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CASE REPORT

Leptospirosis – the unsuspecting culprit a case report and literature review

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Leptospirosis is caused by spirochete bacteria in the genus Leptospira and can present with a vast range of clinical symptoms. We report a case of leptospirosis in a 47-year-old gentleman who presented with sepsis and ended up with multi-organ failure. He was treated with piperacillin/tazobactam and doxycycline was added at a later stage. The patient recovered well with no complications. A literature review follows

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Introduction

Leptospirosis is a worldwide public health problem with 1.03 million annual cases worldwide per year.[1] Patients with leptospirosis may present with predominant pulmonary symptoms, ranging from cough, chest pain, breathlessness and mild to severe haemoptysis to acute respiratory distress syndrome (ARDS). The pulmonary symptoms usually appear between the fourth and sixth day of illness. The evolution of the disease may be very rapid and may result in death in less than 72 hours.[2] The patient can also present with kidney and liver failure. Leptospira bacteria are excreted in bodily fluids including urine and then penetrate their host through abrasions in the skin or via the mucosal membrane. There are a lot of peridomestic animals (rats, horses, cows, dogs, and pigs) and feral animals (bats, coyotes, sea lions, and even frogs) that can carry *Leptospira* bacteria in their kidneys. These animals are then presumed to excrete *Leptospira* in the environment.[1] Occupations that have direct (including veterinarian and farmer) or indirect (such as plumbing or sewer worker) contact with animal excrete are at risk of contacting *Leptospira*.[2]

Case report

A 47-year-old, Gozitan man suffering from diabetes mellitus presented to the Accident and Emergency Department with sepsis. He complained of a three-day history of lethargy, nausea, vomiting, loose stools, 24 hours of fever, decreasing appetite and oral intake. He also had myalgia, especially over his right shoulder and chest. He denied any recent travel. However, on further questioning, he claimed to work in the fields daily and was noted to have several abrasions. The patient was a non-smoker and only drank alcohol socially.

Vital signs in the emergency department were notable for a blood pressure of 106/63mmHg which decreased to 85/46mmHg within an hour and tachycardia at 130bpm. The patient was alert and orientated. The ocular examination was notable for scleral icterus. The skin appeared jaundiced, however, an examination of the heart, lungs, abdomen and lower limbs were unremarkable.

Initial laboratory study results

The initial blood test results are shown in Table 1. Chest radiography was normal and electrocardiography showed sinus tachycardia at 134 beats/min.

The patient was admitted to the intensive care unit for sepsis shock and multiorgan dysfunction. Intravenous piperacillin/tazobactam was initiated with aggressive fluid resuscitation together with noradrenaline as inotropic support.

The following day, he was still dehydrated. Chest auscultation revealed few sparse basal crackles, the abdomen was slightly tender in the epigastric area but there was no guarding/rebound. Serologic test results for acute hepatitis A, B and C infections were negative. An abdominal ultrasound showed hepatosplenomegaly. Doxycycline was added to piperacillin/tazobactam.

Day 2 post-admission, there was bronchial breathing on the right base and CXR confirmed a mild consolidation in the right lung middle field. His CRP increased from 200mg/L to 423mg/L and platelets decreased from 118 x109/L to 96 x109/L. Results also came back positive for the legionella urinary antigen.

Day 3 post-admission, his general condition improved. His CRP decreased from 300mg/L to 197mg/L. Serum Leptospira IgM came back as positive so leptospirosis was confirmed.

Day 4 post-admission, his oxygen saturation dropped to 88% on air. He was given 7L/min oxygen via a normal mask which kept his oxygen saturations at 96%. Bronchial breathing in the right base persisted. He was restarted on metformin which was stopped during admission.

Table 1 Initial blood test results

Investigation		Normal range
White blood cell count	7.3 x 10^9/L	4.3 - 9.43 x10^9/L
Haemoglobin	15.4g/dL	14.1 - 17.2g/dL
Platelets	115 x 10^9/L	146 - 302 x 10^9/L
CRP	200mg/L	0 - 5 mg/L
Sodium	125mmol/L	135 - 145mmol/L
Creatinine	117umol/L	62 - 106umol/L
Bilirubin	66.5umol/L	0 - 17.1umol/L
Alkaline phosphotase (ALP)	72U/L	40 - 129U/L
Aspartate aminotransferase (AST)	118U/L	10 - 50U/L

Day 5 post-admission, he maintained his blood pressure and inotropic support could be stopped. A chest X-ray showed deterioration in the right lung. The consolidation had increased in size involving almost the whole right lung. There was a mild right pleural effusion and there was also a new consolidation in the left lung (Figure 1).

Day 6 post-admission, he was clinically stable but developed respiratory distress. A diagnosis of acute respiratory distress syndrome was made and non-invasive ventilation was started. CRP continued to decrease from 50mg/L to 39mg/L. Computed tomography of the thorax showed the presence of many consolidations commencing from upper lobes and involving both lower lobes bilaterally associated with bilateral pleural effusions (right more than left). There were bulky mediastinal and enlarged hilar lymph nodes. There was some oedema of the right axilla and right chest wall. The spleen was seen to be enlarged (16x10cm). The CT imaging was very suggestive of leptospirosis (Figure 2.)

The clinical picture demonstrated that he was responding to treatment. He was continued on piperacillin/tazobactam 4.5g TDS for a total of 10 days and doxycycline 100mg BD for a total of 7 days. Despite the deterioration after an initial improvement, he did well and recovered fully with no complications on discharge.

Figure 1 Chest X-ray on Day 5

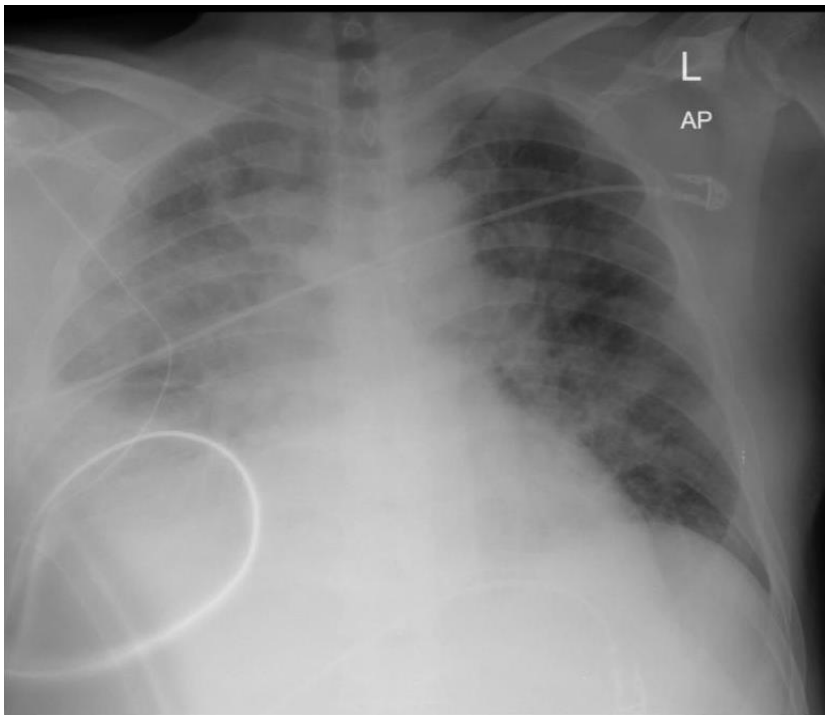
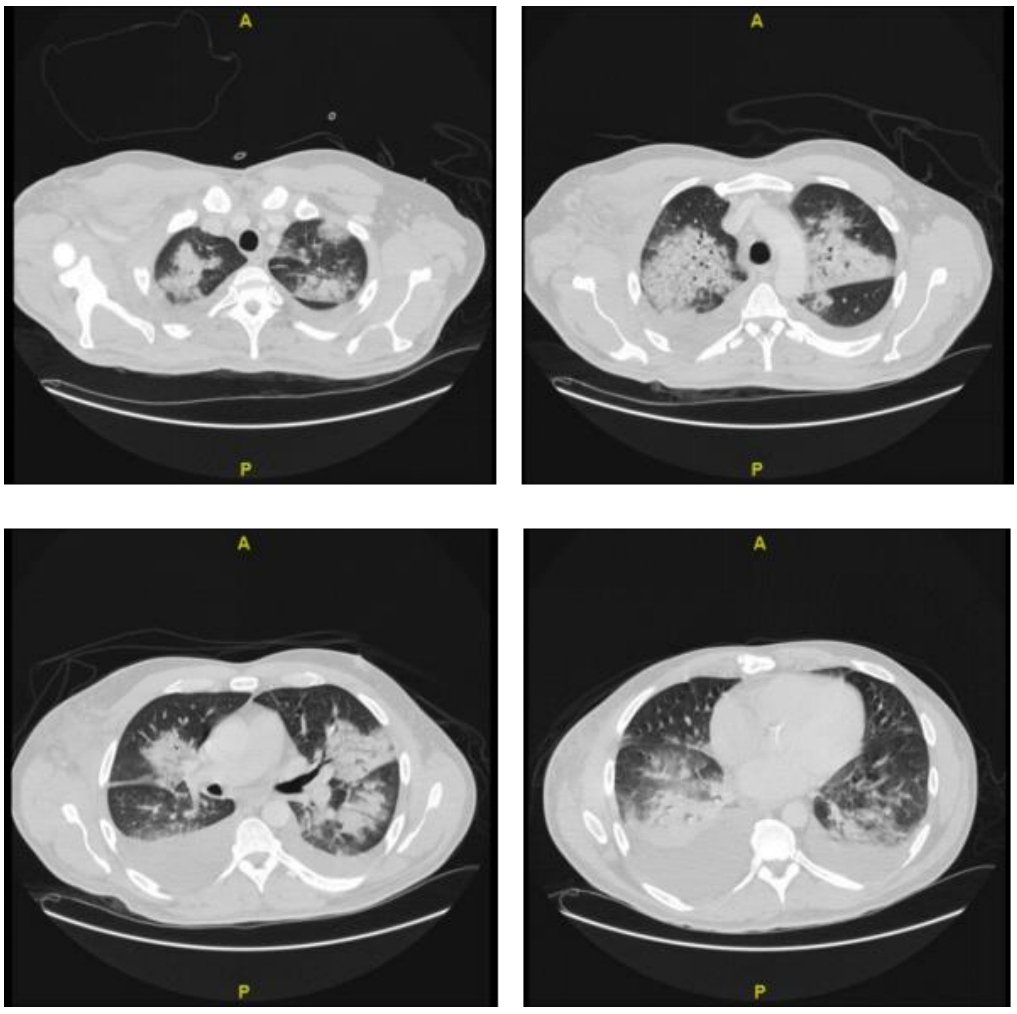


Figure 2 CT thorax on Day 6 suggestive of Acute Respiratory Distress Syndrome



Discussion

Clinical Manifestation and Differential Diagnosis

Leptospirosis usually presents itself as an acute febrile illness and mimics several other diseases.[3] The illness can range from a mild infection with symptoms like influenza to severe disease. Leptospirosis follows a biphasic pattern with an acute septicaemia phase which lasts for 1 week.[4] Then the symptoms resolve when antibodies are produced, and the spirochete is excreted in the urine. Three to four days after remission, fever may recur which is the second phase of the illness. Usually, the illness cannot be clinically distinguished from other febrile illness syndromes. In the second phase of the disease, a severe form of infection, called Weil's syndrome, can happen and is characterised by renal failure, bleeding, and jaundice.[5]

In the acute phase, symptoms vary from fever, headache, severe myalgia, anorexia, nausea, vomiting and conjunctival suffusion without purulent discharge. The headache in leptospirosis is similar to that of dengue fever which is characterised by retro-orbital pain and photophobia.[5] Myalgia is usually in the calf or lumbar areas.[3] In the second phase of the disease, Leptospirosis can affect any organ including the brain, liver, kidney, lungs, heart, and eyes.

The differential diagnosis of Leptospirosis is vast and must take into consideration all local diseases which might present as fever. Infections like influenza, malaria, rickettsioses, arboviral infections (dengue fever, yellow fever, amongst others), Hantavirus, scrub typhus and HIV seroconversion must be considered.[5-6] Severe fever and haemorrhage may make leptospirosis clinically identical to viral haemorrhagic fevers.[7]

Investigations

Early diagnosis of leptospirosis is essential. General laboratory results are very non-specific. One usually finds an increased ESR and liver function tests can be slightly increased. Renal function can be impaired. Leucocytosis can happen when the infection is severe, and platelets have been noted to decrease. Urinalysis can show proteinuria, pyuria, and haematuria.[5] However, these investigations can only give a possible diagnosis of leptospirosis.

Microscopy and culture

Leptospirosis can be detected by microscopic observation of the organism and by isolation of the spirochete in cultures. Body fluids like urine, blood, and cerebrospinal fluid (CSF) can be seen under dark field microscopy to visualise the organism. The timing of the sample is crucial. This method has low sensitivity as $1x10^4$ leptospires/ml must be present, for leptospires to be seen.[3]

Leptospira can be isolated in the acute phase of infection. Cultures from various body fluids and tissues can isolate *Leptospira*. As with direct visualisation, blood cultures can only help in the early phase of the illness, meaning from before the onset of symptoms to the end of the first week, during which leptospiraemia happens. These should be taken before the patient takes antibiotics. Urine cultures can also be taken but should be used during the leptospirosis phase which is one week after onset of symptoms. Other fluids like CSF and peritoneal dialysate can be used to culture *Leptospira* during the first week of infection. After, serological methods and molecular methods can be used to identify the isolated leptospires.[4]

Serological diagnosis

Detection of specific antibodies and antigens can be used to confirm leptospirosis. Serological methods can be genus-specific or serogroup specific. The microscopic agglutination test (MAT) remains the definite serological investigation of choice. Antibodies can be detected in the blood after 5 to 7 days after onset of the infection.[8] In MAT, the patient serum is mixed with leptospiral cultures. These are then examined by dark field microscopy for agglutination. MAT detects IgG and IgM which are serogroup specific. Therefore, all serogroups should be tested. A high titre for a specific serovar signifies that it is the cause of the infection. For a definite diagnosis, paired sera are required. Some disadvantages of MAT are that it is complex, requires maintenance of *Leptospira* cultures and that in the acute phase, sensitivity is low.[4]

Due to the limitations of MAT, other rapid screening tests for the diagnosis of leptospirosis in the acute phase have been developed. IgM antibodies can be identified during the first week of illness.[9] This can be done using techniques like ELISA, dipstick, lateral flow, indirect hemagglutination assay, and latex agglutination.[3] However, there are still limitations of any serological test in the acute phase. Furthermore, rapid diagnostic tests should be confirmed with a reference test.[10]

Molecular Diagnosis

DNA detection by polymerase chain reaction (PCR) has been applied for the detection of Leptospira in the acute setting. DNA has been amplified in several media including blood, CSF, urine, aqueous humour, and tissues.[11] PCR has been demonstrated to be useful in the detection of *Leptospira* when antibody production has not yet begun. On the other hand, the sensitivity of DNA detection by PCR decreases throughout the disease. A limitation of PCR is that it currently cannot distinguish between different serovars.[12] Real-time PCR has also been used to quantify bacterial load in leptospirosis.[13]

In a recent study, investigating the cost-effectiveness of different management concluded that management based on the clinical judgement was most efficient.[14]

Treatment and Prevention

Empirical treatment for leptospirosis usually consists of penicillin or doxycycline. Treatment should be tailored according to how severe the infection is, with oral antibiotics for a simple febrile illness to IV penicillin in severe life-threatening infections.[15]

Treatment should be started during the early stages of diagnosis of leptospirosis and during this period oral doxycycline is advised. In late or severe infections (including Weil's disease), intravenous penicillin has been shown to reduce the length of hospital stay. Treatment should be started as suspicion of leptospirosis is made and should be given for a total of 7 days. In another study comparing IV penicillin G and ceftriaxone, it was shown that there was no difference in mortality, therefore, they are both equally effective.[16] Ciprofloxacin should also be given to patients with associated uveitis.[15]

Leptospira species has a bacterial cell wall. Theoretically, this would make it susceptible to many different antibiotics. A study in 2003, showed that the *Leptospira* species is susceptible in vitro to penicillin, cephalosporins, aminoglycosides, macrolides, quinolones and tetracyclines amongst others. However, leptospira spp. was not shown to be

susceptible to metronidazole, glycopeptides, sulfamides, and rifampicin.[17]

Severe leptospirosis infections can be associated with damage to any organ and even with multi-organ failure. Jarisch-Herxheimer reactions have also been reported. Cases with acute kidney injury or pulmonary haemorrhage (with associated ARDs) sometimes would need further treatment with adjunctive therapies like haemodialysis and mechanical intubation respectively. Pulmonary leptospirosis is usually due to an inflammatory response to the leptospires toxin which damages the host.[15] Corticosteroids can inhibit this response but this is still controversial. A review in 2014 noted that a randomised control study has shown that these are ineffective in pulmonary leptospirosis and can even increase the risk for other nosocomial infections. On the other hand, other studies showed that pulse dose steroids successfully treated leptospiral pulmonary involvement and even renal involvement.[18-19]

Prophylaxis against leptospirosis with doxycycline does not significantly affect the incidence of infection but has been shown to decrease morbidity and mortality during outbreaks of the disease.[20] The prevention of leptospirosis usually entails better sanitation. Leptospirosis is usually carried around by rodents, therefore eradication of rodents in endemic areas is essential. Using personal protective gear can also prevent infections.

Vaccinations are also currently available against leptospirosis. The current vaccinations are killed, whole-cell suspensions (bacterins). These have multiple side effects and have low efficacy. Therefore, better vaccines are needed. In these last two decades, new DNA vaccines have been promising and are an important strategy of minimising leptospirosis infection.[21]

Conclusion

Leptospirosis is an infectious disease present not only in developing countries but also in industrialized nations. Diagnosing leptospirosis may be a challenge in view that it can mimic several other diseases. A high index of suspicion is needed to make the diagnosis based on the history and clinical manifestation since laboratory investigations will take days to confirm leptospirosis.

The disease has a biphasic pattern. Thus, after an initial improvement, deterioration in the clinical picture with multi-organ failure is not uncommon. Early antibiotic therapy should be started in every case of suspected leptospirosis since in most cases, early treatment prevents morbidity and mortality.

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