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Case Report

ACUTE LIVER AND KIDNEY FAILURE AS THE PRESENTATION OF LEPTOSPIROSIS: CASE REPORT OF A RARE DIFFERENTIAL DIAGNOSIS IN CASE OF JAUNDICE

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Leptospirosis is a widespread and potentially fatal zoonosis that is endemic in many tropical regions. It is the most common zoonotic infection in the world, but a rare disease in Latvia. The clinical manifestations and the severity of leptospirosis are highly variable. This case report describes a 64-year-old male without comorbidities, who was admitted to Rīga East University Hospital in the Gastroenterology Department due to expressed jaundice, weakness, and acute kidney injury. The initial inpatient clinical diagnosis was initially acute alcoholic hepatitis, as the patient had consumed alcohol a month before hospitalisation. The clinical and laboratory picture of the patient was dominated by significant hyperbilirubinemia, a relatively small increase in liver transaminases, preserved synthetic liver function, acute kidney failure in the polyuria phase, and severe thrombocytopenia. During hospitalisation, the study of anamnesis and the results of laboratory tests gave grounds for suspecting the diagnosis of leptospirosis, which was subsequently serologically confirmed. Routine laboratory tests are not specific for diagnosing leptospirosis. Diagnosis is made on the basis of the doctor's request and clinical examination, as well as on the basis of blood and urine culture and serological tests. Early initiation of antibiotic therapy plays an important role in controlling infection and reducing mortality.

Keywords: *zoonotic infection, thrombocytopenia, elevated bilirubin levels, acute kidney injury, Latvia.*

INTRODUCTION

Leptospirosis, a zoonotic disease caused by pathogenic spirochetes of the genus *Leptospira*, is one of the most widespread acute febrile illnesses throughout the world, with fatality rate ranging as high as 20–25% in some regions. Leptospirosis is mostly transmitted to humans through ambient water contaminated with the urine of wild and domestic mammals that have been chronically colonised by *Leptospira* (Dianwu Li *et al*., 2022). The morbidity and mortality rates of leptospirosis in humans are estimated at 1 million and 60,000 cases, respectively. Of the reported cases, 2.90 million disability-adjusted life years are estimated to be lost per annum (Harran *et al*., 2022). To date, 38 species of pathogenic *Leptospira* have been described, and new species are continually being discovered (Vincent *et al*., 2019).

The incubation period can vary from 2–20 days, with a mean range between 7–12 days. The disease often has a biphasic clinical presentation with an acute or leptospiremic phase occurring in the first week, followed by an "immune phase". The main nonspecific symptoms appear during the first phase. The second phase of the disease is characterised by IgM production, blood release, and excretion of leptospires in the urine, as spirochaetes settle in the proximal tubules of the kidney (Alexopoulou *et al*., 2024).

Leptospirosis can present in two distinct clinical syndromes, icteric and anicteric. The anicteric syndrome is self-limited and presents with a nonspecific flu-like illness. The onset is usually sudden and can present with a headache, cough, non-pruritic rash, fever, rigours, muscle pain, anorexia, and diarrhea. This form of the illness is rarely fatal and represents approximately 90% of all documented cases of leptospirosis. The anicteric syndrome can also have recurrence several days later, and this phase is called the immune stage during which aseptic meningitis can occur. The icteric phase of leptospirosis is classically known as Weil's disease. This is a severe infection, and the manifestations include fever, renal failure, jaundice, haemorrhage, and respiratory distress. The icteric phase may also involve the heart, CNS, and muscles. This illness is usually severe and may last weeks or months if the patient survives (Wang *et al*., 2022).

In this study, we report on a 64-year-old male patient with the development of jaundice, acute kidney injury, and other serious organ dysfunction. After conducting the necessary examinations, the patient was diagnosed with leptospirosis. A course of antibiotics should be initiated after the first suspicion of the occurrence of this diagnosis. We have demonstrated this severe case and its management.

CASE HISTORY

In the end of December 2023, a 64-year-old male, previously healthy and not treated for any medical issue, was transported by the emergency medical service to the Gastroenterology Department for jaundice. He complained of weakness and was found to have nausea, vomiting, jaundice, febrile fever, and headaches. For the last three days, he experienced a gradual yellowing of the skin and sclera. As part of the medical history, he reported alcohol consumption, and a possible household contact with rat was mentioned in epidemiological anamnesis. No meningeal signs or focal neurological symptoms were observed, and SARS-CoV-2 was ruled out.

Initial investigations showed elevated leucocytosis with neutrophilia (WBCs 26.89 × 10^9u/L, Neu =75.3%), total bilirubin 372 μmol/l, direct bilirubin 351 μmol/l, AST 91 U/l and ALT 113 U/l, and preserved synthetic liver function (prothrombin 100.3%, INR 1.00), as well as kidney failure in the polyuria phase (creatinine 614 mkmol/l, GFR 8.53 ml/min), electrolyte imbalance, thrombocytopenia, subfebrile temperature, intoxication, and high CRP (99 mg/l). The patient denied having any chronic illnesses.

During the subsequent examination, the patient was febrile, mildly hypotensive (100/70 mmHg), and had heart rate of 85/minute and oxygen saturation of 98%. The clinical picture was dominated by icterus of the skin and sclera, signs of dehydration (dry, coated tongue), and palpable enlarged liver (+2 cm). Ultrasound examination showed a dilated common bile duct, small amount of fluid around the liver, and left kidney cyst. The differential diagnosis revealed the following: liver cirrhosis with hepatorenal syndrome, acute viral hepatitis, toxic hepatitis, neoplasms, pancreatic cancer, cholangiocarcinoma, cholangitis, leptospirosis, sepsis, malaria, and autoimmune diseases — autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis.

The diagnostic work-up showed that the viral serological screen was negative for HAV, HBV, HCV, and HIV. Other hepatotropic viruses (anti CMV IgM antibodies, anti EBV IgM antibodies, anti HSV IgM antibodies, anti-HIV antibodies) tested negative. Upper endoscopy showed a duodenal bulb ulcer with scarring deformation, and hyperaemic gastropathy. Computed tomography (CT without contrast agent) demonstrated a mildly dilated common bile duct, without dilatation of intrahepatic bile ducts, and mildly reduced density of the liver. The patient was parenterally rehydrated, given symptomatic treatment (antipyretics, analgesics, vitamins, replenishment of minerals), and monitored for fluid balance. Positive dynamics was observed during therapeutic treatment.

Based on the epidemiological context, compatible symptoms and biological results, an icteric leptospirosis was suspected. The diagnosis of leptospirosis was confirmed by detecting *Leptospira* spp.16s RNA in blood and urine with the polymerase chain reaction. The previously prescribed antibiotic treatment was narrowed to intravenous ceftriaxone and symptomatic therapy.

Magnetic resonance (MRI) revealed bile duct dilatation along the Sg2/Sg3 and Sg5/Sg8 peripheral bile ducts, a visual MRI finding that could be consistent with primary sclerosing cholangitis (Fig. 1).

The autoimmune profile, tested by indirect immunofluorescence, showed a negative result for anti-nuclear (ANA), anti-mitochondrial (AMA), and anti-smooth muscle antibodies. A slight positive reaction for anticardiolipin antibodies (ACA 16.00 U/ml) was detected. All the other autoimmune tests were negative.

A liver biopsy was performed in order to complete the diagnostic work-up. The procedure confirmed the diagnosis of cholestatic hepatitis (Fig. 2). Aetiology that corresponds to this morphology depends on the clinical findings — it is possible in primary biliary cirrhosis, drug-induced liver damage, viral hepatitis, and toxic hepatitis. Therefore, cholestatic changes in a liver biopsy are associated with leptospirosis, but the diagnosis of primary sclerosing cholangitis was not excluded.

During the course of treatment, there was a reduction in inflammatory activity, the serum bilirubin level gradually decreased — total bilirubin 165 mkmol/l and direct bilirubin 153 mkmol/l (Table 1). On the last day of hospitalisation, the patient's medical state clinically improved — all symptoms were gone, except for slightly icteric symptoms that remained (Fig. 3). The patient was discharged after completion of intravenous cefriaxone, with the recommendation for outpatient follow-up.

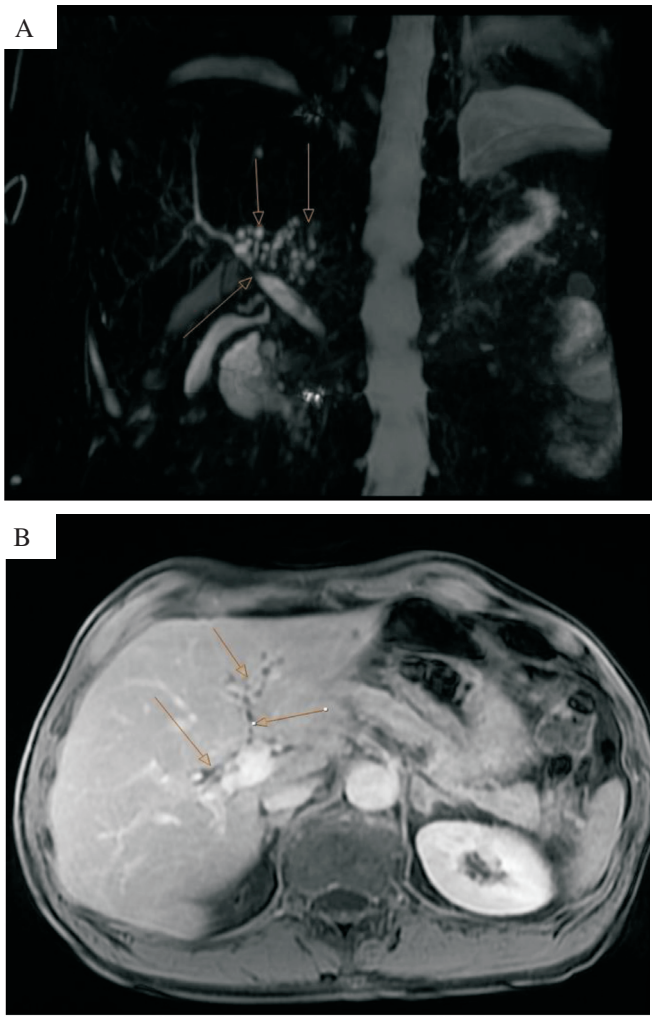

Fig. 1. Abdominal magnetic resonance imaging. Segmentally dilated ductus hepaticus communis (A); dilated intrahepatic bile ducts (B).

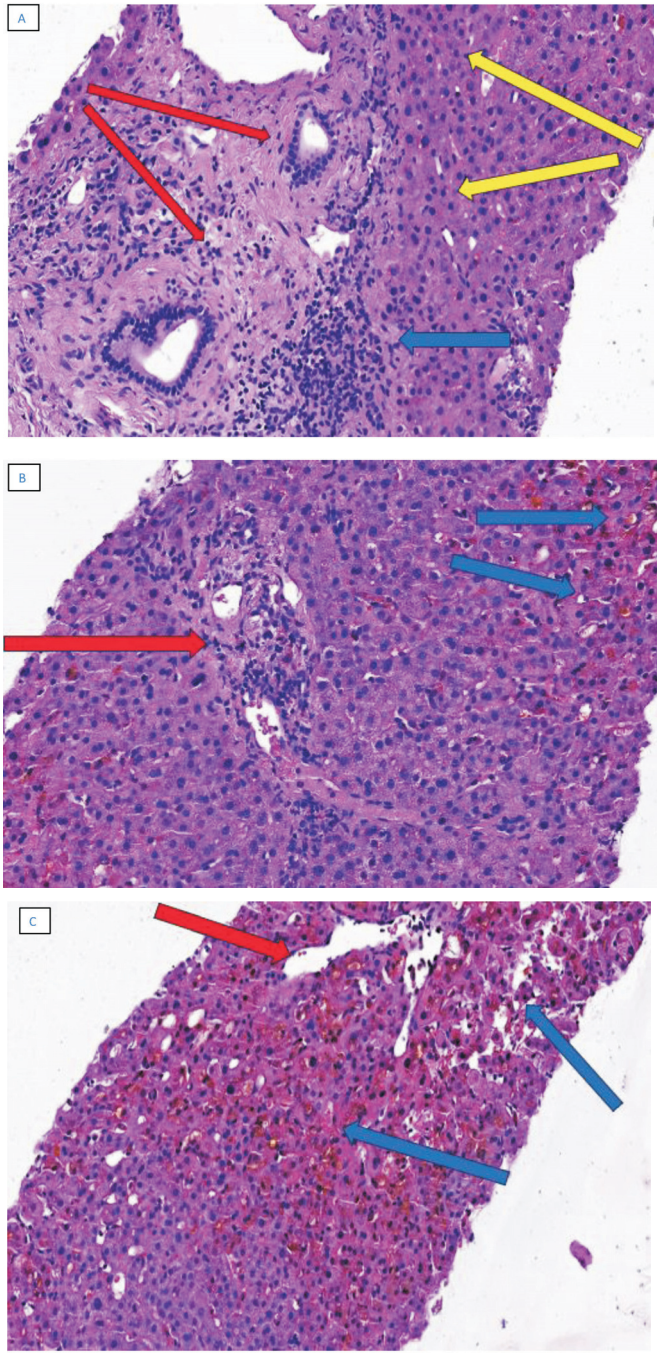

Fig. 2. A, Portal tracts with infiltration of inflammatory cells (blue arrows). Concentric like increased periductal fibrosis of interlobular ducts (red arrows). Reminiscent of primary biliary cholangitis. There is no intercellular oedema. Hepatocytes are not necrotic. There is no intercellular oedema of hepatocytes (yellow arrows) H&E 200×; B, portal field is not expanded, cholestatic changes, red arrow; cholestatic changes (blue arrows) H&E100×; C, central vein (red arrow) with pronounced pericentrolobular cholestasis and necrosis of hepatocytes. Blue arrows show intercellular oedema H&E100×.

DISCUSSION

Leptospirosis is caused by the spirochete genus *Leptospira* and is endemic in many tropical and subtropical regions worldwide. Leptospirosis is often a diagnostic challenge in areas where it is uncommon. Latvia as well is among the low-prevalence regions. Leptospirosis in Latvia belongs to the number of infectious diseases registered in the country, and the number of cases reported during the last 15 years has not exceeded 10 (0–8) cases per year with a prevalence of 0.09–0.4/100,000 inhabitants (Centre for Disease Prevention and Control of Latvia, for years 2016–2020). However, these data should be evaluated critically, without taking into account the variability of clinical course of the disease. It is possible that there are unrecognised cases that have not been reported to the Centre for Disease Control and Prevention.

Leptospirosis is described as a biphasic illness that begins after an average incubation period of 5–14 days (Lau *et al.*, 2018). The illness generally presents with an abrupt onset of fever, rigours, myalgia, and headaches in 75% to 100% of patients, following an incubation period of 2 to 26 days (average 10 days). Severe, potentially fatal illness characterised by jaundice and renal failure (Weil's disease) occurs in a minority of patients. Pulmonary haemorrhage is a potential complication (Von Ranke *et al.*, 2013).

Diagnosis of leptospirosis is based on assays for bacteriological and serological detection, with serological assays

Table 1. Paraclinical evolution of laboratory examinations: favourable dynamics with resolution of the acute renal injury, thrombocytopenia, and hyperbilirubinemia

	16.12.2023	18.12.2023	22.12.2023	29.12.2023	02.01.2024	5.01.2024
WBC (10^3/μl)	20.61	26.89	15.55	6.96	7.95	9.46
PLT (10^3/μl)	53	75	104	382	318	429
Cre (μmol/l)	614	308	102	72	65	76
GFR (ml/min)	8.53	18.91	67.71	101	113.87	95.07
T-bil (μmol/l)	372	422	402	259	200	165
D-bil (μmol/l)	351	402	370	242	183	153
ALAT (U/l)	133.00	91.10	35.00	55.97	50.07	46.20

WBC, white blood cell; PLT, platelet; Cre, creatinine; GFR, glomerular filtration rate; T-bil, total birilubin; D-bil, direct bilirubin; ALT, alanine aminotransferase

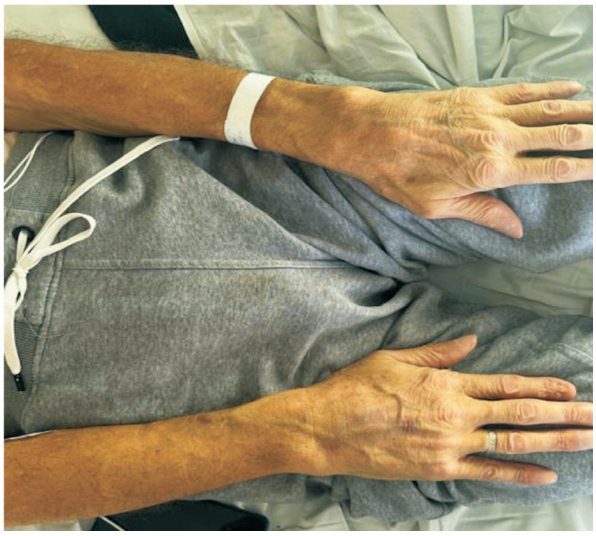

Fig. 3. Photo of the patient arms on the day of discharge. Jaundice slightly remains on arms.

more widely used. Bacteriological detection is possible by direct examination, culture, and PCR, but isolating the organism is challenging. Serological assays determine antibody titres against *Leptospira*, but their relevance depends on the time of infection. IgM antibodies appear from day 5 to day 7 after infection. The sensitivity and specificity of the enzyme-linked immunosorbent assay are 89% and 94%, respectively, while those of the microscopic agglutination test are 63% and 97% (Conreur *et al*., 2023).

The differential diagnosis of leptospirosis is confoundingly broad. The flu-like illness that characterises mild cases may resemble a benign viral syndrome, while more severe cases may resemble meningitis or sepsis (Gompf *et al*., 2021). The differential diagnosis for *Leptospirosis* is extremely large and varies from benign processes like viral upper respiratory tract infections, other viral flu-like illnesses, to severe infections from rarer "travel" conditions including Dengue fever, malaria, hantavirus, haemorrhagic fevers, and typhoid fever. Other more common conditions (which one would be likely to consider unless specific exposure history is known) are cholecystitis, mononucleosis, primary HIV, or if unvaccinated measles or rubella (Wang *et al*., 2022). A possible key to correct diagnosis is a thorough history focusing on the patient's travel history, activities, and exposure to animals. Case clusters, if present, may suggest a common exposure (Gompf *et al*., 2021).

The clinical manifestations and the severity of leptospirosis are highly variable and the lack of pathognomonic presentation for leptospirosis makes a final diagnostic dependent on laboratory tests.

Treatment options in the anicteric form include Doxycycline 100 mg/day per os, Ampicillin 500–750 mg every 6 hours per os, Amoxicillin 500 mg every 6 hours per os and, for the icteric form, Penicillin G 1.5 mil U every 6 hours iv, Ceftriaxone 1g every 12 hours i/v, and Ampicillin 500 mg – 1 g every 6 hours iv. These treatment plans should be administered for 7–10 days according to the guidelines (Bennett *et al*., 2014, pp. 2714–2720).

In our clinical case, diagnostic complications relate not only to toxic alcohol hepatitis as a plausible preliminary diagnosis, but also to an obscure cholestatic hepatitis picture with some similarity to primary sclerosing cholangitis following radiological and liver biopsy results. A clinical picture of cholestatic hepatitis is possible in the case of leptospirosis, including bile thinning and balloon dilation that may be associated with this disease. However, there remains a differential diagnosis with previously undiagnosed, clinically latent primary sclerosing cholangitis as a side illness. A precise diagnosis is not possible in this case, since there are no conclusive pathogenic criteria. The diagnosis could be verified at a time interval, with observation of the patient in dynamics and conduction of repeated analyses, as well as MRI of the liver and biliary tract.

CONCLUSION

Leptospirosis is a common disease in tropical countries but is considered a rare disease in Europe. It is characterised by a variable clinical picture that can be is easily confused with other diagnoses. In a case if physicians are not aware of its existence or if the anamnesis is incomplete and does not include professional or occupational habits, patients will be prescribed the wrong treatment. In a case of physicians' unawareness of this disease's existence or if the picture of anamnesis is incomplete, there is a risk to prescribe the wrong treatment. This case demonstrates that proper exami-

nation of the patient, knowledge about rare infectious diseases and collection of anamnesis leads to correct diagnosis. Leptospirosis should be considered in the early diagnosis of any patient with the following symptoms: acute, nonspecific febrile illness with multisystem involvement or high fever. Weil syndrome is one of the most severe forms of leptospirosis, which can result in complications such as multiple organ failure. Early diagnosis and emergency initiation of empirical antibiotic therapy are vital. Our case underscores the importance of a thorough social history as well as timely recognition of uncommon infections as possible reversible causes of multi-organ failure.

ETHICS

Written informed consent was obtained from the patient for publication of this case report. Ethical approval is not required to publish an anonymous case report.

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AKŪTA AKNU UN NIERU MAZSPĒJA KĀ LEPTOSPIROZES IZPAUSME — RETA DIFERENCIĀLDIAGNOZE DZELTES GADĪJUMĀ: KLĪNISKAIS GADĪJUMS

Leptospiroze ir plaši izplatīta un potenciāli letāla zoonoze, kas ir endēmiska daudzos tropu reģionos, savukārt Latvijā tā ir reti sastopama slimība. Jāņem vērā, ka leptospirozes klīniskā aina var būt izteikti variabla. Šajā klīniskajā gadījumā tiek aprakstīts 64 gadus vecs vīrietis bez blakusslimībām, kurš akūtā kārtā tika stacionēts Rīgas Austrumu klīniskās universitātes slimnīcas Gastroenteroloģijas nodaļā ar izteiktu dzelti, vājumu un akūtu nieru mazspēju. Kā sākotnējā klīniskā diagnoze tika noteikts akūts alkohola hepatīts, ņemot vērā pacienta alkohola lietošanas anamnēzi mēnesi pirms hospitalizācijas. Pacienta klīniskajā un laboratoriskajā ainā dominēja nozīmīga hiperbilirubinēmija, salīdzinoši neliels aknu transamināžu pieaugums, akūta nieru mazspēja (poliūrijas fāzē) un smaga trombocitopēnija. Hospitalizācijas laikā iegūtie anamnēzes dati un laboratorisko rādītāju rezultāti norādīja uz iespējamu leptospirozes diagnozi, kas arī tika seroloģiski apstiprināta. Tā kā leptospirozes apstiprināšanu nosaka pēc asins un urīna kultūras seroloģiskajiem izmeklējumiem, tad rutīnas laboratorijas testi nav specifiski diagnozes noteikšanai. Diagnoze tiek apstiprināta, pamatojoties uz ārsta veikto specifisko klīnisko izmeklēšanu, kā arī uz asins un urīna kultūrām un seroloģiskajiem rādītājiem. Agrīni diagnosticētai leptospirozei un savlaicīgai antibakteriālas terapijas uzsākšanai ir būtiska loma infekciju kontrolē un mirstības līmeņa samazināšanā.