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OLGU SUNUMU / CASE REPORT

Acute renal failure and cold agglutinin disease due to leptospirosis

Leptospiroza bağlı akut böbrek yetmezliği ve soğuk aglütinin hastalığı

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Abstract
Leptospirosis is a zoonosis transmitted through the urine of infected animals. Leptospira can be associated with respiratory, renal, hepatic and hematological complications and most importantly carries a high mortality when untreated. We present a rare cause of acute renal failure, acute hepatitis, hyperbilirubinemia and cold agglutinin disease occurring simultaneously with leptospirosis.
Key words: Leptospirosis, acute renal failure, cold agglutinin disease.

Öz
Leptospirosis, enfeksiyonlu hayvanların idrar yoluyla bulaşan bir zoonozdur. Leptospiroz; solunum, renal, hepatik ve hematolojik komplikasyonlar ile ilişkili olabilir ve tedavi edilmediğinde yüksek mortalite riski taşır. Bu yazıda leptospirozise bağlı akut böbrek yetmezliği, akut hepatit, hiperbilirubinemi ve soğuk aglutinin hastalığı gelişen nadir bir vaka sunulmuştur. ..
Anahtar kelimeler: Leptospiroz, akut böbrek yetmezliği, soğuk agglutinin hastalığı.

INTRODUCTION

Leptospirosis is an often unrecognized zoonotic disease with worldwide distribution and probably a common cause of acute kidney injury (AKI) in low-income countries[1]. Leptospirae colonize the proximal renal tubule of carrier animals. Infection to humans usually involves contaminated water and soil with animal urine. Entry to the body is cut or worn skin, moxa, and conjunctiva. The disease is common in farmers and veterinarians[2]. Leptospira can be associated with respiratory, renal, hepatic and hematological complications and most importantly carries a high mortality when untreated.

CASE

A 61-year-old diabetic woman was admitted to the emergency department of another hospital due to fever, nausea, vomiting, weakness and epigastric pain for 6 hours. Fever and elevated liver enzymes were found. Paracetamol and ceftriaxone were administered and her anti-hyperglycemic drugs Metformin and gliclazide were stopped. Her abdominal ultrasonographic examination was normal. On third day in hospital, anemia, hyperbilirubinemia, thrombocytopenia, high levels of BUN, creatinine, AST, ALT developed. She transferred to our hospital. There was no pathological finding except icterus in her physical examination. She was well but icteric. The laboratory tests are summarized in Table 1.

She was oliguric and leucocyte, leucocyte cylinders and hyalin cylinders were found in her urine sediment. PA chest X-ray and abdominal USG were normal. Blood and urine culture samples were negative for bacterias and fungus. Serological tests including antinuclear antibody, double-stranded DNA, Antinuclear cytoplasmic antibody, Anti SS-A, Anti SS-B Anti-cardiolipin IgM, Anti-cardiolipin IgG, Anti-phospholipid IgM, Anti-phospholipid IgG were negative, and C3 and C4 were normal. No gamma peak was detected in protein electrophoresis. Viral infection markers (HBs Ag, Anti HBs, Anti HBc IgM, Anti HCV, Anti HIV, Anti HAV IgM, Rubella IgM, Herpes simplex virus IgM, CMV IgM, EBV Ig M) were negative.

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Table 1. Summary of laboratory findings of patient

Parameters	Normal	9.8.17	14.8.17	16.8.17	18.8.17	20.8.17	24.8.17	27.8.17	31.8.17	14.9.17	21.9.17	26.10.17
FBG, mg/dL	70-105	158		295		174	240			223		204
BUN, mg/dL	8-20	77	94.4	36	63.8	35	86.5	100	95	31	19.5	15.8
Creatinin, mg/dL	0.4-1	4.04	9.93	5.39	8.29	5.7	7.68	5.7	4.05	1.68	1.43	1.04
T.protein, g/dL	6.1-7.9	4.9			5.4	5.5	6.3			6.6		6.6
Albumin, g/dL	3.5-4.8	2.64		3	2.8	3.1	3.6			4.27		4.07
Uric acid, mg/dL	2.3-6.6	7.5		4.4	6.9	5.4	6.8	6.6	6.3	7.5		4.4
AST, U/L	15-41	206		16	32	16	15		223	21	21	20
ALT,U/L	14-54	71		13	38	20	30		272	22	19	21
ALP, U/L	38-126	64		57	179	93			236			
GGT, U/L	7-50	54			273				438			
T.Bilurubin, mg/dL	0.4-1.2	2.73			0.5		0.5					
D.Bilurubin, mg/dL	0.1-0.5	1.7			0.15		0.12					
LDH, U/L	115-248	2494	392	363	275	281	152					
Ca, mg/dL	8.9-10.3	9.5			8.5	9	9.5		10	9.7	9.9	9.4
P, mg/dL	2.7-4.5	2.8			9.6	6.8	7.5		5.1	3.8	4.2	3.6
Na, mmol/L	136-144	138		134		136	133	130	131	136	140	136
Mg, mg/dL	1.8-2.5	2.62						2.08				
K, mmol/L	3.6-5.1	4.8				4.3	3.8	3.6	3.3	5.5	4.4	4.6
INR	0.85-1.2	1.1						1.02				
PT, m	11-15	12.5						12.1				
APTT,m	20-35	23.9						23.3				
WBC, 10^3/mL	4.8-10.8	11.6			6.67	3.61	4.12	4.72	4.83		5.79	5960
Hgb, g/dL	12-16	9.9	7.3	8	7	6.2	6.6	7.5	8.3		8.8	11.6
Hct, %	36-46	24.9			23.8	18.6	19.5	21.3	23.5		25.8	35
MCV, fL	80-94	89.9			82.6	81.2	80.9	77.5	77.3		83.5	81.2
Plt, 10^3/mL	130-400	64			277	347	297	291	247		200	81.2
B12, pq/mL	126-505	154										
Folat, ng/mL	3.1-19.9	14.9										
TSH, mIU/L	0.38-5.33	2.06										
CRP, mg/dL	0-0.8	19.2						1.3	0.518			
Procalcitonin, ng/mL	0-0.5	27.4						0.127				
Hemodialysis			+	+	+							
Erythrocyte packet			1 unit			1 unit	1 unit					

Brucella agglutination test, Toxoplasma Ig M and mycoplasma Ig M were negative. Clustered agglutinated red blood cells were determined in the peripheral blood smear. Serum LDH and direct/indirect bilirubin levels. Cryoglobulin was negative. INR, PTZ, APTT, and fibrinogen levels were normal. In the Coombs test, cold agglutinin (CA) antibodies were found to be positive. Slight lymphocyte increase was detected in bone marrow aspiration. Bone marrow biopsy was reported as normocellular marrow tissue. In the dark field microscopy, 2-3 moving spirochetes were seen in each field (Figure 1). Ceftriaxone 2x1 gr IV was started. Leptospirosis 16S rRNA-PCR detection confirmed the diagnosis. During hospitalization, 3 units of erythrocyte suspension heated at 370C were administered to the patient. Hemodialysis was intermittently performed 3 times to the patient with

ongoing oliguria and increased BUN, creatinine (Table 1).

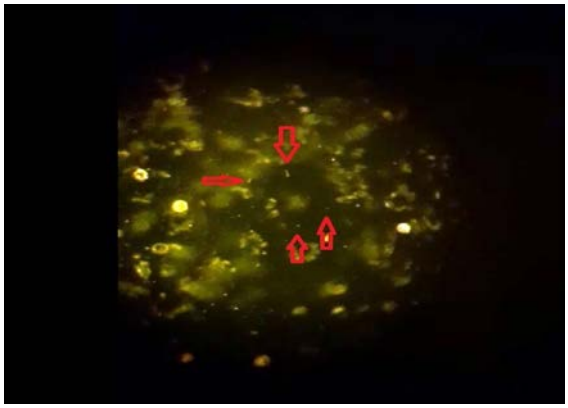

Figure 1. In the dark field microscopy, 2-3 spirochetes were seen in each field.

The patient's condition improved progressively after ceftriaxone therapy. LDH levels returned to normal, thrombocytopenia improved, and erythrocyte replacement was no longer necessary. Following ceftriaxone therapy for 14 days, CA antibodies were found to be negative. One month later she was well her Hb 11,2 g/dL and serum creatinine 1.04 mg/dL at the outpatient clinic visit.

DISCUSSION

We present a rare cause of acute renal failure and multiorgan involvement due to leptospirosis. Our patient was watering her plants in her garden with water provided from a well, and her feet were frequently contact with the water. The infection pathway of leptospirosis was probably the contact of disintegrated skin with water through scratches and clefts. The incubation period of leptospirosis is mostly 5–30 days. leptospirosis may have a clinical course ranging from mild influenza-like form to severe organ-sufficiency. Weil's syndrome is characterized by fever, jaundice, hepatorenal insufficiency, and coagulation disorders[3,4].

In our patient, multiorgan involvement due to leptospirosis such as AKI, acute hepatitis, hyperbilirubinemia, thrombocytopenia, anemia, and cold agglutinin disease (CAD) was detected. No abnormalities such as coagulation disorder and hemorrhage were observed. Most infections are mild, characterized by fever, chills, headache, myalgia with rhabdomyolysis, arthralgia, gastrointestinal symptoms, cough and rash that can mimic many other infections[1].

The first and most important cause of admission in our patient was high fever and gastrointestinal symptoms. Renal involvement is a well-known complication of leptospiral infection. The most common known mechanism of renal damage of leptospirosis is tubulointerstitial nephritis. In addition, hypotension, hypovolemia, hyperbilirubinemia-related tubular injury, and rhabdomyolysis may contribute to acute renal failure. Typically presentation of kidney failure is non-oliguric AKI with hypokalemia[1,3]. When oliguria develops nonetheless, it is a significant predictor of mortality.

Patients with leptospiral AKI usually recover their renal function to the normal range. In our patient with AKI due to leptospirosis, although no kidney biopsy was performed, the presence of leucocytes, leucocyte cylinders in the urinary sediment raise the possibility of tubulointerstitial disease. Hyperbilirubinemia was not at very high levels, but tubular toxicity and renal damage due to hyperbilirubinemia may have contributed in part to the AKI. The oliguric AKI of the patient may have masked hypokalemia, frequently observed in leptospirosis. Although mortality has been reported to be high in oliguric patients, our patient has been successfully treated with early diagnosis and appropriate antibiotherapy.

There is a lack of reference standard for diagnosis of leptospirosis. Available diagnostic approaches; darkfield microscopy, microscopic agglutination test, polymerase chain reaction and serological tests are unfavorable as the organism is a slow grower[5]. The diagnosis was advised by the combination of a clinical pattern of Weil's disease and the history of exposure to contaminated water and then confirmed by serology and PCR. After other possible causes are excluded, patient history, clinical and laboratory findings support leptospirosis. We found moving spirochetes with dark field microscope, which is an easily accessible and inexpensive method (Picture 1). Our diagnosis was confirmed after leptospirosis 16S rRNA - PCR was found to be positive in the blood sample.

CAD is typically characterized by the presence of clinical symptoms related to exposure to cold, hemolytic anemia, and antibodies against polysaccharide antigens on the erythrocyte surface

that are responsible for the agglutination of red cells at low temperatures[6]. CA bind to erythrocyte surface antigens at a temperature of 0–4°C. Attachment of CA to the erythrocyte surface antigen causes agglutination, complement activation, and hemolysis. Primary clinical manifestations of CAD are hemolytic anemia and circulatory system symptoms related to CA[7]. The autoantibodies may be idiopathic and secondary to malignancy, infection and autoimmune disease. Postinfectious CA may be due to various viral and bacterial pathogens including mycoplasma, EBV and legionella[8,9]. Case presentations of CA hemolysis due to Citrobacter, varicella, and influenza have been reported[10].

Paroxysmal nocturnal hemoglobinuria or cryoglobulinemia was not detected in the differential diagnosis of the patient. Moreover, bone marrow biopsy and aspiration were performed to exclude malignancies originating from B lymphocytes. It was also shown that there were no such factors as mycoplasma, EBV or CMV, which are the most common infection factors. The present clinical and laboratory findings suggested that CA antibodies were associated with leptospirosis. Hemolysis and other clinical findings were also resolved with the improvement of leptospirosis with appropriate antibiotic treatment. After the antibiotic treatment, CA antibodies were also found to be negative. In our case, hemolysis due to CA was accompanied leptospirosis with hemolytic anemia, AKI, acute hepatitis, hyperbilirubinemia, and thrombocytopenia. In the English literature, CA associated with Leptospirosis has previously never been reported. As far as we know, this condition was detected in our patient for the first time. Leptospirosis was diagnosed with appropriate tests in consideration of possible contact with infectious water in the gardening patient. As a result of the appropriate antibiotic and supportive therapy, the patient was completely recovered. In deep anemia accompanied by hepatic and renal involvement, CA that rarely cause leptospirosis should be investigated.

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