Title

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CLINICAL VIGNETTE

Rhabdomyolysis with Central Nervous System Lesions due to Legionnaire's Disease: A Mystery Solved by Deep-Sequencing

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Case

A 54-year-old man presented to the hospital with cough, diarrhea, altered mental status, imbalance, and fever. The patient was visiting Southern California from Kentucky. He was traveling for work when his symptoms acutely started three days prior to admission. He reported mild nonproductive cough, followed by diarrhea and two days of fever and chills. He then developed dysarthria, confusion, impaired depth perception, and imbalance resulting in a mechanical ground level fall, which led to his presentation to the hospital. He was a non-smoker with occupational exposure to wooded areas across the continental US, without recent international travel but with remote travel to Southeast Asia and sub-Saharan Africa. Past medical history included hypertension, hyperlipidemia, and elevated ANA of unclear significance. His home medications were lisinopril and atorvastatin.

On admission, patient was tachycardic to the 140s and febrile with a Tmax of 40.0°C, with O_2 saturation >94% on room air. Physical exam was notable for confusion and gait instability as well as crackles in the right lung, but without focal neurologic deficits, rash or cardiac symptoms. EKG showed atrial fibrillation with rapid ventricular response. Labs on admission were notable for leukocytosis with lymphocytopenia, elevated serum creatinine, elevated transaminases, and troponinemia. Procalcitonin was elevated to 24.63 ng/mL. A lumbar puncture showed 58 red blood cells, 5 white blood cells (72% lymphocytes), glucose level of 85, and protein of 40. Urinalysis showed 3+ dipstick blood, with no microscopic hematuria. Urine toxicology was negative for routinely tested drugs and alcohol. Computed tomography (CT) scan of the chest revealed a cavitary lesion in the right middle lobe (Figure 1). A brain MRI revealed a non-enhancing lesion within the splenium of the corpus callosum with diffusion restriction and mild FLAIR signal abnormality (Figure 2). The patient was started on vancomycin and piperacillin-tazobactam on admission. Doxycycline was started on hospital day 2. On hospital day 2 a creatinine kinase was obtained and was elevated at 17,523 U/L.

Initial blood and respiratory cultures were negative for bacterial or fungal pathogens. Antibiotics were narrowed to ceftriaxone and doxycycline after blood and respiratory cultures returned negative at 48 hours. He was treated with aggressive fluid resuscitation for rhabdomyolysis. His atrial fibrillation and troponinemia quickly resolved after the first day, and his creatinine improved to a normal baseline. His mental status and functional ability progressively improved with supportive treatment and antibiotics. He continued to have persistent rhabdomyolysis with CK levels stable in the 20,000 range (Figure 3). While the initial cause of rhabdomyolysis was thought to be the mechanical fall, the persistently elevated CK was concerning for an ongoing systemic illness. He had no muscle pain or proximal weakness, and his gait improved to a normal baseline over the hospital course.

On admission, it was difficult to reconcile a single unifying diagnosis that would explain the pulmonary consolidation seen on CT scan of the chest, his persistent rhabdomyolysis, the abnormal MRI findings, and his presenting altered mental status. The initial concerns included meningitis or encephalitis, however, the cerebrospinal fluid findings were inconsistent with an infectious meningoencephalitis. Another explanation was severe sepsis from a pneumonia, including atypical pneumonias such as Legionella. However, all respiratory cultures and legionella urine antigen/cultures were negative. The patient's persistently elevated CK indicating ongoing rhabdomyolysis unresponsive to fluid resuscitation required consideration of alternate causes of continued muscle injury, including rheumatologic etiologies and statin-induced rhabdomyolysis. Given his extensive travel history and the consolidation seen on CT scan, the infectious testing was broadened to include other atypical organisms, such as region-specific endemic and other fungal diseases, viral infections, tick- and mosquito-borne pathogens, *Mycobacterium tuberculosis*, and *Leptospirosis.*

Initial testing revealed no causative organism on routine blood, urine, sputum, or cerebrospinal fluid cultures. In addition, microbiologic testing for tick and mosquito borne illnesses, *Leptospira* PCRs of the blood and urine, as well as sputum AFB smears and PCR probes for *Mycobacterium* tuberculosis were all negative. Blood smears for malaria were obtained when the patient became febrile, but no intracellular organisms were seen. To assess for Legionnaire's disease, UAT was performed using BinaxNow™ *Legionella* urine analysis card for the qualitative detection of Lp1, following the manufacturer's recommendation (Abbott, San Diego, CA). *Legionella* culture was performed on respiratory secretions on BCYE media for 3-5 days at 35°C, with the growth of the bacteria monitored per

the laboratory protocol. Plasma was submitted to Karius (Redwood City, CA) for Karius testing (KT).

On hospital day six, the KT results returned showing presence of *Legionella pneumophila* at 298 DNA molecules per microliter (MPM). The patient was switched from oral doxycycline to IV azithromycin. His CK rapidly decreased from 25,000 to 14,000 over the next 24 hours. His other symptoms had already fully resolved by this time. He was discharged on oral azithromycin, relieved to have a definitive diagnosis and treatment.

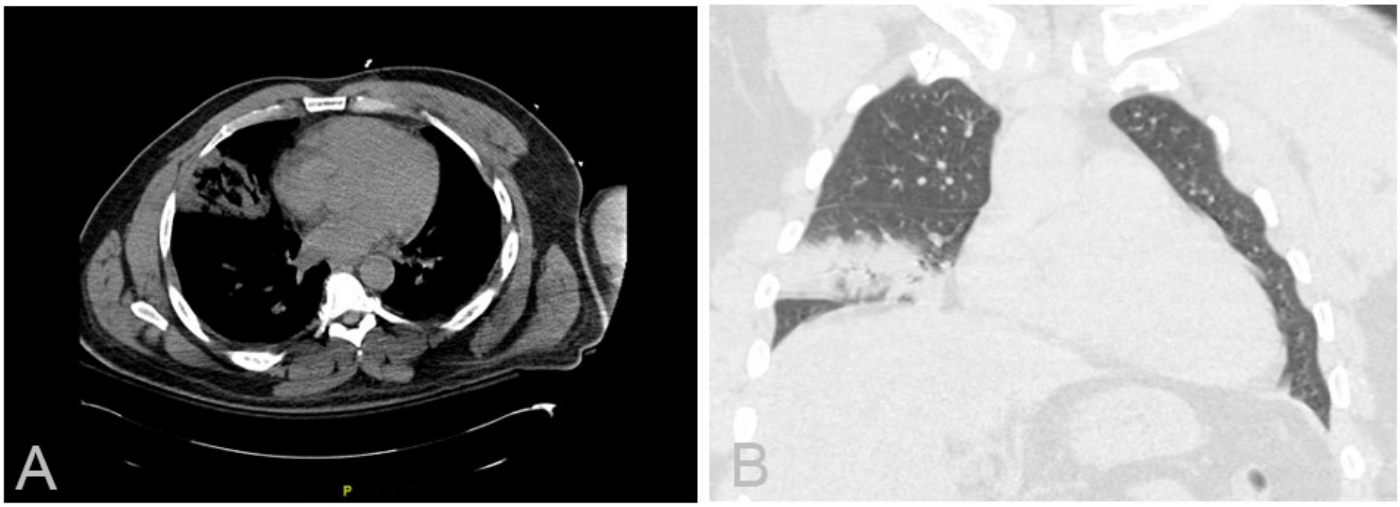

Figure 1. CT Chest imaging done on admission (A) Axial soft tissue windows demonstrating right middle lobe consolidation. (B) Sagittal lung windows demonstrating right middle lobe consolidation.

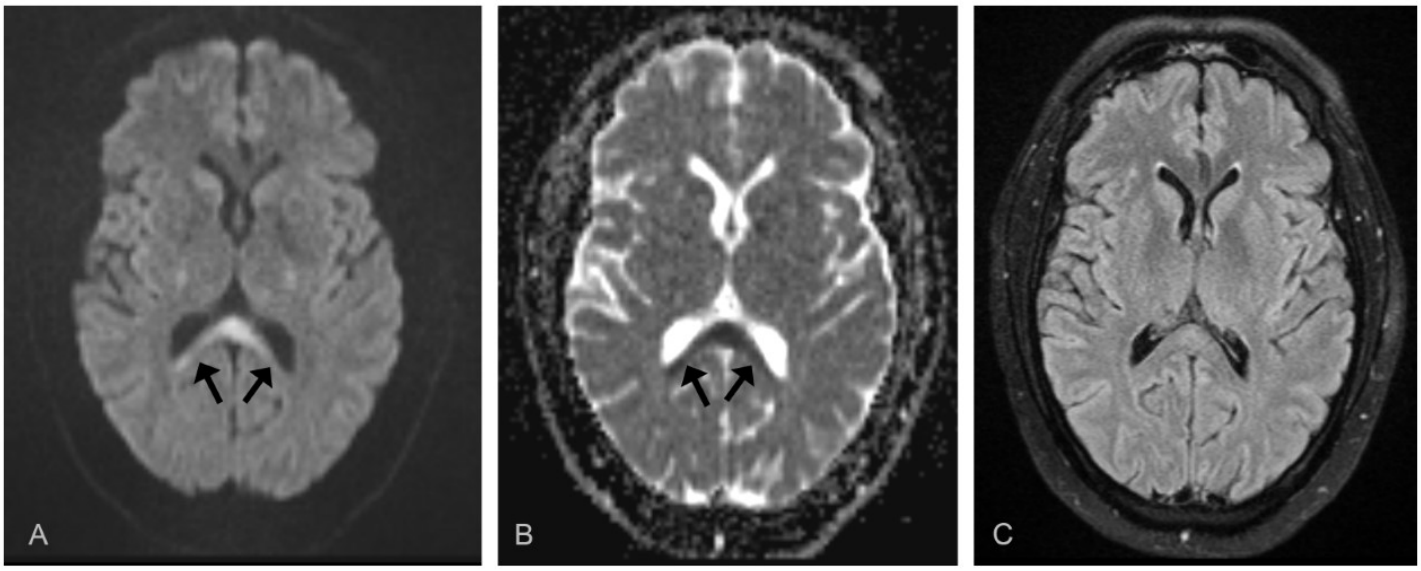

Figure 2. MRI Stroke protocol done on admission. (A) Fluid-attenuated inversion recovery (FLAIR) Imaging demonstrating symmetric, bilateral white-matter lesion in the splenium of the corpus collosum. (B) Apparent diffusion coefficient (ADC) imaging similarly demonstrating symmetric, bilateral white-matter lesion in the splenium of the corpus collosum. (C) Diffusion-weighted imaging (DWI) without any abnormal findings.

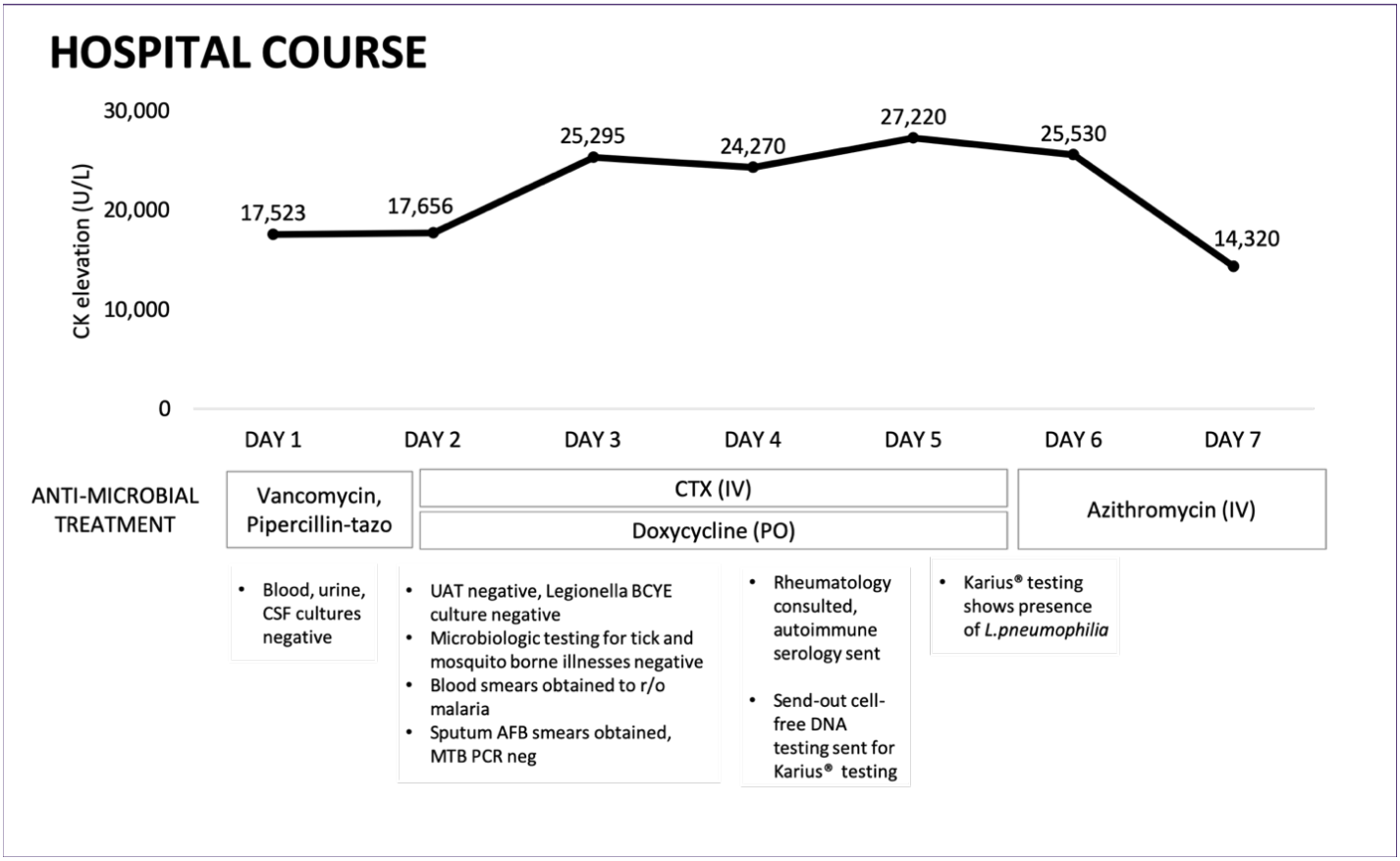

Figure 3. A visual representation of this patient's CK trend during the hospitalization as it relates number of hospital days and antimicrobial treatment.

Discussion

Infection due to *Legionella* spp presents clinically as an atypical pneumonia, but may also include other findings such as rhabdomyolysis and a characteristic neurological syndrome.[1,2] To the best of our knowledge, this is the first Legionnaire's disease (LD) case where the patient presented with both rhabdomyolysis and a characteristic neurological syndrome attributable to the LD. When the patient first presented, LD was on the differential given the consolidative pneumonia, septic presentation with high fevers, and concurrent gastrointestinal symptoms. However, when both diagnosis tests returned negative, suspicion for LD decreased. This case demonstrates the importance of having a high index of suspicion for LD in the setting of a consistent clinical picture, and adding appropriate therapies such as azithromycin to the roster of empiric treatments.

The prognosis of LD depends on the severity of the clinical presentation, the patient's immune status, and how quickly treatment is initiated. The presence of rhabdomyolysis is associated with higher mortality and morbidity, is likely secondary to subsequent renal failure.[3] Our patient rapidly improved with supportive care including fluids and antibiotics, with his acute kidney injury (AKI) resolving over days without requiring hemodialysis. However, his rhabdomyolysis persisted. Oral doxycycline that was initiated on day 2 likely played a role in his improvement, but was suboptimal to IV azithromycin for severe LD and failed to reverse the ongoing rhabdomyolysis.

While rhabdomyolysis is not commonly associated with LD, the literature includes multiple cases of Legionella pneumonia presenting with rhabdomyolysis,[4-7] which may rapidly escalate to acute renal failure requiring dialysis despite appropriate antimicrobial treatment.[8,9] It is unclear what factors protected our patient from rhabdomyolysis-induced renal failure, but the rapid recognition of muscle injury and fluid resuscitation may have played a role. The pathophysiology of Legionella-associated rhabdomyolysis has yet to be elucidated, but is suspected to involve direct bacterial invasion of myocytes, similar to the influenza virus, or release of bacterial endotoxins.[7] From previous studies, it is not clear that patients with LD experiencing rhabdomyolysis were asymptomatic as in our patient.[4-7] Recognizing rhabdomyolysis facilitates quick administration of aggressive fluid resuscitation. This case also illustrates the importance of considering non-hepatic pathology when the transaminases are elevated in isolation.

Our patient initially presented with neurologic abnormalities, including imbalance, widened gait, dysarthria and altered mental status. The MRI on admission was significant for sym-

metric lesions within the splenium of the corpus collosum. The differential for these findings is broad and includes cytotoxic insults, malignancy, infection, seizure, and metabolic derangements. However, lesions in the corpus collosum, brainstem, and basal ganglia have been reported in cases of Legionella-associated neurologic disturbances.[1] In particular, similar lesions within the splenium of the corpus collosum have been reported in two cases accompanied by similar neurologic deficits.[10,11] These MRI findings appear to improve on repeat imaging following treatment of LD. The etiology of these lesions is unclear; some appear to resemble demyelinating lesions, raising concern for an immune-mediated process such as acute disseminated encephalomyelitis. There is no evidence for direct bacterial invasion of the central nervous system. Brain biopsies on patients with *Legionella* presenting acutely with encephalitis have not demonstrated intracellular bacteria.[12] However, it is also theorized that *Legionella* could produce an endotoxin or exotoxin responsible for these lesions.

The use of UAT and culture in combination is recommended since UAT detects only Lp1, which accounts for about 84% of all cases globally, and negative results does not rule out LD.[13] Although both tests have high specificity, sensitivities can vary widely, especially for non-Lp1 species.[14-16] In our case, the negative UAT followed by negative culture lowered the initial clinical suspicion for LD. Definitive diagnosis of LD was only established when KT showed presence of *Legionella pneumophila* DNA in the patient's plasma, which prompted the switch to preferred treatment with azithromycin. KT is a commercially available metagenomic next-generation sequencing test that can identify cell-free microbial DNA from a large number (over 1,200) of pathogens. The turn-around-time is fast and in certain clinical scenarios the assay may offer higher sensitivity for pathogen detection compared to conventional diagnostics, facilitating diagnosis and targeted antimicrobial therapy with otherwise negative infectious testing.[17]

Conclusion

Prolonged unexplained rhabdomyolysis in the setting of a clinical pneumonia may indicate LD as a possible etiology of undifferentiated infectious disease**.** Similarly, LD should be considered when diagnosing an infectious syndrome accompanied by white-matter lesions and neurologic symptoms. Metagenomic next-generation sequencing can be clinically useful in an undifferentiated case of sepsis with persistent clinical manifestations after initial improvement.

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