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Case Report

A 54-year-old Philippine sailor with fever and jaundice

Christophe Van Dijck[1], Marjan Van Esbroeck[2], Robert Rutsaert[1]

[1]Intensive Care, Hospital GZA Sint-Vincentius, Antwerp, Belgium, [2]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

A 54-year-old man presented with fever, vomiting, jaundice and conjunctival injection. These clinical signs, together with the presence of mild inflammation, hepatitis and severe acute kidney injury, lead to the suspicion of leptospirosis. Infection was serologically confirmed and treatment with ceftriaxone and intermittent haemodialysis was followed by rapid clinical and biochemical recovery. Worldwide, leptospirosis is an emerging pathogen as a result of overpopulation and flooding, but due to increasing tourism also in other regions. In Belgium, clinicians must be aware of endemic as well as imported cases of leptospirosis and differentiate them from hantavirus infections. Leptospirosis is a zoonosis that is transmitted through the urine of chronically colonized animals, mainly rats. Infection can be asymptomatic, present as a mild inflammatory syndrome or cause a severe icterohaemorrhagic disease with multiple organ failure and a high mortality rate. Initial serological diagnosis requires confirmation with a microscopic agglutination assay in a reference laboratory. Treatment is mainly supportive. Antibiotics are often used although mild acute infection often is self-limiting and there is uncertainty about the influence of antibiotic therapy on the duration of fever or mortality. In general, patients fully recover with no remaining organ damage.

Keywords: Leptospirosis, Jaundice, Acute kidney injury, Hepatitis, Philippines

Case Presentation

A 54-year-old Philippine sailor was referred to the emergency department of a Belgian hospital because of fever, dull abdominal pain and intractable vomiting. He presented 6 days after onset of fever (post onset of symptoms, POS).

The pain was located in the right upper quadrant. There had been no diarrhoea and no hematemesis. He had no urinary complaints. There was faint dyspnea, but no cough or sputum production, nor hemoptysis. The patient reported cramps in the upper legs and calves. There was no arthralgia and no headache.

Six days before onset of fever, the patient left home from Manila, the Philippines, by aeroplane. After 2 brief stopovers at the airport of Hong Kong and Frankfurt, he arrived in Aarhus (Denmark), where he got on to a cargo ship. His task was to inspect the engines. After one day at sea, he started vomiting and a shipmate noticed his jaundice.

The past medical history was unremarkable, apart from the resection of a lipoma on the right thigh. He did not smoke and had not recently used alcohol, illicit drugs or mushrooms. He took acetaminophen against pain and fever. Laboratory investigation in the Philippines, conducted 3 months before departure, showed no particularities.

Correspondence to: Christophe Van Dijck, Antwerp University Hospital, Wilrijkstraat 10, 2650 Antwerp, Belgium. Email: christophe.vandijck@student.uantwerpen.be

Physical examination at presentation showed a generally ill man, with a body mass index of 23 kg/m². There was no fever at arrival. The blood pressure was 131/79 mm Hg, the heart rate 80 beats per minute and the peripheral blood oxygen saturation 94% with the patient breathing ambient air. Consciousness was normal. Skin and sclera were markedly jaundiced and there was conjunctival injection. The right upper abdominal quadrant was sensitive to palpation. There were no abdominal masses or lymphadenopathies palpable. There was no neck stiffness.

Laboratory investigation revealed a leukocytosis and increased C-reactive protein (CRP) level. There was a normochromic, microcytic anaemia and thrombocytopenia. The serum creatinine was markedly increased and electrolyte disturbances, including hyponatremia and hyperphosphatemia, were present (Table 1). A thick and thin blood smear were negative for malaria. There was slight microscopic haematuria (56 red cells/μL) and pyuria (62 cells/μL) and a trace of proteinuria.

Abdominal ultrasound was normal.

Ophthalmological evaluation because of reported blurred vision revealed no disturbance of visual acuity but the presence of scleritis.

He was admitted to the intensive care unit. With extensive intravenous fluid resuscitation, the urine output was 0,4 mL/kg/h and hemodiafiltration was initiated. After

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Table 1 Laboratory results

Number of days POS	6 (admission)	9	24	Reference value	Units
CRP	62.7	185.6	9.0	0.0–10.0	mg/L
WBC	20.5	32.6	5.3	3.3–9.3	10^9/L
Neutrophils	93.3	–	54.4	40.2–74.7	%
Haemoglobin	11.7	8.8	9.2	13.3–17.6	g/dL
Thrombocytes	103	131	322	131–360	10^9/L
Urea	410	111	36	19–43	mg/dL
Creatinine	15.35	5.07	1.37	0.66–1.25	mg/dL
GOT	46	58	39	17–49	U/L
GPT	60	63	70	21–72	U/L
Alkaline phosphatase	243	583	183	38–126	U/L
Gamma-GT	302	297	177	15–73	U/L
Bilirubin (total)	16.89	12.84	0.51	0.20–1.30	mg/dL
Bilirubin (direct)	15.88	11.68	0.00	0.00–0.30	mg/dL
Creatine Kinase	281	–	–	55–170	U/L
Sodium	132	138	140	137–145	mmol/L
Potassium	4.84	4.4	4.58	3.70–5.10	mmol/L
Chloride	88	101	101	98–107	mmol/L
Calcium	1.70	1.03	1.22	2.10–2.55	mmol/L
Phosphate	2.99	1.67	1.67	0.81–1.45	mmol/L
Magnesium	1.61	0.79	0.72	0.66–0.95	mmol/L

2 days, serology for hepatitis A, B and C, toxoplasmosis, cytomegalovirus, Epstein Barr, HIV and syphilis appeared to be negative.

On day 9 POS, the CRP increased to 185 mg/dL and fever developed. Empiric therapy with ceftriaxone was initiated. Serology for hantavirus, performed with an ELISA detecting IgM and IgG antibodies against Puumala virus and IgM/IgG Western blotting for Hantaan and Seoul virus remained negative. Leptospirosis was confirmed by the presence of *Leptospira* IgM antibodies by an immunochromatographic test on day 6 POS and by the microscopic agglutination test (MAT) on paired serum samples from day 6 and 21 POS. The MAT showed reactivity against serogroups Icterohaemorragiae, Canicola, Javanica, Pomona and Semaranga with low titers (≤1/200), except for serovar Semaranga patoc.

The patient remained afebrile and felt better after the first dialysis. The vomiting stopped, appetite recovered and abdominal pain disappeared. In total, four dialysis sessions were carried out at days 6, 7, 9 and 11 POS. Antibiotic therapy was continued for 14 days. The creatinine level at discharge was 1.37 mg/dL. White blood cell count (WBC), CRP and bilirubin normalized completely, but liver enzymes remained slightly elevated. At repatriation on day 28 POS, the patient was entirely asymptomatic.

Discussion

This patient presented with a febrile syndrome of acute kidney injury (AKI stage 3 following international KDIGO guidelines) and hepatitis with jaundice and myalgia. This constellation of findings is most consistent with an infection with *Leptospira* or hantavirus. Both have a worldwide prevalence and similar clinical, laboratory and even histopathological findings. Recent publications attract attention to the possibility of co-infection with both pathogens.[1] Therefore, laboratory examinations for both leptospirosis as well as European and Asian hantavirus infections were performed in this case.

Leptospirosis infection occurs through contact of damaged human skin or mucosa with urine (or water contaminated with urine) from colonized animals. These asymptomatic carriers, mainly rodents and in particular rats, but also cattle, goats, sheep, horses and dogs, wear leptospires in the proximal renal tubules and spread them through the urine. Some pathogenic species can survive in water for several weeks.[2]

Leptospirosis is one of the most frequent zoonotic diseases with an increasing incidence worldwide. The annual incidence is 0.1–10 per 100 000 inhabitants in areas with a temperate climate and is 10 times higher in tropical areas. According to the WHO, the death rate is around 10%, depending on the severity of the disease and the availability of medical facilities.[2] Also in Belgium the disease exists (see also https://www.wiv-isp.be/Epidemio/epinl/plabnl/plabannl/11_046n_r.pdf), but actually there is no requirement for notification. Recently, Clement *et al.* reported data on concomitant *Leptospira*- hantavirus infections in Belgium.[1] In Manila (the Philippines), leptospirosis is endemic with a mortality rate of 12–14%, mainly due to severe acute kidney injury or pulmonary haemorrhage. The exact incidence is unknown but appears to be increasing in association with overpopulation, deforestation and frequent floods.[3]

The incubation period of leptospirosis is 2–30 days.[2] The clinical picture can vary from asymptomatic to a severe syndrome with high mortality from multi-organ failure.[4] The disease typically evolves in 2 phases. In the acute stage, which lasts 3–10 days, there is bacteremia with fever and other symptoms such as headache, myalgia (especially in the calves), conjunctival congestion and non-specific signs such as cough, lymphadenopathy, rash, anorexia, nausea and vomiting.[2, 5] In the transition to the second stage, there is a short fever-free period. The second stage lasts 4–30 days and is characterized by antibody production and the disappearance of leptospiral spirochaetes from the blood. At this stage, they are shed in the urine.

Damage to liver and kidneys is reversible. Yet at this stage, the disease could derail into a serious icterohaemorrhagic syndrome with an increasing acute renal and hepatic failure and a high mortality: Weil's disease.[2, 5]

Almost every organ system can be affected. Pulmonary infection may lead to severe pneumonitis with pulmonary hemorrhage. Renal failure, as a consequence of interstitial nephritis, usually is non-oliguric. The presence of oliguria has been reported to be a significant predictor of death.

In most cases, there is a moderate and transient increase in transaminases (around 100 U/L) with a slight increase of alkaline phosphatase. The serum bilirubin levels can rise for days or weeks up to 30–40 mg/dL. This is the result of sepsis-related cholestasis and inhibition of bilirubin secretion in the bile ducts. Terminal liver failure is rare. Half of the patients present with thrombocytopenia, which correlates with the severity of disease. As a result of circulating toxins or direct invasion of muscle tissue by *Leptospira*, there is almost always myalgia and a rise in creatine kinase (CK), but rarely severe muscle damage. Cardiac arrhythmias are common but did not occur in the presented case. Atrial fibrillation, atrioventricular block and T-wave abnormalities are the most frequent electrocardiographic abnormalities. There is often severe headache with photophobia and features of aseptic meningitis in the liquor. In the acute phase, conjunctival congestion is common. One-third of patients reports visual damage. This is probably due to either an immunological effect or to the presence of leptospires in the eye.[4, 5]

Leptospira are spirochaetes, like *Borrelia spp*. and *Treponema spp*. Over 300 serotypes are divided into 20 serogroups, including 6 non-pathogenic saprophytes, 9 pathogenic and 5 intermediate pathogenic species whose virulence has not been demonstrated experimentally.[2] Spirochaetes live in aerobic conditions and have properties of both Gram-positive and Gram-negative bacteria. They measure approximately 0.25 × 6–25 µm. Because they can hardly be visualized with classical staining methods, dark field microscopy or phase contrast microscopy is needed in order to see them.[4]

Diagnosis is supported by a quick serological test demonstrating IgM-antibodies to an extract of *Leptospira*. The sensitivity and specificity of this test vary depending on the kind of test used. The test result must be confirmed by PCR, culture, or a MAT, which is carried out in a reference laboratory. MAT is the gold standard. Serial dilutions of the patients' serum are added to cultures of live *Leptospira* from different serogroups. Dark field microscopy is used to assess the degree of agglutination. Cross-reactivity between different serogroups is common, particularly in the initial stage of the disease and there is not always a correlation between the serogroup that is indicated through MAT and the one that is identified by PCR, or culture. This cross-reactivity is useful, as a non-pathogenic serovar (such as Semaranga patoc, as used in this case) can serve as an indicator of infection with a serovar that is absent in the panel of leptospires tested. In a non-endemic area, a titer threshold of 1/50 is diagnostic, while in endemic regions a titer of 1/400 or higher is required for diagnosis. Final confirmation of infection is obtained by demonstrating seroconversion or a fourfold rise in titer between paired sera.[2] In the presented case, a repeat MAT on a convalescent serum sample of day 21 POS did not show a clear rise in antibodies for any of the strains mentioned above. This, together with the low titers except for serovar Semaranga patoc, can probably be explained by the fact that the responsible serogroup was not included in the panel of strains tested which is based on the Belgian epidemiological situation. This may be in accordance with the fact that the patient was probably infected in the Philippines.

PCR is on the rise and is beginning to replace the serological tests in endemic areas because of greater sensitivity and earlier results. PCR can detect 10 to 100 leptospires per mL of blood or urine, but does not indicate the exact causative serovar.[2]

Treatment is mainly supportive, with renal replacement therapy when necessary. There is controversy about antibiotic treatment as mild acute infection would be self-limiting and there is no proven difference in outcome with or without antibiotic treatment. On the other hand, in case series, administration of antibiotics within 2–4 days POS has been reported to reduce the duration of illness and in severe cases, even late initiation of antibiotics has resulted in decreased mortality rates.[4] These findings should be weighed against the possibility that unrecognized dual infections with *Leptospira* and hantavirus have biased earlier findings.[1]

Usually, doxycycline is the drug of choice for mild infections and penicillin or a cephalosporin (ceftriaxone or cefotaxime) for severe disease.[4]

Hypotension, oliguria, hyperkalemia, pulmonary rales, dyspnea, leukocytosis >12 900/mm³, repolarization disorders on the electrocardiogram, alveolar infiltrates on X-ray imaging of the thorax, hemoptysis, metabolic acidosis and thrombocytopenia all make the prognosis worse.[5]

Preventive measures like protective clothing and hygienic measures should be taken in case of exposure to a potentially contaminated environment. Chemoprophylaxis with doxycycline is only recommended for high-risk individuals such as military personnel or aid workers in disaster areas or in remote endemic areas. A safe and effective vaccine has not yet been developed.[4]

After an acute infection, leptospires are shed in the urine for several weeks. In theory, transmission through sexual contact, blood or breastfeeding is also possible. However, person-to-person transmission has never been proven epidemiologically.[4]

Conclusion

Worldwide, a rising incidence of leptospirosis is reported due to factors such as overpopulation and floods, but also to increasing tourism and water sports activities in endemic areas. European doctors should be vigilant to detect both indigenous and imported cases.

Leptospirosis is a zoonosis transmitted through the urine of chronically infected animals, especially rats. The disease has a diverse presentation ranging from asymptomatic to a severe icterohaemorrhagic syndrome with multi-organ failure and a high mortality rate. The main differential diagnosis is infection with hantavirus, another rat-borne zoonosis with completely similar presentation. Co-infection has been reported. The differential diagnosis is based on serology and confirmation of leptospiral antibody production with a MAT in a reference laboratory. Treatment is mainly supportive. There is no certainty that the use of antibiotics reduces duration of fever or mortality in all cases. In general, doxycycline, penicillin or ceftriaxone are used and organ damage is reversible.

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Conflicts of interest

None.

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