospira PCR		+	+	+	+	+	+

CRP: C reactive protein, ESH: Erythrocyte sedimentation rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CK: Creatine kinase, LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase, GGT: Gama glutamyl transferase, PTT: Prothrombin time.

day follow-up, and the patient was prescribed levofloxacin 1x500 mg tablets and discharged. The *Leptospira* PCR test was reported positive one week later.

Case 2: A 69-year-old man living in a village and engaged in farming was using moxifloxacin 1x400 mg iv and inhaler therapy for pneumonia diagnosed at an external center due to fever, cough, phlegm production, shortness of breath, and muscle pain commenced one week previously. Following the onset of hypoxemia and atrial fibrillation, the patient was taken to the coronary intensive care unit (ICU) and stabilized with cordarone infusion. Deep thrombocytopenia and acute kidney failure developed, and the patient was transferred to our hospital tertiary ICU for follow-up in a center with a hematology and nephrology clinic. He had no known disease, and neither smoked nor consumed alcohol. The patient had come into contact with mice when clearing the banks of a stream in his village one week previously. At physical examination, his general condition was average, and he was lucid and cooperative, but tended to somnolence. Body temperature was 36.6º C, heart rate 98 beats/min, blood pressure 100/80 mmHg, and respiratory rate 26/min. The sclera were icteric. Rales in the bilateral middle and inferior zones at pulmonary examination and pretibial edema were present. Maculopapular eruptions turning pale when touched were present in the lower extremities. Complete blood test and biochemistry, the Wright agglutination test, CRP, blood and stool culture, peripheral smear, anti-HIV, anti-HAV-IgM, HbsAg, anti-HCV, *Leptospira* PCR, hantavirus PCR, *Legionella* PCR, and influenza PCR were requested. Complete urine analysis was unremarkable. Treatment was maintained with piperacillin-tazobactam 4x2.25 mg iv, levofloxacin 500 mg 1x1 iv once in 48 h, and oseltamivir 1x75 mg via the oral route. At the advice of the nephrology department, the patient was taken for dialysis due to the increase in creatinine values and presence of electrolyte disorder. The patient was intubated due to low saturation and was started on noradrenalin infusion due to his hypotensive course. Pooled platelet replacement was performed following platelet monitoring. Toxic granulation and left shift were present

at peripheral smear. Hepatomegaly was present at abdominal ultrasonography. Renal replacement and platelet suspension support was administered based on daily renal function tests and complete blood count monitoring. The patient failed to respond to the existing treatment and replacements and died on the sixth day of treatment. *Leptospira* PCR studied at the PHGD Microbiology Reference Laboratory was reported positive.

Case 3: A 34-year-old man with known diagnosis of hypertension but not using regular medication presented to our emergency department due to fever and diarrhea. Two days following symptomatic treatment at the emergency department, the patient presented to the department due to fever, muscle and joint pain, icterus, diarrhea, cough, and phlegm. The patient worked as a clerical officer and hunted as a hobby. One day before the onset of symptoms he had been fishing by the side of a stream and had swum in the fresh water. He drank mineral water. He had a history of chronic alcohol consumption for the previous nine years and smoked nine packs/year. Tests at the emergency department revealed acute renal failure, leukopenia, thrombocytopenia and bilirubin elevation. He was admitted to our hospital's infectious diseases clinic with preliminary diagnoses of Weil's disease and hantavirus. At physical examination, the patient's general condition was average, and he was lucid and cooperative. Body temperature was 37.6ºC, heart rate 98/min, blood pressure 100/80 mmHg, and respiratory rate 24/min. The sclera were icteric. Rales were present in the bilateral lower lobes at pulmonary examination. Complete blood count, biochemistry, blood and stool culture, peripheral smear, brucella tube agglutination, anti-HIV, anti-HAV-IgM, HbsAg, anti-HCV, *Leptospira* PCR, hantavirus PCR, *Legionella* PCR, and influenza PCR were performed. The patient was started on meropenem 1x1 gr iv, and oral tetradox capsules 2x100 mg. Increased bilateral reticular radio-opacity was present at lung x-ray. Hemoptysis developed at follow-up, and platelet suspension and fresh frozen plasma replacement were administered. Frequent complete blood count and replacement as required were performed. Acute respiratory failure syndrome developed on the second day of follow-up, and the patient was transferred to the ICU. The patient was started on 1 mg/kg prednol at the advice of the thoracic diseases department. Fever was present every day. Teicoplanin at a loading dose of 2x400 mg and a maintenance dose of 1x400 mg once every 72 h was added to the existing treatment. No growth occurred in blood or urine culture. The patient was intubated on the third day and died from cardiac arrest on the fifth day of treatment. *Leptospira* PCR studied at the PHGD Microbiology Reference Laboratory was reported positive.

Case 4: A 54-year-old man with hypertension and developmental dysplasia of the hip was referred to our hospital due to body temperature elevation and muscular and articular pain. He had presented with these symptoms to a family practitioner four days previously and had been prescribed for upper respiratory tract infection. Complete blood count performed due to persistence of the symptoms despite drug therapy revealed a low platelet count, CRP elevation, and acute kidney failure. The patient was then admitted to the infectious diseases ward for investigation of the etiology of the fever. His history revealed that he lived in a house with a garden and drank mineral water. The conjunctiva were hyperemic at physical examination, while other system examinations were normal. Blood culture, the Wright agglutination test, toxoplasma IgM, *Borrelia burgdoferi* IgM, anti-HIV test, *Leptospira* PCR, hantavirus PCR, Crimean-Congo Hemorrhagic Fever (CCHF) PCR, *Coxiella burnetii* (Q FEVER) IgG (Faz II), *Coxiella burnetii* (Q Fever) IgM (Faz II), peripheral smear and echocardiography were requested. The patient was started on ceftriaxone 2x1 gr iv and oral doxycycline 2x100 mg, and iv fluid support was administered for the acute kidney failure. No vegetation was observed at echocardiography. No growth occurred in blood culture. The anti-HIV and Wright agglutination tests were negative. Toxic granulation and platelet inhibition were present at peripheral smear. B12 and folic acid levels were low, and replacement was performed. At follow-up the platelet count increased, but the fever persisted. Blood culture was taken at time of fever, but no growth occurred. Control echocardiography was performed, and no vegetation was observed. Fundus examination was normal. Since the fever persisted on the seventh day, ceftriaxone was halted. The patient was started on piperacillin-tazobactam 3x4.5 gr iv, and doxycycline therapy continued. The fever was brought under control on the eighth day. Kidney function tests

improved. *Leptospira* PCR was reported positive. The patient completed 14 days of doxycycline therapy and seven days of piperacillin-tazobactam therapy wand was discharged in a healthy condition.

Case 5: A 46-year-old man with no known history of disease presented to our hospital with fever, shortness of breath, articular pain, icterus, nausea and vomiting. We learned that onset of symptoms occurred after fishing in a stream. The patient was a farmer and lived in a house with a garden. Bovine animals and mice lived around the house. He had a history of drinking village water. He smoked 80 packs/year but did not use alcohol. Bilirubin elevation and a low platelet count were present, and the patient was admitted to the infectious diseases ward for investigation of the etiology of the fever. Increased bilateral reticular opacity was observed on lung x-ray. O_2 saturation at room temperature was 94%. Blood culture, the Wright agglutination test, toxoplasma IgM, *Borrelia burgdoferi* IgM, anti-HIV testi, *Leptospira* PCR, hantavirus PCR, CCHF PCR, *Coxiella burnetii* (Q FEVER) IgG (Phase II), *Coxiella burnetii* (Q Fever) IgM (Phase II), peripheral smear and echocardiography were requested. The patient was started on ceftriaxone 2x1 gr iv, oral doxycycline 2x100 mg, and oral oseltamivir 2x75 mg. The thoracic diseases department was consulted due to shortness of breath. Prednisolone 80 mg/die iv was started. Thoracic tomography was compatible with acute respiratory distress syndrome, and the patient was transferred to the ICU. No fever occurred at follow-up. Complete blood count, biochemistry, and arterial blood gas were monitored. Urinary output decreased. The patient was taken for hemodialysis. Plasmapheresis was advised, and the patient was transferred to a center where plasmapheresis was performed. The patient's clinical condition resolved after two sessions of plasmapheresis at that center, and he was discharged in a healthy condition on the 12th day of follow-up. *Leptospira* PCR was reported positive.

Case 6: A 62-year-old man presented due to fever, muscular pain, and icterus in the eyes and body three days after drinking village water one week previously. Acute renal failure, hyperbilirubinemia, and thrombocytopenia were present, and he was admitted to our hospital ICU. At physical examination his general condition was good, and he was lucid and cooperative. Body temperature was 36.7ºC, heart rate 80/min, and blood pressure 120/80 mmHg. The skin and sclera were icteric, and the conjunctiva were hyperemic. Other system examinations were normal. Blood and urine cultures were taken, and anti-HAV-IgM, anti-Hbc IgM, anti-HIV, CMV IgM, HSV 1-2 IgM, the Wright agglutination test, and *Leptospira* and hantavirus PCR were requested. Lung x-ray was normal. Empiric piperacillin-tazobactam 4x2.25 mg iv, and oral doxycycline 2x100 mg were started. Renal replacement was planned due to rising creatinine and decreasing urine output. Platelet suspension was administered for a low platelet count. No growth occurred in blood or urine cultures. Viral markers were negative. Improvement in kidney function tests commenced after five days, and bilirubin returned to normal levels. The patient was transferred back to the ward following 12-day follow-up in the ICU. *Leptospira* PCR was reported positive, and antibiotic therapy was discontinued on day 12. Creatinine improved but did not return to normal levels. The patient was placed under follow-up as a chronic kidney patient. He was then discharged and advised to attend polyclinic controls.

DISCUSSION

Leptospirosis caused by *Leptospira* species is a common global bacterial zoonosis. The annual incidence in temperate regions is 0.1-1/100,000, rising to 10-100/100,000 in tropical regions with abundant rainfall [7]. The true incidence in Turkey, which lies in the temperate belt, is unknown, although cases have been reported from regions of the country with more abundant rainfall in particular [3, 8, 9].

The patient's occupation and activities are important risk factors for leptospirosis. The disease is frequently seen in farmers, veterinarians, sewage workers, and people engaging in hunting and water sports. Since the people who engage in these activities are generally men, the disease is also more common in men. Another risk factor is travel to tropical regions where the incidence of the disease is high. These factors must be carefully investigated during history-taking [2, 3, 10]. In their study of four leptospirosis cases, Demiroğlu et al. reported that three subjects lived in rural areas and worked in farming [9]. Another study reported leptospirosis in individuals who fished

as a hobby and worked in farming [8]. All of our cases were male, five were farmers, and two were clerical workers, and all had a history of contact with suspected contaminated water. Risk factors for leptospirosis were present in all our cases.

Approximately 300,000-500,000 severe leptospirosis cases are seen across the world every year, of which 3-% are fatal [7]. One study reported a mortality rate of 26% [11]. Studies from Turkey have reported mortality rates of approximately 17% [3, 12]. Two of our cases (33.3%) also resulted in mortality. The mortality rate in the present is consistent with the previous literature.

The clinical manifestation in leptospirosis can range from mild, flu-like infection to severe complications and Weil's disease [4]. One study of 41 patients diagnosed with leptospirosis observed fever in 100% of cases and bilirubin elevation in 20% [10]. Another study of 12 cases of Weil's disease reported fever in all cases and icterus in 91.6% [12]. Turhan et al. evaluated 22 cases of leptospirosis and described fever as the most common symptom, with icterus being present in two (10%) [13]. In another study of leptospirosis case, Esen et al. reported fever in 61.1% of patients and icterus in 75% [3]. Consistent with previous studies, we observed fever in all our patients (100%) and icterus in four (66.6%).

Leukocytosis and thrombocytopenia are common laboratory findings in leptospirosis, and anemia may also be seen in severe cases [2]. de Vries et al. determined leukocytosis in 24.4% of cases, leukopenia in 7.3%, thrombocytopenia in 36.6%, and low hemoglobin levels in 19.5% [10]. Another study reported leukocytosis in 38% of cases, leukopenia in 10%, and thrombocytopenia in 33% [13]. Esen et al. observed thrombocytopenia in 75% of surviving cases and 83.3% of cases resulting in mortality [3]. Leukocytosis was determined in two (33.3%) of our cases, and leukopenia in only one (16.7%). In contrast to previous studies, thrombocytopenia was observed in all our cases (100%). We think that this may be due to cases in which Weil's disease did not develop being in the majority in previous studies, and also to our low case number.

Other laboratory findings in leptospirosis may include moderate elevation in transaminases, hyperbilirubinemia, and creatinine and creatine kinase elevation. However, since these laboratory findings are not specific to leptospirosis, several infections such as HIV infection, influenza, Dengue fever, viral hemorrhagic fevers, typhoid, malaria, brucellosis, rickettsioses, viral hepatitis, infectious mononucleosis, encephalitis, poliomyelitis, pneumonia, and hantavirus infections must also be considered at differential diagnosis of leptospirosis patients [2]. Transaminase elevation was determined in 36.6% of cases in one study, creatinine elevation in 41.5%, and bilirubin elevation in 19.5% [10]. Demiroğlu et al. reported transaminase, bilirubin, and creatine kinase elevation in all their cases, and creatinine elevation in 50% [9]. In the present study, bilirubin and creatine kinase elevation was present in five cases (83.3%), and creatinine elevation was present in four (66.6%). Moderate elevation was observed in only one of the patients with high bilirubin levels, while elevation was sufficiently high to produce clinical findings in the other cases. In addition, hepatic enzyme elevation was determined in all cases (100%), with elevation being five-fold greater than basal values in one case but increasing only moderately in the others.

Several factors are responsible for kidney failure in Weil's disease. The principal factors involved in kidney function disorders are hypovolemia, endotoxin-induced vasoconstriction, ischemia, and acute tubular necrosis [14]. Since renal involvement is one of the main causes of mortality, close monitoring of kidney functions, rehydration, and hemodialysis if required are particularly important during patient follow-up [2]. One study evaluating four patients diagnosed with leptospirosis reported that chronic kidney disease remained as a sequela in one case [9]. Acute kidney failure was detected in all our cases (100%), and hemodialysis was required in three (50%). Only one of the patients who recovered after treatment was placed under follow up for chronic kidney disease.

Leptospira spp. is sensitive to several antibiotics. The most effective antibiotics in the treatment of leptospirosis include penicillin and doxycycline. Early treatment reduces the risk of complications developing [15,16]. One study showed that even if penicillin therapy is started in the late stage of the disease in severe leptospirosis cases it still results in a shorter hospital stay, although another study showed that penicillin therapy initiated in the late stage (four days after onset of symptoms) was not beneficial [17, 18]. In studies from Turkey, patients have been given antibiotic therapy

including in the late stage of the disease [8, 9, 12]. In the present study, too, all patients were started on antibiotic therapy, including in the late stage.
In conclusion, leptospirosis manifests with very different clinical findings and is one cause of hospitalization due to febrile disease. Early diagnosis is important since the infection involves severe complications, especially in patients developing Weil's disease. Since the patient's occupation and activities will be a useful guide to diagnosis in addition to clinical and laboratory data, attention must be paid to these during history-taking.

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Conflict of interest
We have no conflict of interest to declare.

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