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Case Report

Severe Leptospirosis Observed in a Man Who Had Just Returned from Abroad

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ABSTRACT

Leptospirosis, a re-emerging zoonosis caused by pathogenic *Leptospira*, has a low incidence in Bulgaria. This paper reports a case of leptospirosis in Pleven, Bulgaria, in which the subject was infected after wading through irrigative canal in northern Greece. Two days later, he had a fever, myalgia and vomiting followed by jaundice, darkness of urine and oliguria. The patient was admitted to Clinic of Infectious Diseases at University Hospital-Pleven after returning to Bulgaria. The history and laboratory findings suggested icterohaemorrhagic leptospirosis. Penicillin G was prescribed and intensive supportive treatment was initiated. Dialysis was performed two hours after admission and was followed by poliuric stage of acute renal failure (peak urine output 16 600 mL/day). Microaglutination test (MAT) for sero-diagnosis was positive (*L. hardjo* 1:1600, *L. icterohaemorrhagiae* 1:800). The patient was discharged after sixteen days with improved renal and liver functions. In conclusion, The probability of leptospirosis should not be ignored in patients with fever after returning from abroad. The prompt dialysis and adequate treatment improve prognosis.

Key Words: Leptospirosis, acute renal failure, dialysis

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Introduction

Leptospirosis is a spirochetal bacterial infection of great public health importance in several tropical and subtropical countries and in temperate climate zone occurs as sporadic cases. The source of infection in humans is usually either direct or indirect contact with urine of infected animals. Leptospira infect humans by entering through abraded skin, mucous membranes, conjunctivae (1, 2). It is a sporadic disease in Bulgaria, more often due to bad living conditions and water-related accidents during professional or re-creative activities (1). After an incubation period of one to two weeks usually, Leptospirosis manifests as a biphasic illness with the leptospiraemic phase followed by an immune phase (2). This disease is characterized by the development of vasculitis, endothelial damage, and inflammatory infiltration. Leptospirosis mostly affects tissues of the liver and kidney (1-4). Rarely, other organs such as brain, pancreas, lung, heart, gallbladder, and ophthalmic tissues are involved, mainly due to severe vasculitis (1, 2, 5, 6). Clinically, it shows a broad spectrum of manifestations which varies from subclinical infection and self-limited anicteric febrile illness (80-90% of all cases) to icteric leptospiropirosis known as Weil's disease, a severe and potentially fatal disease characterized by hemorrhage, acute renal failure (ARF) and jaundice (2).

From this point of view, this paper reports a case of leptospirosis presenting as Weil's disease in an adult patient treated at a Clinic of Infectious Diseases at University hospital in Pleven, Bulgaria. Medical records of this patient were retrospectively reviewed in preparation of the case.

Case Report

A 39-year-old male patient from north-west of Bulgaria was admitted in the emergency department of University Hospital in Pleven on June 6th, 2010. The man pastured cattle in a little village in northern Greece three months before the accident. He waded through water in irrigative canal two days before the clinical onset and wet his legs. He had a fever of 39.8°C increased on the third day after that accidental event (the duration of fever was five days), shivering, generalized muscular pains (violent in the calf muscles), vomiting. A darkness of urine, jaundice on the sclera and the skin appeared in the following days. Consecutively, urine output extremely decreased and the man's condition worsened. He was treated with clarithromycin and paracetamol without effect. He returned to Bulgaria and was admitted to Clinic of Infectious Diseases at University Hospital-Pleven on the ninth day after the clinical onset. The man complained of severe pain in the legs, weakness and lack of urine output. Prior to those complaints, he reported as known disease only duodenal ulcer, operated due to bleeding ten years ago. The patient denied contact with icteric people, blood transfusion and drug abuse, except for small amount of alcohol of daily consumption. He had contact with contaminated water eleven days before coming to the hospital. On physical examination, he was in poor condition, oriented, with hiccup. He had an intensive

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jaundice, petechial rash on the chest, conjunctival suffusion. His temperature was normal. Pulse rate was 84 beats/minute without rhythm abnormalities. Blood pressure was 95/65 mm Hg, with no dyspnea and with normal cardio-pulmonary and abdominal auscultation. His abdomen was flat, flaccid, and there was hepato- and splenomegaly with tenderness on the liver palpation. The neurological examination did not reveal abnormalities. The laboratory investigations are shown on Table 1. On admission (on the ninth day of initial symptoms), first serum sample for MAT testing for leptospirosis was obtained and sent to Reference Laboratory of National Center of Infectious and Parasitic Diseases-Sofia, Bulgaria. Immediately, the patient was put on intravenous rehydration and started penicillin G (16 g/day), methylprednisolon (initial dose 160 mg/day) with famotidine gastro-protection (40 mg/day) and medication for the symptoms' relief. The patient' condition was discussed with nephrologists (after unsuccessful furosemide test to provoke urine output) and dialysis was performed after an informed consent. A dialysis séance began four hours after admission and finished without complications. The patient had 600 mL urine output at the end of dialysis and 1000 mL in next four hours with urine density 1008. Except of above mentioned therapeutic measures, he received native plasma and thrombocyte concentrate without complications.

On the second day in the hospital, the patient was afebrile, adequate, with reduced hiccup and painless calf muscles, haemodynamically stable. Intensive jaundice was persistent and enlarged tender liver was palpated. Splenomegaly was also established at the examination. No haemorrhagic symptoms appeared except petechial rash on the chest. The urine output increased to maximal volume of 16 600 mL/day with density 1006. Laboratory investigation revealed worsening of bilirubin binding function of the liver (on Table 1). Because of that, ademetionine started (1000 mg/day) and human albumin 20% 100 mL was infused twice. A metabolic acidosis presented and correction with sodium-hydrogen-carbonate 8.4% 140 mL intravenously was performed.

On the fourth day, the patient continued to be intensively icteric and the jaundice became more evident-total serum bilirubin level increased to 1023 μmol/L (direct bilirubin 858 μmol/L), but renal functions improved-daily urine output decreased to 10700 mL with urine density 1012, a creatinine level decreased. Platelets' count gradually increased-90x10^9/L, followed by 103 and 121x10^9/L on the fifth and seventh day respectively.

Table 1. Laboratory findings of reported patient during hospitalization

Day Test	1st	2nd	4th	6th	16th	Reference values
Haemoglobin (g/L)	99	79	88	92	104	120-188
Haematocrit	0.27	0.22	0.22	0.25	0.32	0.35-0.55
Leucocytes (cells to 109/L)	23	12.9	14.5	27.2	9.9	4.0-11.0
Neutrophils (%)	89	85	78	81	67	50-80
Platelets (cells to 109/L)	67	66	90	447	514	150-400
Urea (mmol/L)	34	35	28	16	7.5	1.7-8.3
Creatinine (μmol/L)	558	375	219	141	119	44.2-134
K+ (mmol/L)	5.05	4.0	3.6	3.6	4.6	3.5-5.6
Na+ (mmol/L)	112	120	132	136	141	130-151
Total bilirubin (μmol/L)	561	804	1023	493	62	3.4-21
Direct bilirubin (μmol/L)	392	753	858	400	59	0.8-8.5
Aspartate aminotransferase (IU/L)	479	183	129	27	31	≤37
Alanine aminotransferase (IU/L)	185	141	213	120	77	≤40
γ-glutamyltransferase (IU/L)	71	55	81	70	51	15-28
Alkaline phosphatase (IU/L)	131	76	112	133	111	50-260
Serum amylase (IU/L)	492	-	-	350	247	30-300
Lactate dehydrogenase (IU/L)	1960	1130	1640	693	387	100-360
Creatine kinase (IU/L)	10438	1198	185	-	-	80-190
Total protein (g/L)	55.6	45	53	52.3	63.3	58-80
Albumins (g/L)	30.2	26.7	33	30.8	33.1	35-55
Fibrinogen (g/L)	6.6	3.7	3.1	3.3	3.8	2.0-4.5
Prothrombin index (%)	106	120	114	111	110	80-110

On the sixth day, the patient was without fever and the jaundice was less evident. Total bilirubin decreased, as shown on Table 1. The patient's blood pressure was stable and no vasopressors needed. An electrocardiogram did not show any dysfunction. The patient has never manifested dyspnea during his clinical evolution. The abdominal ultrasonography showed enlarged liver with steatosis and enlarged spleen. Pathological signs in the kidneys, pancreas and gallbladder were not to be observed. The therapy with penicillin continued.

On the following days, the patient had no complaints except weakness. A mild improvement on laboratory findings was also noted. From hospital day 8th, the patient did not show signs of fever, headache or pains, although he remained icteric. His creatinine level gradually returned to normal levels.

By the twentieth day of initial symptoms (on eleventh day after admission to hospital), second serum sample for MAT testing for leptospirosis was obtained and sent to Reference Laboratory of National Center of Infectious and Parasitic Diseases-Sofia, Bulgaria. The received results were positive: in first sample-*L. hardjo* and *L. icterohaemorrhagiae*-titers respectively 1:1600 and 1:800. The second sample confirmed the increased titer of specific antibodies (reference value ≤1:100).

On hospital day 16, there was a significant recovery and the patient was able to stand up and walk normally. At discharging (on July 1th 2010), he was asymptomatic but remained with slightly elevated levels of bilirubin-total bilirubin 62 μmol/L and direct bilirubin 58 μmol/L. The nitrogen parameters were normal (urea level was 7.5 mmol/L and creatinine level-119 μmol/L). Appropriate instructions for follow-up care after 10 days were given.

Two control examinations were performed after discharge: on July 1th 2010 the patient have weakness; on July 21th the patient have not any complaints. The blood count, serum bilirubin levels and nitrogen parameters were normal.

Discussion

Leptospirosis is the most widespread zoonosis. The annual incidence varies from 0.1 to 1.0 of 100.000 population in countries with temperate climate and more than 10 of 100.000 in the tropical regions. This parameter varies from 0.12 to 0.67 of 100.000 (1976-2005) in Bulgaria (1). Leptospirosis has protean manifestations and early clinical diagnosis is not easy due to high variability in severity and different combinations of clinical syndromes (1, 2). A delay in diagnosis and treatment could be worsening the prognosis (7). The relevant epidemiological scenario should be kept in mind and facilitates the diagnosis.

It is known that *L. icterohaemorrhagiae* causes icterohemorrhagic leptospirosis presenting with intensive jaundice and ARF-so called Weil's disease, but other serovars also have potential to cause severe leptospirosis (1, 2, 7). *L. icterohaemorrhagiae* and *L. hardjo* were confirmed at the reported patient in significant titers by MAT (MAT is a "golden standard" with high sensitivity and specificity mainly after the 7th day of clinical onset). Lomar et al. (8) had considered icterohaemorrhagic leptospirosis as severe form of the disease with clinical manifestations, resembling bacterial sepsis, and with high mortality rate. There are reports of severe cases with alveolar bleeding (without or with minimal hepato-renal disorders) and acute respiratory distress syndrome in the recent years (2, 9, 10). Turhan et al. (11) had considered that the jaundice is not always the rule for the diagnosis of leptospirosis and anicteric leptospirosis cases can also be complicated with renal involvement and progress to acute or chronic renal failure. We also had considered in previous study that a presence of jaundice is not obligate criterion for assessment of severity and prognosis of leptospirosis (9). However, the case presented here was with stable vital functions independent of extremely intensive jaundice.

An affecting of the kidneys has greatest impact upon severity of leptospirosis. The range of kidneys damage is wide and correlates with severity. The mildest cases usually are without renal dysfunction. In severe cases, ARF presents with marked oliguria to anuria after fourth or fifth day and progressively increasing of blood nitrogen products with maximal levels in sevent to nineth day after the clinical onset. Jaundice is common (1-4). ARF had found in 48% in previous research (1), but Covic et al. (3) and Sitpridja et al. (4) found ARF in more than 70% of cases of leptospirosis. The rate of increasing of blood nitrogen parameters correlates with severity (1-4, 7). The creatinin was high at the patient reported here but early dialysis and an adequate fluid intake successfully improved the renal function.

Myocardial dysfunction is common in severe leptospirosis and myocarditis is independent prognostic factor for unfavourable outcome (6, 7). The reported patient was hemodynamically stable and evolution was favorable independent of intensive jaundice and ARF.

The haemorrhagic syndrome is an important criterion for assessment of severity. In moderate and severe cases of leptospirosis haemorrhagic rash and visceral bleeding appear in fifth to ninth day from the clinical onset-at different studies in 50% to 80% of severe cases (2, 3). According to the data of Gancheva (1) a haemorrhagic syndrome had observed in 57% of severe cases. The products of metabolism and destruction of leptospires had considered as causing damage of vessels wall resulting in increased capillary permeability. It is followed by generalized vasculitis-striking patho-morphological feature in leptospirosis. In addition thrombocytopenia also impairs haemostasis. There is mild correlation between the liver dysfunction and severity of haemorrhagic syndrome in leptospirosis. It has considered that vasculitis and thrombocytopenia are the leading factors (1, 2, 7). We found only petechial rash with favourable resolution at the reported patient.

Neurological involvement in leptospirosis is not rare. The neurological manifestations result from the effect of the organism on the central nervous system (CNS) and the host immune response to the agent. Following infection, leptospires reach the CNS rapidly. The changes in cerebrospinal fluid are later manifestation, and it has therefore been suggested that some of the inflammatory neurological manifestations of leptospirosis result not from the agent itself but from the antibody response to it. The prognosis after primary neuroleptospirosis is generally good but altered sensory and seizures herald a worse prognosis. Encephalitis is uncommon (2). Aseptical meningitis occurs in moderate and severe leptospirosis

but encephalitis is criterion for severe course (1, 2, 7). There was not involvement of CNS at the reported patient.

Acute pancreatitis is a rare clinical manifestation in leptospirosis. Rather asymptomatic pancreatitis with increased serum amylase level founds (1, 2, 5, 7). Acute pancreatitis more often is found on autopsy but Daher et al. (5) consider that in all severe cases is necessary to search signs of pancreatic involvement. There were not found signs of pancreatic dysfunction in case reported here.

The early clinical diagnosis of leptospirosis is important but difficult. Since leptospirosis cases exhibit a wide clinical spectrum it may be confused with a many diseases. Therefore the application of specific laboratory tests, capable of being performed everywhere and easily, is of great importance, particularly in anicteric leptospirosis cases. It must not be forgotten that leptospirosis is a potentially widespread infection. Therefore all cases presenting with fever and multiorgan involvement together with the kidney must be examined with regard to leptospirosis, even if not icteric, particularly if accompanied by a high serum CPK level and/or thrombocytopenia and lymphocytopenia (12).

Treatment of severe leptospirosis is antimicrobial and supportive. Penicillin is antibiotic of choice but ceftriaxon is alternative. Glucocorticoids are needed because of intoxication and vasculitis, and for protection of Jarish-Herxheimer' reaction. Supportive therapy includes stabilization of vessels wall, hepatoprotective and gastroprotective drugs, vitamins, fluids, substitution of blood cells losses (1, 2). The management of ARF is of greatest importance-the missed effect of diuretics in anuric phase must be followed by early dialysis (no later than 48 hours after hospital admission) (1-4). The patient reported here had once dialysis séance immediately after admission with good effect.

The incidence of leptospirosis is low in Bulgaria, and annually reported cases are few. Leptospirosis in reported case was caused by wading through contaminated water. The probability of leptospirosis should not be ignored when physicians see to patients with fever of unknown origin after returning from abroad. This case is interesting with its favorable outcome, independent of severe jaundice but at absence of CNS, myocardial and pancreatic involvement. The prompt dialysis and adequate treatment improved prognosis.

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