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CASE REPORT

Immensely High Creatine Kinase Levels in a Case of Rhabdomyolysis Due to Legionnaires' Disease in a Patient on Tofacitinib: A Case Report and Literature Review

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Abstract

A 58-year-old female patient presented with altered mental status, diarrhea, and fever. She was hospitalized for acute kidney injury [AKI] and a patchy right lower lobe infiltrates on chest X-ray. Subsequent testing revealed rhabdomyolysis and a positive urinary Legionella antigen test. Creatinine kinase [CK] level peaked at 512,820 U/L and was managed with aggressive intravenous hydration and appropriate antibiotic treatment. With clinical signs of resolution of pneumonia, the CK level declined rapidly, however renal function returned to baseline only after 2 months requiring hemodialysis in the meantime. The patient was also on tofacitinib which can rarely contribute to rhabdomyolysis. Legionella infection can cause severe rhabdomyolysis and AKI. Timely diagnosis of Legionella-associated rhabdomyolysis, and prompt treatment with aggressive IV hydration and appropriate antibiotics is required to prevent morbidity and mortality.

Keywords: Tofacitinib, Rhabdomyolysis, Legionella, Pneumonia, Legionnaires' disease, Acute renal failure

1. Introduction

Underreported and under-recognized, Legionnaires' disease can be deadly with a case fatality rate of about 10%. Each year 5000 cases of Legionnaires' disease are being reported in the United States. There are 60 different known species of Legionella, *Legionella pneumophila* serogroup 1 being the most common pathogen.[1] *Legionella pneumophila* infection can manifest as Legionnaires' disease or Pontiac fever. Legionnaires' disease is a constellation of extrapulmonary manifestations, including gastrointestinal such as nausea and diarrhea, hyponatremia, renal and skeletal muscle abnormalities with severe pneumonia requiring hospitalization and most commonly intensive care, whereas Pontiac fever is a milder, influenza-like illness that usually does not require hospitalization and intensive care.[2] Legionnaires' disease is responsible for 2–9% of community acquired pneumonia cases that require hospitalization and it is the second most common cause of pneumonia needing admission in an intensive care unit.[3] However, accurate numbers are not available because of underutilization of diagnostic testing. The first case of Legionnaires' disease was reported in 1976. The association of Legionella and rhabdomyolysis was first described in 1980,[4] after which there have been several published case reports on the direct correlation between rhabdomyolysis, renal failure and Legionnaires' disease.[5] Rhabdomyolysis is defined as a clinical syndrome with elevated serum creatine kinase [CK], exceeding 20,000–30,000 U/L and myoglobinuria leading to renal dysfunction.[6] Although the most common causes are crush injury, overexertion, alcohol abuse, it is known to be caused by infectious agents as well. Among infectious causes, Legionella species is the most common, others including Streptococcus species, *Francisella tularensis* and the Salmonella

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species. Among the cases of rhabdomyolysis with infectious etiology, 57% of cases result in acute renal failure and death occurs in 38% of cases.[7] The risk factors for Legionnaires' disease include heavy smoking, chronic alcoholism, age >50 years, diabetes, end-stage renal or pulmonary disease, and immunodeficiency.[8,9]

2. Case presentation

A 58 year old female was brought to the emergency room from home with complaints of lethargy, fever and watery, non-bloody diarrhea for 2 days. In the 48 h prior to admission, the family reported that the patient was initially confused and progressively became lethargic. She also had associated fever, with a maximum temperature of 39.4 °C at home. There was no history of loss of consciousness, shortness of breath, cough, recent travel or exposure to sick contacts. She is known to have hypertension on losartan, rheumatoid arthritis [RA] on tofacitinib 11 mg once a day orally, chronic kidney disease [CKD] stage 3A and chronic obstructive pulmonary disease not on home oxygen. She is a current smoker and has a smoking history of 20 pack-year. There is no history of alcohol or illicit drug use.

On initial examination, vital signs were a temperature of 39.4 °C, heart rate of 112 beats per minute, respiratory rate of 20 per minute, blood pressure of 127/75 mm Hg and oxygen saturation of 85% on room air which improved to 100% on 3 L nasal cannula. She was drowsy and would intermittently follow commands. She had clear breath sounds bilaterally, normal heart sounds. Abdomen was non-distended, non-tender with normal bowel sounds. When awake she was oriented to place and person but not to time, no focal neurological deficits, no neck rigidity and meningeal signs were negative. No rashes were seen upon skin examination.

Laboratory findings revealed the following white blood cells [WBC] 17,400 cells per μL with 87% neutrophils, hemoglobin 10.7 g/dL, platelet count 235,000 per μL, sodium 126 mEq/L, potassium 3.0 mEq/L, bicarbonate 19.3 mEq/L, blood urea nitrogen 32 mg/dL, creatinine 2 mg/dL (baseline creatinine 1.3 mg/dL), aspartate aminotransferase 260 Units/L and alanine aminotransferase 40 Units/L, Creatine kinase 347,700 units/liter. Hepatitis A IgM antibody, hepatitis B surface antigen, hepatitis B core IgM antibody and hepatitis C antibodies were negative. Stool studies showed no WBC in stools with normal osmolality and calprotectin. Urine, blood and stool cultures were negative. Urine legionella pneumophila serogroup 1 antigen was positive. Urinalysis showed 51–100/hpf of WBC, 6–10/hpf of red blood cells, and 3+ occult blood.

Chest X ray [Fig. 1] showed new bibasilar densities, right greater than left [Fig. 1].

Computed tomography [CT] of head showed no acute intracranial abnormality. CT of her chest, abdomen and pelvis without contrast showed patchy right basilar opacities and a small right pleural effusion [Fig. 2]. There were signs of colonic diverticulosis without evidence of diverticulitis.

On admission the patient was started on broad spectrum antibiotics, because of sepsis of unknown source. Once the urine legionella antigen became positive, antibiotics was changed to azithromycin. Despite improvement in mental status and diarrhea, her renal function and creatine kinase [CK] continued to worsen resulting in anuria and showed signs of volume overload. So she was started on hemodialysis and was transferred to the intensive care unit [ICU] due to vasopressor requirements. She remained in ICU over the next 7 days. She received a 14 day course of azithromycin as she was on immunomodulatory medication (tofacitinib), prior to admission. She was weaned off pressors, supplementary oxygen requirement and started on midodrine once her rhabdomyolysis started to resolve. After 17 days of hospital stay she was discharged with follow up hemodialysis as an outpatient. Eventually she attained complete renal recovery in 2 months.

3. Discussion

Legionnaires' disease typically presents as pneumonia clinically.[1] But our patient presented with chief complaints of confusion, fever and diarrhea, which is an atypical presentation for pneumonia. This made the diagnosis challenging, but the presence of AKI, hyponatremia, hypoxia requiring

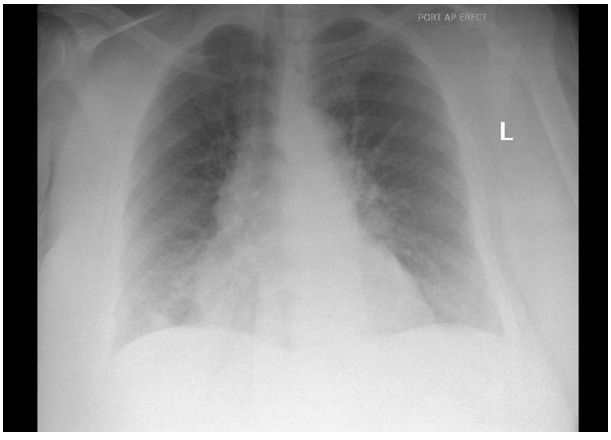

Fig. 1. Chest X ray showing bibasilar opacities.

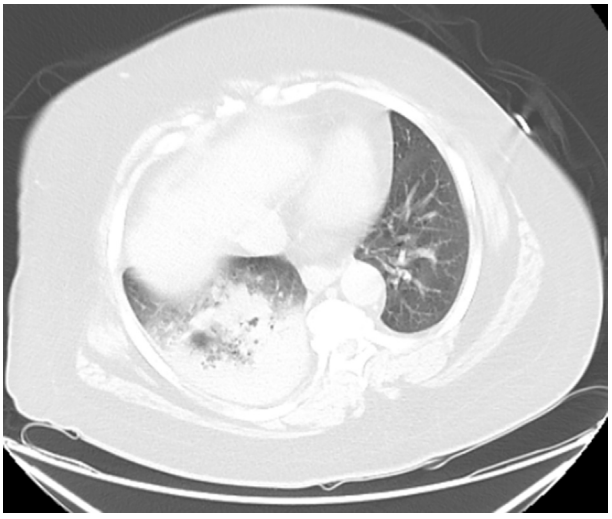

Fig. 2. CT chest showing right basilar opacities.

supplemental oxygen, elevated CK prompted further work up leading to diagnosis. The triad of pneumonia, rhabdomyolysis and acute kidney injury [AKI] has been described in Legionnaires' disease. Rhabdomyolysis and AKI continue to be rare but deadly complications of the disease and increase the mortality up to 40%.[5] There are case reports of Legionella associated rhabdomyolysis causing acute kidney injury, with many cases requiring dialysis. A PubMed MeSH search with the terms "Legionella", "rhabdomyolysis", "renal failure" and "kidney injury", yielded 30 published cases.[3–6,9–11] The etiology of rhabdomyolysis is thought to be from an endotoxin or exotoxin release from *Legionella pneumophila*.[5] There are two theories regarding the etiology of AKI; immune and infection related. Shimura et al. demonstrated the presence of myoglobin casts occluding the distal tubules and negative immune-staining for legionella firmly supporting that the etiology of AKI is because of rhabdomyolysis induced acute tubulo-interstitial nephritis.[10] Conversely, Shah et al. demonstrated the presence of Legionella by immunofluorescence microscopy in renal biopsy specimens of patients with Legionnaires' disease.[11] Up to 55.5% of these cases require hemodialysis, with the mortality rate reaching 51%. The mortality rate is 15% in patients without any evidence of acute renal failure.[12] Antibiotics and intravenous rehydration can help avoid hemodialysis if the diagnosis is made early and before severe AKI develops. Aggressive intravenous hydration with target urine output of 200–300 mL/h, is to be continued until the CK level drops below 5000 U/L.[13] However, our patient also had CKD with likely underlying hypertensive nephrosclerosis, which most likely increased her risk for AKI. Hypovolemia and hypotension from gastrointestinal fluid losses were additional factors that contributed to the AKI. She also had an exceptionally high CK (see Fig. 3), peaking at 512,820 units/L. Her urinalysis showed 3+ blood with just a few red cells, which is also consistent with AKI from rhabdomyolysis. Tofacitinib has been shown to cause reversible elevations in CK levels, the timing of which appeared idiosyncratic and did not result in rhabdomyolysis. Therefore there is currently no clear role for routine CK monitoring in patients on tofacitinib.[14] Our patients' tofacitinib was stopped on admission but her CK continued to be elevated for five days, raising suspicion for ongoing muscle injury. It was most likely from the Legionella

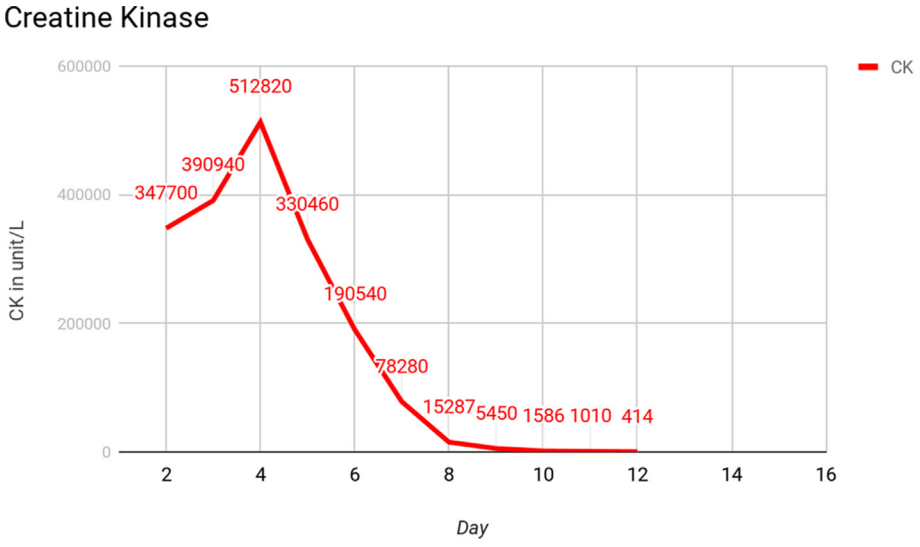

Fig. 3. Trend of Creatine kinas levels.

infection given the patient's fevers had largely resolved by hospital days four to five, corresponding well with the drop in CK, which also supports an infectious cause. Hyponatremia has consistently been described as an associated finding in Legionnaires' disease. Although the mechanism remains unclear, hyponatremia is considered an independent indicator of severity of Legionnaires' disease.[15]

Urinary detection of the *Legionella pneumophila* antigen is still used as the first line test to diagnose Legionnaires' disease due to its ease of performance and rapid results.[16] However it has poor sensitivity for non-*Legionella pneumophila* serogroup 1 strains and some false positive results are seen in patients with Pontiac fever. Real time polymerase chain reaction [PCR] of respiratory specimens is the molecular method of choice for detection of legionella. It identifies 18–30% more Legionella infections than the urine legionella antigen test.[17] The gold standard is culture and sensitivity of lower respiratory secretions, lung tissue, pleural fluid, or a normally sterile site with isolation of Legionella on media that supports growth of Legionella (Buffered Charcoal Yeast Extract agar). It can detect Legionella species and serogroups that the urinary antigen test does not. However, it is difficult to perform and can take more than 5 days to grow.[1] In our case the urine antigen testing clinched the diagnosis.

The recommended treatment for Legionnaires' disease is empiric therapy with azithromycin or quinolones as monotherapy. In most cases, therapy is initiated with azithromycin. If the patient deteriorates, a decision may be made to switch to quinolone therapy.[16] Azithromycin or quinolone are usually given in combination with a beta lactam while cultures or legionella specific tests are pending, as in our case. The optimal duration of treatment has not been determined by studies and depends on severity of illness and patient's response to therapy. In general, a minimum of 5 days of treatment is required. Severe illnesses will often require 7–10 days of therapy. Patients with complications such as lung abscess or extrapulmonary infection, will need prolonged courses. Immunocompromised patients receive a minimum of 14 days of treatment. This was the treatment chosen in our case, due to the patient being on tofacitinib. For pontiac fever, antibiotic treatment should not be prescribed. It is a self-limited illness where patients usually recover within 1 week.[1] For patients who have persistent rhabdomyolysis, a new therapy being evaluated for rhabdomyolysis is Cytosorb™. It is a detoxification system where Cytokines (10–50 kDa) are adsorbed by polymer beads within a cartridge perfused via extracorporeal circulation. It's effectiveness in removing myoglobin in vitro from saline solution and donated blood serum, has been demonstrated in 2009. However, in vivo data is missing so far.[18]

4. Conclusion

Physicians should anticipate rhabdomyolysis and check for its presence in patients with Legionnaires' disease. Timely aggressive intravenous hydration and antibiotics can prevent progression to renal failure. It is also important to note that early and judicious use of dialysis in cases complicated with rhabdomyolysis and renal failure, can prevent mortality and lead to good outcomes, as in this patient who achieved renal recovery.

Conflict of interest

No conflict of interest.

Acknowledgement

Not applicable.

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