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Case report

Established association of legionella with rhabdomyolysis and renal failure: A review of the literature

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ABSTRACT

Legionella causes 2–15% of community acquired pneumonia cases that require hospitalization and it is the second most common cause of serious pneumonia that needs admission in an intensive care unit. Since the first published case in 1980, there are a further 22 published case reports on the direct correlation between rhabdomyolysis, renal failure and Legionnaires' disease. All but two patients survived with antibiotics and dialysis. Clinicians should be cognisant of this established triad and correlation of Legionnaires' disease, renal failure and rhabdomyolysis, as failure to do so and initiate treatment early has proven to increase mortality significantly in affected patients.

1. Case report

A 39 year lady, Ms M, with no known previous comorbidities was brought to the emergency department with a history of acute onset deteriorating level of consciousness and difficulty breathing. There was no history of a seizure. On arrival, her Glasgow Coma Scale (GCS) was 7/15 and an arterial blood gas on room air revealed a severe normal anion metabolic acidosis with type one respiratory failure (PaO2: 58 mmHg; PaCO2: 47 mmHg). She was intubated.

Upon further inquiry, she and her husband had returned from a local holiday one and half weeks prior to her presentation. She developed symptoms of a lower respiratory tract infection for which she received unknown antibiotics at her local clinic. A few days later her husband had presented with similar symptoms, collapsed and demised when emergency personnel were unable to resuscitate him.

On physical examination, Ms M had global course crackles on respiratory auscultation and an associated tachycardia. She had normal reflexes and muscle tone globally.

On laboratory investigation, it was confirmed that she was human immuno-deficiency virus negative, with severe renal dysfunction and a refractory hyperkalaemia. Her creatinine phosphokinase was 12 182 U/L. Her C-reactive protein was 491 mg/L and she had a white cell count of 37.80 × 109/L, blood urea nitrogen of 19.7 mmol/L and creatinine of 614 μmol/L. An urgent computerised tomogram (CT) of the brain and cardiac echocardiography was normal. At this point, within 24 hours of admission, she required inotropic support and was started on empiric amoxiclavulanic acid.

She was transferred to the Intensive Care Unit and continuous renal replacement therapy was commenced. She was successfully weaned off inotropes but still required ventilatory support and a macrolide antibiotic was added to her treatment.

Viral pharyngeal swabs for influenza A and B and RSV were negative as were cultures for chlamydophyllia and mycoplasma. Urine sent for the legionella antigen was positive, which was confirmed by a PCR on tracheal aspirates.

Ms M's stay in ICU was further complicated by a nosocomial multilobar pneumonia, a bacteraemia caused by Acinetobacter Baumanii and an iatrogenic right sided pneumothorax, all of which was treated appropriately. After 17 days in ICU she was discharged to the ward. Her renal function had normalised and she was comfortable on nasal prong oxygen. Ms M was discharged home within a month of admission.

2. Discussion

Legionella are gram negative, aerobic, intracellular parasites, known with several serogroups. In 90–98% of cases, *L. pneumophila* is most often involved; especially serogroup 1 [1]. Legionella causes 2–15% of community acquired pneumonia cases that require hospitalization and it is the second most common cause of serious pneumonia that needs admission in an intensive care unit [2]. A study of 392 cases of

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community acquired pneumonia revealed 12.5% due to Legionella and 20.4% of those requiring ICU admission [3]. Overall mortality associated with Legionella is 54%. Mortality associated with nosocomial and community acquired cases is 79% and 42%, respectively [4]. Legionnaires' disease (the most important or more severe form of Legionella) presents with extra-pulmonary manifestations as well, including gastrointestinal, neurological, renal and skeletal muscle abnormalities. The latter two complications in this list are the focus of this specific case and discussion.

The first report that associated Legionella and rhabdomyolysis was published in 1980 by Posner et al. [2] It is a recognized but rare cause of rhabdomyolysis [5,6]; a clinical syndrome characterized by elevated serum concentrations of creatinine phosphokinase (CPK) and myoglobinuria leading to renal dysfunction [7]. In a prospective study of 25 cases of Legionella, Kennedy et al. found that 78% of patients had elevated levels of CPK [8] (unfortunately, renal failure and the implementation of dialysis were not sampled in this study). Rhabdomyolysis is not typically caused by infectious agents, but when it is it can be caused by a variety of bacteria, with Legionella species being the most frequently cited agent. This is followed by the Streptococcus species, Francisella tularensis and the Salmonella species. Significant morbidity (57% of cases with acute renal failure) and mortality (death in 38% of cases) are associated with bacterial causes of rhabdomyolysis [9]. Table 1 highlights the most important infectious causes of rhabdomyolysis.

In patients with septicemia without direct muscle infection, muscle damage may be from associated fever, rigors, and dehydration [10,11]. The proposed mechanisms of muscle injury by bacteria include toxin generation and direct bacterial invasion. Legionella is believed to release an endotoxin or exotoxin [12,13] that causes rhabdomyolysis. Biopsy specimens that are negative for the organism [14–16] by immunofluorescence support this hypothesis. Williams et al. [17] hypothesize that the endotoxin may have a vasoconstrictive effect on small blood vessels leading to local ischemia-induced changes. A toxin has been isolated from the phenol extraction of the Legionella, but it has been shown to be biologically different from the classic endotoxin, associated with Gram-negative organisms, which causes fever and shock [13].

There are two postulates regarding the aetiology of acute kidney injury (AKI), immune and infection related. With regards to the mechanism of injury of this: the AKI could be indirectly associated with Legionella via rhabdomyolysis or directly affected by Legionella itself. Shimura et al. propose that because the pathological specimen of their patient with Legionnaire's disease showed the presence of myoglobin casts that occluded the distal tubules and immune-staining for Legionella was negative; it is firmly supported that the diagnosis is that of rhabdomyolysis-induced acute tubulo-interstitial nephritis [18]. Conversely, Shah et al. demonstrated the presence of Legionella by immunofluorescence microscopy in a renal biopsy specimen of a patient with Legionnaire's disease as well as documenting only three prior cases where this was found too [12], supporting the latter theory. There is evidence therefore, for both an immune and infective mediated mechanism for acute kidney injury in Legionnaire's disease.

The causes of AKI are, however, usually multifactorial. Hypovolemia and hypotension due to gastrointestinal fluid losses may be additional factors for its development [19]. The frequency of acute renal injury in Legionnaires' disease ranges from 13 to 15% [20,21]. From our review of the literature, the majority of the patients with renal complications of Legionella became progressively oliguric with worsening renal indices during their hospital admission, eventually requiring dialysis. In most of the cases, this was only initiated after forced diuresis and urine alkalinisation, with or without intravenous rehydration, produced a poor clinical response.

A review by Nishitarumizu et al. [22] illustrated different causes of acute kidney injury and consequent failure in Legionnaires' disease. 45 cases of acute renal failure in the context of Legionnaires' disease was reported, among whom 15 had a renal biopsy. The following results were found: tubulo-interstitial nephritis in 5, acute tubular necrosis in 6, crescentic glomerulonephritis in 1, proliferative mesangial glomerulonephritis in 1 and pyelonephritis in 2. Haemodialysis was necessary in 55.5% of these cases, and the mortality rate reached 51% (versus 15% in patients without any evidence of acute renal failure).

Table 1
Infectious causes of rhabdomyolysis.

Bacteria	*Legionella* species, *Francisella tularensis*, *Streptococcus pneumoniae*, *Salmonella* species, *Staphylococcus aureus*, Group B *Streptococcus, Streptococcus pyogenes, Listeria* species, *Vibrio* species, *Staphylococcus epidermidis, Brucella* species, *Bacillus* species, *Escherichia coli, Herbicola lathyri*, *Leptospira* species, Polymicrobes *(E. coli, Clostridium* species, *Klebsiella* species), *Borrelia burgdorferi, Clostridium perfringens,* Viridans streptococci
Viruses	Influenza virus types A and B, HIV, Coxsackie virus, Epstein-Barr virus, Echovirus, Cytomegalovirus, Adenovirus, Herpes simplex virus, Parainfluenza virus, Varicella-zoster virus
Other	*Plasmodium* species, *Candida* species, *Aspergillus* species

Since the first published case in 1980, there are a further 22 published case reports on the direct correlation between rhabdomyolysis, renal failure and Legionnaires' disease. All but two patients survived with antibiotics and dialysis; or antibiotics and intravenous rehydration if the diagnosis had been made early and before severe AKI had developed [1,2,5–7,12,19,22–34]. The association of rhabdomyolysis, renal failure and Legionella has been documented to increase the mortality of Legionnaire's disease up to 40% [12], highlighting once again the poignancy of early recognition and initiation of targeted treatment.

3. Conclusion

Legionnaire's disease and its clinical manifestations may cause multiple morbidities, including rhabdomyolysis and renal failure. Recognising this important association will lead to timely dialysis and early targeted treatment. Whilst we did not have biopsy specimens to confirm the direct cause of both these symptoms as being Legionella in our patient, blood culture results did not allude to any other aetiology. Clinicians should be cognisant of this established triad and correlation of Legionnaires' disease, renal failure and rhabdomyolysis, as failure to do so and initiate treatment early has proven to increase mortality significantly in affected patients.

Declaration of competing interest

We declare that there are no conflicts of interest with regards to our work.

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