A fatal case of leptospirosis

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Abstract - Leptospirosis is a zoonosis caused by Leptospira species, occurring predominantly in the tropics with a variety of symptoms that include involvement of the cardiovascular system. We describe a 51-year-old patient who presented with flu-like symptoms. Despite being given antibiotics, his clinical situation deteriorated rapidly and he died of progressive cardiogenic shock due to cardiac infiltration of leptospires. This case illustrates the potentially aggressive nature of the disease. In patients with suspected cardiac leptospirosis, transferral to a cardiothoracic centre should be considered. To obtain an early diagnosis, the early use of real-time PCR is recommended in cases of suspected severe leptospirosis.

Keywords - leptospirosis, myocarditis, the Netherlands

Introduction

Leptospirosis is caused by the pathogenic species of Leptospira. There are several species of this bacteria of which L. Interrogans contains most pathogenic serovars. Weil's disease is the icteric form of leptospirosis and is most commonly caused by L. Interrogans serovars Icterohaemorrhagiae and Copenhageni.

Leptospirosis is distributed worldwide with the majority of cases occurring in the tropics; this is mainly due to longer survival of leptospirosis in an environment with warm, humid conditions [1,2]. The incidence ranges from 0.1 to 1 per 100,000 per year in temperate climates to or more per 100,000 population per year in the tropics [2]. In 2007 the incidence in the Netherlands of serologically confirmed leptospirosis was 41 people [3]. Half of these patients had been infected whilst abroad on holiday in Asia or Latin America. Leptospirosis is transmitted to humans by environmental water contaminated by urine of infected mammals. The disease is maintained in nature by chronic infection of the renal tubules of host animals. Mammals chronically infected by leptospires are wild and domestic mammals, especially rodents [2].

Leptospirosis can manifest as a subclinical illness, a self-limited systemic infection or a severe, potentially fatal illness accompanied by multiple organ failure [1,2,4]. The disease is often not recognized because of the variety of symptoms. Involvement of the cardiovascular system is an important complication of leptospirosis but the exact incidence is unknown. However, it remains an under-estimated and under-diagnosed critical clinical factor [5,6]. We describe a patient with a fatal course of leptospirosis who died of heart failure due to cardial vasculitis and myocarditis caused by leptospirosis.

Case description

A 51-year-old immunocompetent Caucasian male was admitted to a hospital in the city of Apeldoorn, five days after the onset of fever, myalgia, arthralgia, diarrhoea and a painful neck. On the day before admission, the patient's general practitioner had prescribed doxycyclin 1x 100mg. The patient's medical history revealed no prior diseases.

On physical examination, the patient's body temperature was 40.1°C, his blood pressure 128/58 mmHg, his heart rate 115 beats/min and consciousness was normal. His hand joints were swollen and

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Figure 1a. Cut-surface of the heart with a mottled appearance. The left anterior descending coronary artery showed complete occlusion by a thrombus (LV: left ventricle; RV: right ventricle).
painful. Further examination revealed no abnormalities. Laboratory investigations on admission showed: C-reactive protein 266 mg/l (n <10), leukocytes 10.5x10^9/l (n 4.0-10.0), haemoglobin 8.4 mmol/l (n 8.5-11.0), thrombocytes 156 10^9/L (n 150-450), urea 16.2 mmol/l (n 2.5-7.5), creatinine 149 umol/l (n 70-110), sodium 129 mmol/l (n 135-145). Urine was positive for protein and erythrocytes. Urinary antigen tests for legionella and pneumococcus were negative. Chest x-ray and CT scan of the brain showed no abnormalities. After these test results our differential diagnosis was as follows: An infection (Chlamydia pneumoniae, Mycoplasma pneumoniae, Chlamydia psittaci, Coxiella burnetii, Legionella pneumophila or parvovirus), auto-immune disorders or malignancy. The latter two were not likely because of the abrupt onset of symptoms and no other symptoms prior to this episode. The patient had not been abroad in recent years. Serological tests for Chlamydia pneumoniae, Mycoplasma pneumoniae, Chlamydia psittaci, Coxiella burnetii, Rickettsia conorii, Legionella pneumophila and parvovirus were all negative. On admission intravenous ceftriaxone 1x2g and metronidazole 3x500mg were administered.

During the next few days, a conjunctivitis was noticed and there was no clinical improvement. Therefore, on the third day the antibiotic regimen was switched to erythromycin 4x 1g while ceftriaxone was continued. On the sixth day the patient developed a hemiparesis and aphasia. Cerebral involvement or meningitis was suspected and a CT scan of the brain and lumbar puncture to collect cerebrospinal fluid were performed. Both tests showed no abnormalities. Due to further clinical deterioration, the patient was transported to the hospital's intensive care unit (ICU).

On further evaluation of the patient's background, we learned from his wife that her husband had been working on a drainpipe where no rats had been seen, a week prior to the onset of symptoms. After one day in the ICU the patient developed arrhythmia and heart failure. Cardiac ultrasound revealed wall-motion abnormalities suggesting myocarditis. Electrocardiogram revealed atrial fibrillation, third degree atrio-ventricular conduction abnormality and ST-segment elevations. His clinical situation deteriorated rapidly and he died of progressive cardiogenic shock.

Cultures taken from the patient’s urine and blood remained negative. Blood and urine samples were sent to the KIT Biomedical Research Centre for culture, the micro-agglutination test (MAT) and Enzyme-linked immunosorbent assay (ELISA) for the detection of specific immunoglobulin M (IgM) antibodies for leptospirosis. The micro-agglutination test and ELISA remained negative for leptospirosis. Postmortem samples were submitted for histopathological examination, immunofluorescens included. PCR analysis was performed on the heart, spleen and liver tissues. The real-time PCR used, was based on the SYBR Green technology targeting the secY gene. PCR analysis of postmortem samples of the heart and liver were positive for Leptospirosis interrogans serogroup Icterohaemorrhagiae, serovar Copenhagi or Icterohaemorrhagiae. The water near the patient’s house was negative for leptospires. A dilated heart was found at postmortem investigation. The lumina of all three coronary arteries were occluded by a fibrin thrombus (Figure 1a). Microscopically all three coronary vessel walls showed an acute partly necrotizing inflammation consisting of neutrophils involving the intima (Figure 1b), surrounded by a granulomatous inflammation characterised by macrophages, lymphocytes and multinucleated giant cells (Aschoff cells). Furthermore, cells with rod-shaped nuclei and an owl-eyed or wavy “ribbon-like” appearance surrounded by abundant pale eosinophilic cytoplasm, so-called Anitschkow cells, were also identified (Figure 1c). The myocardial interstitium of the left and right ventricles showed an inflammatory infiltrate; this mainly consisted of scattered neutrophils and mononuclear inflammatory cells associated with focal myocyte necrosis (Figure 1d). Several spirochetes separately and in small clusters were stained with immunofluorescence (Figure 1e).

**Discussion**

We describe a patient with fatal myocarditis due to leptospirosis. Leptospirosis is presumed to be the most widespread zoonosis worldwide [2].

![Figure 1b](image_url) **Figure 1b.** Microscopic overview (HE, 2x) of the left anterior descending coronary artery. There is a severe vasculitis with complete obstruction by a fibrin thrombus.

![Figure 1c](image_url) **Figure 1c.** Anitschkow cell (HE, 60x).
The first serologically confirmed case of leptospirosis in the Netherlands was described in 1924. In the thirties there was an incidence of 100 patients a year which has subsequently decreased to an incidence of approximately 30-40 cases of leptospirosis per year today [7]. The Netherlands has a low annual incidence of 1.9/1000000 of leptospirosis in comparison with other countries [8].

The classic clinical presentation of leptospirosis is biphasic, with the acute or septicaemic phase lasting about a week, followed by the immune phase, characterized by antibody production and excretion of leptospiroses in the urine. Most of the complications of leptospirosis occur during the second week of the illness [1,2]. The spectrum of symptoms is broad and mimics the clinical presentation of many other diseases. Clinical and laboratory findings reported in previous cases include fever, myalgia, jaundice, conjunctival suffusion, meningitis, hepatitis, myopericarditis, kidney failure and haemorrhages. Our patient had almost all described symptoms reported in former case studies, except for jaundice [5,6,9-17]. Our patient had a conjunctival suffusion which is an important, but frequently overlooked sign [17].

The reference method for serological diagnosis of leptospirosis is the micro-agglutination test (MAT). This test can only confirm the disease in a sub-acute stage, because anti-Leptospira antibodies generally become detectable only 5 to 7 days after the onset of illness. The test has a specificity of 97% and a sensitivity that ranges from 30% to 63% in acute-phase specimens [18]. Both the micro-agglutination test and ELISA were negative in our patient. The MAT and ELISA were performed on the tenth day of illness while antibiotics were already being administered, which could explain the negative test results. Leptospires take weeks to grow on specialized media, therefore blood cultures are only marginally useful for obtaining the diagnosis [18]. Cultures taken from our patient remained negative. This could also be due to the fact that antibiotics had already been administered prior to presentation at the hospital. The real-time polymerase chain (PCR) technique has a diagnostic sensitivity (Dse) and specificity (Dsp) of 100% and 93% respectively. The real-time PCR has fewer false positive results than conventional PCR by reducing the risk of carry-over contamination. The Dse is highest in the first four days after the onset of disease and declines to 69% in days five to ten after onset of the disease. This is probably due to high bacteria load at the early stage of the disease. This seems a promising tool for early laboratory diagnosis. After approximately ten days leptospires are excreted in urine and PCR can be performed. Nevertheless, PCR on urine can lead to false-negative results because of natural inhibitors that interfere with the test. Because of the relatively late appearance of leptospires in urine and these inhibitors, PCR on urine is not routinely performed [19]. In our patient, L. interrogans serovar Copenhageni or Icterohaemorrhagiae was confirmed by PCR in liver tissue and the heart.

Postmortem investigation of our patient revealed involvement of multiple organs. Most prominent was the involvement of the cardiovascular system. The heart showed cardiomegaly (595 grams) with slight hypertrophy of the left ventricle. The interstitium of the ventricular myocardial cells showed an inflammatory infiltrate with focal myocyte necrosis (figure 1d). This finding of myocarditis at histopathological examination was a predominant feature found in other case studies [5,6,13,20]. In our patient, the lumina of all three coronary arteries were occluded by a fibrin thrombus with concurrent infiltration of the vessel wall including the presence of characteristic Aschoff and Anitschkow cells. In half of the cases in the study by Chakurkar, the coronary arteries were involved. These features have also been described in other reports [5].

The direct cause of death in our patient was arrhythmia and heart failure caused by leptospirosis. The electrocardiogram in patients with myocarditis shows sinus tachycardia with non-specific ST-segment and T-wave abnormalities. Rhythm disorders, conduction system abnormalities and refractory hypotension have been described in clinical studies. These disorders have been attributed to myocarditis or pericardial involvement. The myocarditis could be secondary to the vascular involvement. The damage to endothelial cells of small blood vessels is due to the toxic components of the leptostral cell wall (septicaemic phase) as well as deposition of the immune complexes (immune phase). This pathogenetic mechanism can also explain the lung haemorrhages.

Figure 1d. Interstitial myocardial inflammatory infiltrate mainly consisting of neutrophils associated with myocyte necrosis (arrow) (HE, 10x).

Figure 1e. A cluster of spirochetes staining with immunofluorescence (60x).
and the presence of petechiae. These symptoms are often seen in an infection with *L. icterohaemorrhagiae* [14,16,20,21]. The use of a left ventricular assist device has been described to serve as a bridge to cardiac recovery in patients with acute myocarditis. A transferral to a cardiothoracic centre should therefore be considered [22].

Penicillin and doxycycline are suggested as useful agents in the treatment of leptospirosis [23]. One comparative trial of the efficacy of ceftriaxone and penicillin for severe leptospirosis found no significant differences between the two drugs in terms of complications and mortality rates [24]. Another open-label randomized study compared parenteral cefotaxime, penicillin G, and doxycycline for the treatment of suspected severe leptospirosis. There was no significant difference between antibiotics with regard to associated mortality, defervescence, or time to resolution of abnormal laboratory findings. Therefore, doxycycline, cefotaxime, or ceftriaxone are a satisfactory alternative to penicillin G for the treatment of severe leptospirosis [25]. Our patient received adequate antibiotic treatment. If leptospirosis is not treated in the first 2-3 days it can progress in severity. It is presumed that intravenous antibiotics given in a later course have no beneficial effect on survival [26], although this has been disputed by others [27].

**Conclusion**

Cardiovascular involvement, in particular myocarditis is a frequent feature in Leptospirosis, and its presence is frequently overlooked. Transferral to a cardiothoracic centre should be considered in order to enable treatment with a left ventricular assist device. Furthermore, we recommend the early use of real-time PCR in suspected severe leptospirosis rather than the MAT to obtain an early diagnosis.

**References**


