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# Case of leptospirosis causing pancytopenia

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## SUMMARY

We present the case of a young female landscaper who presented to an Australian tertiary hospital with persistent fevers and new pancytopenia. Extensive initial workup for her presenting illness did not identify a cause; however, a detailed history of her occupation revealed she worked heavily with soil on farms that had domestic livestock in addition to rodents. Hence, further serological testing for leptospirosis was performed, revealing a diagnosis of infection with *Leptospira interrogans* serovar Hardjo. Treatment covering leptospirosis was commenced, and she improved clinically, and her cell counts returned to normal. Pancytopenia is a rare manifestation of leptospirosis and has only been reported in a handful of case studies. We highlight that leptospirosis should be considered as a differential diagnosis in those with fever, and new pancytopenia, particularly in patients with relevant risk factors for exposure.

## BACKGROUND

Leptospirosis is a zoonosis with protean clinical manifestations that range from non-specific febrile illness to multiorgan failure leading to death. Warmer areas with higher rainfall and a propensity for flooding provide ideal conditions for the spirochaetes' enzootic lifecycle. Transmission between rodents and other animals (domesticated and livestock) occurs through *Leptospira*-contaminated urine, which may persist in soils, vegetation and water for weeks.<sup>1</sup> Rodents are the main carriers in urban areas; however, cattle are another major transmission source in rural regions.<sup>1</sup> Human infection occurs via bacterial entry through mucosal membranes and abraded or macerated skin.

The diagnosis of leptospirosis is often delayed due to its variable, non-specific presentation. It is described as a biphasic illness with an acute bacteraemic phase lasting 5–14 days, followed by immune-mediated organ damage.<sup>2</sup> Severe leptospirosis may present as pulmonary haemorrhage, jaundice, acute renal injury and neurological complications (encephalitis, aseptic meningitis).<sup>2</sup> Leptospirosis often presents with haematological disturbances, most commonly isolated thrombocytopenia<sup>3</sup> and, in a handful of cases, manifests as pancytopenia; however, the mechanism of this is still not well defined.

In this case, we highlight the importance of bearing an index of suspicion for leptospirosis in patients with fever and new pancytopenia with the relevant occupational risk factors such as exposures to soil, water and animals are present, even in non-endemic areas.

## CASE PRESENTATION

A young woman was admitted with 2 days of lethargy, headache, photophobia, neck pain, diarrhoea, arthralgias and myalgias. A medical history includes Crohn's disease managed with allopurinol and mercaptopurine. On admission, she was febrile (39.1°C) and tachycardic (130 bpm), hypotensive (96/65 mm Hg) and tachypnoeic (26 br/min). Physical examination did not reveal any potential focus of infection, and there was no evidence of meningism, lymphadenopathy, joint synovitis or conjunctival suffusion. Due to ongoing fevers and abnormal vital signs, she was admitted for observation and further investigation.

Initial laboratory investigations demonstrated lymphopenia of  $0.6 \times 10^9/L$  (reference interval (RI),  $1.0\text{--}3.5 \times 10^9/L$ ), C reactive protein of 119 mg/L (RI  $<5$  mg/L), borderline hyponatraemia 134 mmol/L (RI 135–145 mmol/L), mild liver function test derangement (alanine aminotransferase 102, aspartate aminotransferase 111, gamma-glutamyl transferase 99, alkaline phosphatase 14, bilirubin  $6 \mu\text{mol/L}$ ). Further workup for a febrile illness included a urinalysis microscopy, culture, sensitivities, which revealed erythrocytes  $52 \times 10^6/L$  and 32 leucocytes  $\times 10^6/L$  without casts or growth. Respiratory multiplex nucleic acid test for influenza A and B, respiratory syncytial virus, Bordetella, Rhinovirus, Parainfluenza viruses and SARS-CoV-2 was negative. Electrocardiography and chest X-ray were normal.

Throughout her admission, she was clinically deteriorating with no resolution in symptoms and had ongoing fevers. It was also noted that she had continuing decrease in her cell counts, progressing from initial thrombocytopenia to pancytopenia. The nadir of the pancytopenia occurred on day 3 of admission with haemoglobin 111 g/L (RI 135–145 g/L), leucocytes  $1.7 \times 10^9/L$  (RI  $4\text{--}12 \times 10^9/L$ ), neutrophils  $1.1 \times 10^9$  (RI  $2\text{--}8 \times 10^9/L$ ) and thrombocytopenia (platelets  $79 \times 10^9/L$ , RI 150–400  $\times 10^9/L$ ). A blood film showed anaemia with occasional elongated cells, neutropenia and moderate thrombocytopenia with no schistocytes.

Given the diagnostic uncertainty, haematology, rheumatology and infectious disease were consulted, and further laboratory tests were conducted to try and establish a unifying diagnosis, including infectious mononucleosis, Epstein-Barr virus, Cytomegalovirus, HIV, hepatitis A, B, C infection all of which were negative. Blood cultures incubated for 5 days did not reveal a bacteraemia.

Due to ongoing headache and fever, a CT imaging of the brain was performed and was unremarkable.



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Lumbar puncture (LP) was performed for cerebrospinal fluid (CSF) analysis ruling out meningitis with  $1 \times 10^6$ /L Leucocytes, glucose 3.4 mmol/L (RI 2.2–3.9 mmol/L) and total protein 0.33 g/L (RI <0.45 g/L) with no growth on culture. Furthermore, multiplex qualitative nucleic acid test on CSF did not reveal a pathogen, and no cryptococcal antigen was detected.

With ongoing fevers and no clear explanation, the social and occupation history was revisited. On questioning her work as a landscape gardener with limited personal protective equipment, her job resulted in significant exposure to greenhouses, mulching and potting mix, and rodents and rat excrement. Furthermore, she owned two dogs and worked on properties that contained livestock. This history raised the suspicion of leptospirosis despite the patient living in a non-endemic area, and leptospirosis serology was ordered as PCR testing was not available.

Although there was ongoing diagnostic uncertainty due to ongoing clinical and biochemical deterioration, she was empirically commenced on broad-spectrum antibiotic therapy, which would cover atypical infections, including leptospirosis. She was treated with intravenous benzylpenicillin 1.2 g four times per day and oral doxycycline 100 mg two times per day. Six hours following the administration of antibiotics, she developed a fever (40.1°C) and rigours, tachycardia (140 bpm), likely consistent with a Jarisch-Herxheimer reaction.

Postadministration of antibiotics, her condition rapidly improved, and pancytopenia resolved within 72 hours. She was discharged after 8 days with a plan to complete a 1-week total course of oral doxycycline. One week postadmission, her leptospirosis serology showed an elevated *Leptospira interrogans* (IgM) with serovar Hardjo titre of 100 with other serovars demonstrating a titre of <50 (Arborea, Australis, Canicola, Copenhageni, Gippotyphosa, Pomona, Tarassovi, Zanoni).

## OUTCOME AND FOLLOW-UP

Repeat serology 4 weeks after discharge revealed *L. interrogans* (IgM) serovar Hardjo titre rose from 100 initially to 3200. The patient had remained asymptomatic following the 1-week course of doxycycline and has since been able to return to work. At follow-up, her pancytopenia had resolved, and her liver function enzymes and sodium had returned to normal. Given the patient's occupational risk factors, counselling was provided regarding the importance of personal protective equipment, hand hygiene and minimising environmental contamination risks.

## DISCUSSION

Leptospirosis is caused by the spirochete genus *Leptospira* and is endemic within many tropical and subtropical regions worldwide. Leptospirosis often poses a diagnostic challenge in areas where it is uncommon. It is described as a biphasic illness that begins after an average incubation period of 5–14 days.<sup>2</sup> The acute, bacteraemic phase manifests with fever, myalgias, and headaches and lasts around 7–10 days.<sup>2</sup> Other symptoms include a non-productive cough, abdominal pain and diarrhoea. Conjunctival suffusion, marked by conjunctival redness, can help distinguish leptospirosis from other infectious illnesses.<sup>2</sup> Immune-mediated organ damage and systemic complications usually begin more than 7 days from symptom onset.<sup>1</sup>

The most common laboratory findings include mild transaminitis, neutrophilia and hyponatraemia,<sup>4</sup> and abnormal urinalysis (microscopic haematuria, pyuria and proteinuria).<sup>3</sup> LP is often prompted, given that severe headache is a common symptom. The LP may demonstrate an aseptic

meningitis picture with a neutrophilic or lymphocytic pleocytosis, normal glucose and mild elevation in protein.<sup>3</sup>

Thrombocytopenia is a well-documented haematological complication of infection. It is often mild and is often associated with renal failure and a poorer prognosis. It occurs in up to half of Leptospiral infections, with underlying pathophysiology still unknown. It is thought a combination of (1) disseminated intravascular activation (DIC), (2) platelet death induced by Leptospiral toxins, (3) decreased production of platelets by the bone marrow megakaryocytes, (4) platelet overactivation by bacterial components leading to platelet consumption and (5) platelet clearance mediated by platelet autoantibodies.<sup>5</sup>

Pancytopenia is reported in only a number of cases as a haematological manifestation in Leptospiral infections, and the true incidence is unknown. A case series described in Israel reported pancytopenia in 28% of patients.<sup>6</sup> More recent case reports do not corroborate this high incidence.<sup>7</sup> The underlying mechanisms are not fully understood, and may be several processes working in tandem or independently to affect the blood cell lineages. Bone marrow aspirates noted in previous case reports indicate that the cytopenias may arise from bone marrow suppression marked by significant cellular hypoplasia.<sup>3, 6</sup> Some authors suggest that the pancytopenia could be attributed to DIC, a toxin, or cytotoxin-mediated mechanism as a direct complication of leptospiral vasculitis or as a general phenomenon of septicaemia.<sup>8</sup>

The definitive diagnosis of leptospirosis can be made by isolating *Leptospira* from clinical specimens or, more commonly, looking for at least a fourfold rise in microscopic agglutination test titre in the convalescent-phase sera compared with the acute-phase sera, taken at least 2 weeks apart. In addition, a single *Leptospira* microagglutination titre greater than or equal to 400 supported by a positive ELISA IgM result can be diagnostic of a leptospirosal infection.<sup>9</sup> PCR serves as suggestive laboratory evidence and is becoming increasingly available, bearing the advantage of earlier positivity compared with serology<sup>10</sup> and is valuable in guiding timely diagnosis in those with a clinical suspicion of leptospirosis.<sup>2</sup> However, *Leptospira* DNA (in blood, urine or CSF) is only present during the acute/bacteremic phase of the illness.

There are over 200 *Leptospira* serovars, of which 30 are considered to be clinically significant.<sup>1</sup> This is the first described case of pancytopenia caused by *L. interrogans* serovar Hardjo. The actual serovar may not be clinically relevant, typically due to the delay in confirmatory testing and if clinical suspicion of leptospirosis is high, empiric treatment should begin before diagnosis.

Infection prevention should be aimed at avoiding direct contact with Leptospire and implementing thorough washing after potential exposure. Counselling regarding occupational exposure risk should be addressed. It is advised to wear adequate personal protective equipment (glasses, masks, gloves, boots) when in high-risk environments and to work within well-ventilated areas. It is also important to minimise environmental contamination, such as exposure of soils to floodwaters and reducing surrounding rubbish, which attracts rodents.

This case highlights pancytopenia as a rare manifestation of Leptospirosis and the importance of maintaining a high index of suspicion in the setting of occupational exposure, even in non-endemic regions. Additionally, it showcases the reversibility of pancytopenia when treated appropriately.

## Learning points

- ▶ Pancytopenia is an atypical and rare haematological manifestation of leptospirosis.
- ▶ There are a large number of aetiologies to consider when patients present with fever and pancytopenia. Clinicians are required to undertake in-depth interviews, in order to generate an appropriate differential diagnosis.
- ▶ Although rare, leptospirosis should be considered on the differential list in those patients with pancytopenia and fever who have the appropriate environmental exposure

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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