



## Case report

## Hypertriglyceridemia and massive rhabdomyolysis in a patient with disseminated legionella

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## ABSTRACT

Legionella most commonly presents as pneumonia but can have disseminated involvement, presenting as extra-pulmonary disease involving gastrointestinal, neurological, cardiac, renal, and musculoskeletal systems, and skin and soft tissues. We present a case of a patient with pneumonia, rhabdomyolysis, renal failure, hypertriglyceridemia, pancreatitis, and cutaneous involvement. This case highlights the breath of involvement legionella can have, including the never previously documented manifestation of hypertriglyceridemia and severe rhabdomyolysis with the highest creatinine kinase recorded.

## 1. Case report

A 41-year-old African American male with no known PMH presented to our hospital with confusion and shortness of breath. On admission he was noted to have a blood pressure of 170/110, pulse of 120, respiratory rate of 26, and a pulse oxygen saturation of 98% on 100% non-rebreather. He required intubation in the emergency department for worsening respiratory and mental status, he was initially sedated with propofol. On physical examination, patient was 183 cm in height and 96.7 kg in weight with a BMI of 28. His pulmonary exam was pertinent for coarse breath sounds in right lower lung field, his neurologic exam was non-focal, he had no muscle tenderness or swelling, and skin examination did not show any rashes or lesions.

Initial laboratory findings showed a white blood cell count of  $20.3 \times 10^3$  cells/ul with 83% neutrophils and 7% bands, hemoglobin of  $13.6 \times 10^3$  cell/ul, platelet count of  $170 \times 10^3$  cells/cubic mm, sodium of 126 mmol/L, potassium of 3.5 mmol/L, chloride of 88 mmol/L, bicarbonate of 11 mmol/L, BUN of 54 mg/dL, creatinine of 7.8 mg/dL, glucose of 158 mg/dL, calcium of 5.7 mg/dL, LDH of 6910 IU/L, creatine kinase of 370,000 U/L, AST of 2290 IU/L, and ALT of 374 IU/L. Chest radiograph showed a right lower lobe airspace opacity (Fig. 1). His electrocardiogram showed sinus tachycardia with left atrial

enlargement. He was started on broad spectrum antibiotics with vancomycin, cefepime, and metronidazole and was admitted to the intensive care unit for management of acute respiratory failure secondary to pneumonia, AKI with severe metabolic acidosis and massive rhabdomyolysis.

Over the next 48 hours, his CK level continued to rise peaking at 780,000 U/L despite aggressive IV fluid replacement. His kidney function continued to decline, and he ultimately required continuous renal replacement therapy. His echocardiography showed moderate left ventricular hypertrophy with a hyperdynamic left ventricular ejection fraction. Comprehensive infectious work up, including HIV, was negative except for positive urine legionella antigen. Antibiotics were narrowed to Levaquin only for legionella pneumonia. On day 2 of admission he was noted to have hypertriglyceridemia with levels up to 1883 mg/dL. His lipase levels were noted to be elevated at 147 and his CT abdomen was concerning for early pancreatitis. Sedation was switched from propofol to midazolam. He had hyper-triglyceride induced pancreatitis that was initially managed with fluids and insulin infusion. Despite treatment, his triglyceride level continued to rise necessitating plasma exchange. After 2 sessions of plasma exchange, his triglyceride level declined. On day 5 a single 1cm superficial clean based ulcer in the left groin was identified (Fig. 2). Biopsy of the lesion (Fig. 3) revealed

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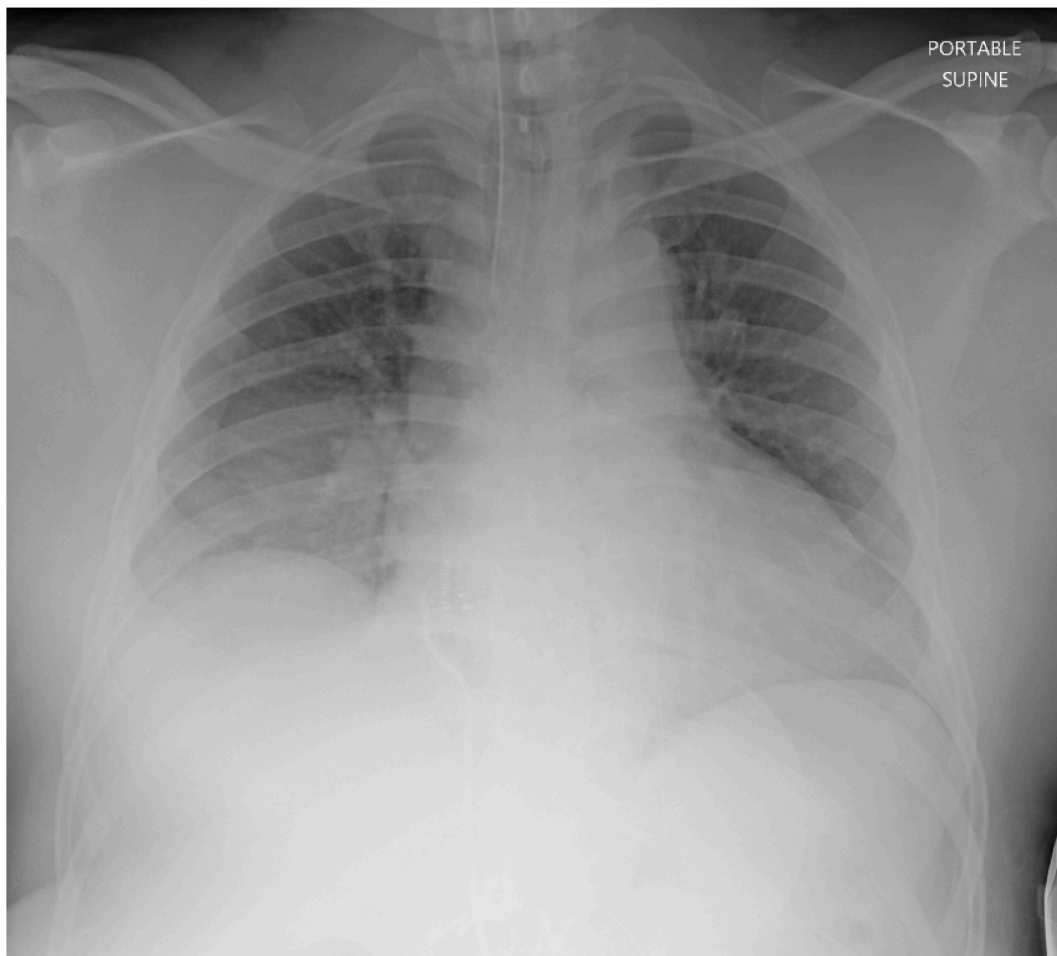


Fig. 1. CXR showing right lower lobe airspace opacity.

pseudoepitheliomatous hyperplasia with underlying dermal micro abscess favoring an underlying infectious process. Tissue stain and culture were negative for legionella or any other infectious organism.

His clinical picture started to improve thereafter with antibiotic therapy. 2 weeks after his admission, his triglyceride and lipase levels normalized at 145 and 40, respectively. His respiratory status improved to where he was able to be weaned from the ventilator. Renal function, however, was not able to recover necessitating long-term dialysis.

## 2. Discussion

*Legionella pneumophila* is an aerobic, gram-negative bacilli, and facultative intracellular bacteria [1]. *Legionella* species are typically found in the environment in bodies of water and soil. Infection in humans typically occur through inhalation of aerosols from a water or soil source [2]. Risk factors for developing this infection include impaired cell-mediated immunity, older age, smoking, and chronic lung, cardiovascular, or renal disease [3]. Our patient lacked any of these risk factors. He was an immunocompetent young man with no known medical conditions.

*Legionella pneumophila* infection most commonly presents as pneumonia, causing between 2 and 15% of community acquired pneumonia requiring hospitalization [4]. Clinical findings of gastrointestinal symptoms, hyponatremia, elevation of hepatic enzymes, and failure to respond to beta-lactam monotherapy can help indicate legionella as the etiology. Rarely, it can present as extra-pulmonary disease involving skin, soft tissues, gastrointestinal, neurologic, cardiac, renal, and musculoskeletal systems [5].

There are several case reports of extra-pulmonary manifestations of legionnaire's disease. Some of these include rhabdomyolysis [4–6], renal failure [4–6], pancreatitis [7], myocarditis [8], and meningoencephalitis [9]. The rare triad of legionella pneumonia, rhabdomyolysis and renal failure has been associated with a worse and sometimes fatal outcome [4–6]. Mortality for legionella was noted to be as high as 79% for nosocomial infections and 42% for community acquired infections [10]. Our patients' course is unique as he had multiple manifestations of disease including rhabdomyolysis with the highest CK ever reported, renal failure, hypertriglyceridemia, pancreatitis, and cutaneous lesion associated with his legionella pneumonia.

Few case reports have described rhabdomyolysis in Legionnaires' disease. The highest reported CK level in disseminated legionella cases was 165,600 U/L [11]. Our patient had a peak CK level at 780,000 U/L, indicating severe myositis. The mechanism of action of rhabdomyolysis in Legionnaires' disease is still unclear. Direct bacterial invasion into the muscle, and the release of endotoxin into the bloodstream leading to muscle damage have been postulated as possible causes [12,13]. Early, aggressive fluid repletion was used to manage this patient's massive rhabdomyolysis and associated acute kidney injury. Despite our best efforts, he went into renal failure with need for continuous renal replacement therapy and continued to need hemodialysis.

He had severe hypertriglyceridemia and associated pancreatitis for which there was no clear precipitating factor, potentially indicating legionella infection. One point to acknowledge was that he was initially sedated with propofol, which has been associated to cause hypertriglyceridemia; with higher risk when prolonged use and higher doses of propofol used. One study noted that the median dose was 50 mcg/kg/



Fig. 2. Left groin 1 cm shallow based ulcer with central clearing.

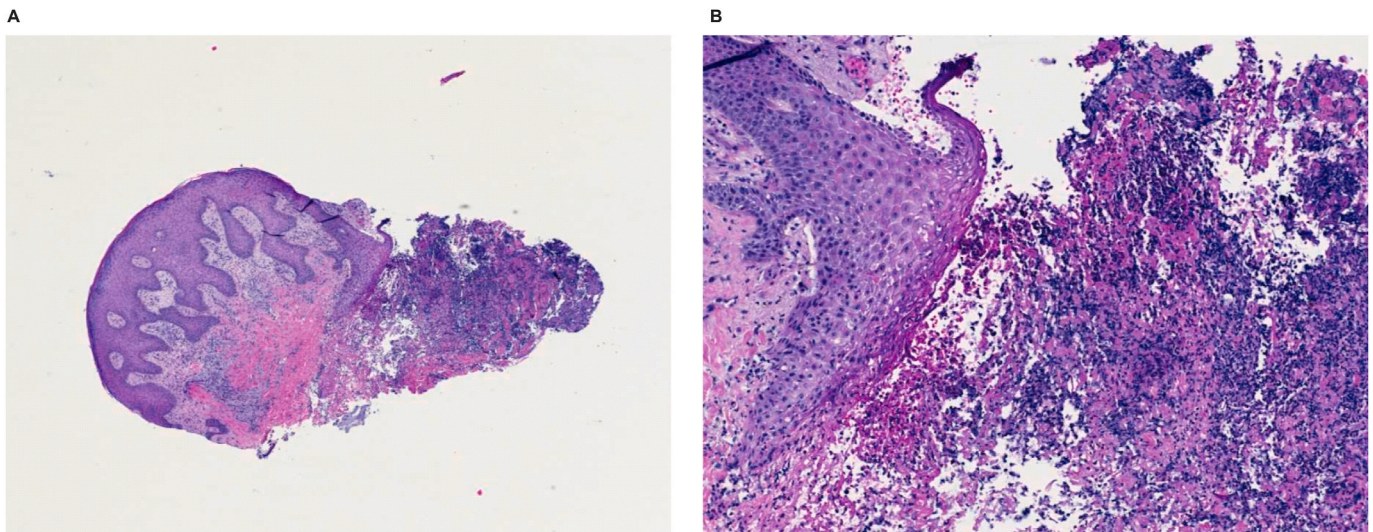


Fig. 3. a: Histopathology of left thigh ulcer. Low power image showing pseudoepitheliomatous hyperplasia of the epidermis. b: Histopathology of left thigh ulcer. High power photomicrograph reveals dermal inflammatory cells forming microabscess.

min (range of 5–110), duration was 54 hours (range 14–319), and a triglyceride level of 696 mg/dL (range 403–1737) [14]. Considering the severity of the hypertriglyceridemia (peak of 1883 mg/dL), the sedation dose of 20 mcg/kg/min, and a duration of less than 36 hours, it is unlikely for propofol to explain this finding. To our knowledge this is the first case report of hypertriglyceridemia associated with legionella infection in humans. Hamblen et al. reported elevated triglyceride levels in guinea-pigs infected with legionella pneumonia [15,16]. The high triglyceride level was thought to be due to increased rate of synthesis in the liver.

The pathogenesis of our patient pancreatitis is unclear. It is likely that he had hypertriglyceridemia induced pancreatitis however he may have had pancreatic injury secondary to legionella pancreatic cell infection, or legionella toxin release or cytokines induced inflammation. Megarbane et al. reported acute pancreatitis in three patients with legionella pneumonia, however no triglyceride level was reported in that series [7]. The management of hypertriglyceridemia and associated pancreatitis involves supportive care with intravenous fluids and insulin treatment or sometimes plasma exchange. Currently there is no consensus on first line therapy in these cases, as there are no randomized

controlled trials indicating superiority [17,18]. There are observational studies showing no difference in mortality or outcomes between the two. Insulin is typically used first due to ease of delivery and cost of therapy. However, due to our patient's lack of improvement of hypertriglyceridemia, he was treated with plasma exchange.

Skin lesions in the setting of legionnaire's disease is rare, but review of literature shows a variety of presentations [19]. His skin lesion was very similar to the cutaneous manifestations previously reported. The tissue biopsy stain and culture results did not identify any organisms including a Steiner stain specifically for spirochetes. However, the stain isn't particularly sensitive, and the pathology strongly favored an underlying infectious process nonetheless.

The recommended treatment for disseminated Legionnaires' disease is azithromycin or quinolones as monotherapy, or in combination with a beta-lactam antibiotic. The duration of treatment is unclear, but patients are typically treated for a minimum of 14 days, consistent with what our patient received.

In conclusion, legionella infections typically present as pneumonias however they may disseminate and can involve multiple organ systems. Our patient had multiple manifestations of this disease including massive rhabdomyolysis with a CK elevation never documented before, hypertriglyceridemia associated with legionella for the first time, renal failure, pancreatitis, cutaneous infection, in addition to legionella pneumonia. Our case emphasizes the fact that early recognition of the different manifestations of disseminated legionella is crucial as this condition is associated with high mortality when the triad of pneumonia, renal failure, and rhabdomyolysis is present.

#### Declaration of competing interest

All authors above indicate no conflicts of interest.

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