CASE REPORT

Acute *Legionella pneumophila* infection masquerading as acute alcoholic hepatitis

Jonathan Michael Hunter,^{1,2} Julian Chan,¹ Angeline Louise Reid,^{1,3} Christopher Tan¹¹Department of Medicine, Redcliffe Hospital, Brisbane, Queensland, Australia²Department of Medicine, University of Queensland, Brisbane, Queensland, Australia³Department of Intensive Care, The Prince Charles hospital, Brisbane, Queensland, AustraliaCorrespondence to
Dr Jonathan Michael Hunter,
jonhunter@live.com.au**SUMMARY**

A middle-aged man had deteriorated rapidly in hospital after being misdiagnosed with acute alcoholic hepatitis. Acute Legionnaires disease (Legionellosis) was subsequently diagnosed on rapid antigen urinary testing and further confirmed serologically. This led to appropriate antibiotic treatment and complete clinical resolution. Physicians caring for patients with alcohol-related liver disease should consider *Legionella pneumophila* in their differential diagnosis even with a paucity of respiratory symptoms.

BACKGROUND

To our knowledge, this is the first reported case of serologically proven acute Legionnaires disease (Legionellosis) presenting as fulminant hepatitis.

This is an important case that adds to growing evidence that Legionellosis can present as a multi-system disease and can lead to acute liver failure in a few select patients. It illustrates how Legionellosis can masquerade as other diseases, often with minimal initial respiratory symptoms and signs. Lastly, it further validates the utility of the *Legionella* urinary antigen test, prompting correct treatment leading to a successful outcome.

CASE PRESENTATION

A 56-year-old man presented to the emergency department with a 7-day history of malaise, left-sided abdominal pain and rapidly worsening jaundice. Multiple falls following these symptoms had finally prompted him to seek medical attention. His medical history was unremarkable apart from treated hypercholesterolaemia.

He was on no other regular medications apart from 20 mg atorvastatin daily and infrequent paracetamol use.

He owned and ran his own light industrial business. He was a current 20 pack/year smoker and had a moderately heavy alcohol intake of a 700 ml bottle of rum weekly for the last few years.

On examination, he was markedly icteric with a tender hepatomegaly. There were no peripheral stigmata of chronic liver disease. Initial observations revealed a heart rate of 125 bpm, blood pressure 110/60 mm Hg and an oxygen saturation of 95% on room air. Initial chest auscultation was unremarkable.

Over the course of the next 3 days, the patient developed signs of encephalopathy, characterised by drowsiness, confusion and hepatic asterixis. This coincided with further elevations in serum ammonia, bilirubin and hepatic transaminases (table 1).

He showed signs of systemic inflammatory response syndrome (SIRS) with documented rigours, fever and hypotension. He continued to complain of abdominal pain and was noted to have non-bloody diarrhoea.

INVESTIGATIONS

Liver function tests (table 1) initially showed a mixed hepatocellular and cholestatic picture. An elevated International Normalised Ratio (INR) and hypoalbuminaemia suggested an impaired synthetic function of the liver. Other significant abnormalities included an elevated C reactive protein, mild hyponatraemia and hypophosphataemia.

The total bilirubin which was a mixed hyperbilirubinaemia, subsequently rose to 410 µmol/l (<20). Albumin fell to 19 g/l (35–50) and serum ammonia peaked to 110 mmol/l (<50).

Full blood count revealed a leuco-erythroblastic blood film with toxic changes. Haemoglobin was 117 g/l (115–160) with a raised mean cell volume of 101 fl (80–100). White blood cells were $6.9 \times 10^9/l$ (4.0–11.0) and platelets were $115 \times 10^9/l$ (140–400).

Hepatitis (A, B and C), cytomegalovirus IgM and HIV serologies were all negative. Several blood cultures taken during the admission were all negative.

Stool culture was negative for enteric bacterial pathogens as well as for clostridium-difficile toxin.

An initial chest x-ray (CXR) (figure 1) showed early subtle left lingula consolidation which was only fully appreciated following a second interval CXR which showed (figure 2) a worsening consolidation. A CT abdomen was performed (figure 3) to investigate his abdominal pain and diarrhoea. This showed diffuse colonic oedema with surrounding fat stranding suggestive of colitis. The CT abdomen (figure 4) also showed hepatomegaly with radiological fatty infiltration and ascites (arrow). Note that there were no radiological features of cirrhotic liver disease such as portal vein enlargement, splenomegaly, varices or recanalisation of the umbilical vein.

Legionella urinary antigen was positive for *Legionella pneumophila* (subtype 1). Although the serology for *L pneumophila* (subtype 1) was initially negative (<64), the results had risen a week later to a total antibody (IF) of 512 and IgM of 256.

TREATMENT

The patient was initially diagnosed and treated for acute liver failure due to acute alcoholic hepatitis. He was prescribed high doses of thiamine intravenously, vitamin K and multivitamins and was monitored for alcohol withdrawal. Lactulose therapy was

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Table 1 Hospital stay and convalescent blood investigations

	Initial blood tests	1 week	2 weeks	3 weeks	Discharge blood tests	Convalescent blood tests
Alt (U/l)	104	68	141	275	43	35
Ast (U/l)	451	240	433	447	63	42
Total bilirubin (μmol/l)	175	242	410	218	40	12
Ammonia (NH ₄) (μmol/l)	110*	90	63	30	35	
Albumin (g/l)	28	26	20	19	24	34
INR	1.3	1.5	1.4	1.3		
CRP (mg/l)	152	159	80	80	54	16
Phosphate (PO ₄) (mmol/l)	0.27	0.63	1.1	0.8	1.39	

At 48 h admission.

CRP, C reactive protein; INR, International Normalised Ratio.

withheld due to concurrent diarrhoea and he required intravenous phosphate replacement. His initial Maddrey's Discriminant Score for alcoholic hepatitis was 19 (>32) and was therefore not prescribed glucocorticoid therapy. Following interval CXR progression of the left pulmonary infiltrate, he was commenced on third generation cephalosporin and metronidazole to treat possible aspiration pneumonia. Once positivity of the urinary Legionella antigen was ascertained, he was treated with intravenous azithromycin, followed by a prolonged course of oral roxithromycin.

OUTCOME AND FOLLOW-UP

The patient had a protracted hospital stay of several weeks and required a short stay in the rehabilitation unit. While he had a number of out-of-hours emergency medical consultations for haemodynamic instability, he was not admitted to an intensive care unit. Gradually, following initiation of the macrolide antibiotic, his inflammatory markers and liver function tests returned to near normal. This coincided with normalisation of haemodynamic status, cerebral, respiratory and bowel function. He was discharged back to independent living some weeks later and had made a complete clinical and biochemical recovery.

DISCUSSION

Legionnaire's disease or Legionellosis was first recognised in July 1976 following outbreak of a mysterious severe pneumonia occurring at the 58th convention of the American Legion.¹

It was not until 1977 that the causative aerobic gram-negative rod-shaped organism *L pneumophila* was cultured by McDade *et al.*² Of the 40 Legionella species reported, *L pneumophila* subtype 1 is the most pathogenic and is responsible for over 70% of all cases.³

Horwitz^{4 5} showed how *L pneumophila* entered human monocytes via novel coiling phagocytosis, after which it resides in a unique phagosome that avoids lysosomal destruction. It replicates intracellularly, later killing its host cell by either apoptosis or necrosis.⁶

Studies from Europe and North America cited Legionellosis as being responsible for 2–15% of hospitalisations for community-acquired pneumonia.⁷ Cases of pneumonia due to Legionellosis are more likely to be classified as severe, with evidence of multiorgan involvement and patients were more likely to be admitted to an intensive care unit.⁸ Historically, clinical features classically associated with Legionella infection include high fevers (>38.9°C), confusion and diarrhoea.^{9–11} Respiratory failure is the usual mode of death with death rates being quoted between 5% and 30%.¹²

Risk factors for developing Legionellosis are well described and include the male gender, cigarette smoking, alcoholism and immunosuppression.^{11 13 14}

Historically, diagnosis of Legionellosis has relied on direct culture of the organism or detection of a fourfold increase in serum antibody over several weeks. This has obvious limited

Figure 1 Initial chest x-ray on presentation.

Figure 2 Interval chest x-ray showing worsening consolidation.

Figure 3 CT of the abdomen showing radiological features of colitis.

utility in early diagnosis and both have only low-to-reasonable sensitivity.¹⁵

It has been known since the early 1980s that at least 80% of patients with subtype 1 Legionellosis secrete detectable urinary antigen during the course of the disease.¹⁶

Diagnosis and early antibiotic treatment has been facilitated by the use of urinary antigen testing. Studies cite a sensitivity of between 70% and 100% with specificity for detecting subtype 1 Legionellosis as 100%.¹⁷ Caveats to sole dependence on urinary antigen testing are due to its specificity to *L pneumophila* subtype 1, with Legionellosis caused by other subtypes and species being potentially missed.

Extrathoracic Legionella infection was first described in 1980 in a lymphoma patient with fatal pneumonia.¹⁸ This lent support to the theory of a bacteraemic phase of infection which was postulated after the organism was grown from blood antemortem.¹⁹

Since then, the Legionella species has been implicated in cases of pyrexia of unknown origin, sinusitis, cellulitis, pancreatitis and

pyelonephritis. The most common extrapulmonary site, however, is the myocardium with various case reports of myocarditis, pericarditis, postcardiotomy syndrome and endocarditis.^{20–23}

Since the initial description of the Legionellosis syndrome, there have been tantalising clues of predilection of Legionella species for the hepatocyte. Postmortem studies by Watts *et al*¹⁸ noted the finding of intact bacteria in hepatic sinusoidal cells seen on electron microscopy, as well as the detection of *L pneumophila* antigen by direct immunofluorescence in the liver and spleen. It has been noted that Legionella pneumonia is the most common pneumonia to cause raised serum hepatic transaminase, and indeed it has been historically proposed as one of the methods to distinguish Legionella pneumonia clinically from other forms of pneumonia.²⁴

Tokunaga *et al*²⁵ in 1992 reported an immunofluorescently-proven Legionella infected hepatic graft in a 2.5-year-old liver transplant recipient who died of respiratory complications. La Scola *et al*²⁶ isolated Legionella from multiple liver abscesses in a 7-year-old girl with acute lymphoblastic leukaemia. Mofredj *et al*²⁷ reported a fatal case of probable Legionellosis with severe hepatitis, as evidenced by a positive Legionella urinary antigen. Postmortem liver examination showed hepatic necrosis and centrilobular cytolysis with inflammation.

To our knowledge, this is the first case of serologically proven (greater than fourfold increase of serum antibody titres) Legionellosis presenting as a fulminant hepatitis, with subsequent survival following appropriate treatment.

Learning points

- ▶ *Legionella pneumophila* has the potential to cause acute or fulminant hepatitis.
- ▶ Alcoholism is a risk factor for developing Legionellosis.
- ▶ All reversible causes of liver failure should be sought, especially in patients deemed to be alcohol dependent.
- ▶ When patients are unable to give an adequate history, there is a high capacity for misdiagnosis.
- ▶ Utility of Legionella urinary antigen testing is well validated (for pneumophila subtype 1) and may be invaluable when diagnosis is uncertain.

Competing interests None.

Patient consent Obtained.

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Figure 4 CT of the abdomen showing ascites.

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