Immune-Mediated Encephalopathy in the Setting of Legionnaires Disease: A Case Report and Review of the Literature

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Received date: 08 January 2021; Accepted date: 10 February 2021; Published date: 17 February 2021

Citation: Abdel-Rahim M, Chow J, Singhal M. Immune-Mediated Encephalopathy in the Setting of Legionnaires Disease: A Case Report and Review of the Literature. Asp Biomed Clin Case Rep. 2021 Feb 17;4(1):54-59.

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Abstract

Background: Legionnaires disease is the systemic manifestation of an infection by the gram-negative bacterium Legionella pneumophila. It most commonly presents with pneumonia, but can also cause extrapulmonary manifestations like cardiac, renal, gastrointestinal as well as neurologic symptoms like encephalopathy. It tends to occur in people who are elderly, immunocompromised and those with impaired respiratory (smokers) or cardiac (advanced heart failure) functions. The Legionella Urinary antigen is commonly used to diagnose Legionella infection. Almost half of the patients diagnosed with Legionnaires disease exhibit neurologic signs and symptoms. These neurologic abnormalities are usually not evident on neuroimaging, laboratory findings, and neuropathology.

Keywords
Legionella, Legionella pneumonia, Legionnaires disease, encephalopathy

Key Clinical Message
We present a case of Legionnaires disease in a patient with clinical features of pneumonia who was found to develop signs and symptoms of encephalopathy. Neuroimaging and lumbar puncture was negative for an identifiable cause of encephalopathy.

Introduction
Legionella is a group of gram-negative aerobic coccobacilli which can cause pneumonia through inhalation of infected aerosols and aspiration of contaminated water. Most of the cases of Legionella pneumonia are caused by Legionella pneumophila [1]. The reported incidence of Legionnaires’ disease is approximately 1.4 to 1.8 cases per 100,000 persons in the United States, Europe, and Australia [2]. A Legionella infection presents in two different forms – Legionnaires’ disease and Pontiac Fever. Pontiac Fever is a self-limiting flu like illness. Legionnaires’ disease presents as atypical pneumonia with extrapulmonary manifestations, which includes high-grade fever, neurological, gastrointestinal, and renal manifestations [3]. Gastrointestinal symptoms can be prominent and include diarrhea, nausea, and vomiting. The neurologic symptoms may include headache, lethargy, and encephalopathy. Risk factors include age over 50 years, chronic lung or cardiovascular disease, immunosuppression, smoking, traveling abroad, and being a professional driver [4].
Sputum and bronchoscopy samples are preferred to detect *Legionella*. PCR can detect clinically important legionella species and serotypes, provided that an adequate sample type can be obtained from the patient. The most common laboratory test used to diagnose a *Legionella* infection is the *Legionella* urinary antigen. *Legionella pneumophila* is an intracellular pathogen. Macrolides, quinolones, tetracyclines, and rifampin are effective in treating *legionella* due to their ability to accumulate intracellularly and be bioactive [4]. The usual duration of treatment for Legionnaires’ disease without complication is around 7-14 days [4].

Metabolic encephalopathy is a potential complication of Legionnaires disease. Direct invasion of CSF by *Legionella* has been demonstrated to be the cause of the neurologic manifestations. An endotoxin and cytotoxin produced by *Legionella* has been described as a cause of this encephalopathy [5]. Neurologic symptoms of Legionnaires disease include confusion, dysarthria, and cerebellar signs of ataxia. Up to 50% of patients with Legionnaires disease will develop neurologic symptoms; however, neuroimaging and neuropathology is predominantly normal [6]. This case report describes a 53-year-old man who had developed metabolic encephalopathy in the setting of Legionnaires disease. His metabolic encephalopathy was deemed to be most likely immune-mediated in nature.

**Case Report**

A 53-year-old male was brought to the Emergency Room by his wife for concerns of confusion and slurred speech. History was obtained from the patient’s wife. The wife reported that prior to his confusion, he complained of generalized weakness, dry cough, and diarrhea. He recently drove with a colleague to a city that was severely affected by a hurricane. The colleague also had similar but milder symptoms. The review of systems was otherwise negative. The patient’s past medical history was not significant. The patient was a former smoker and denies alcohol or illicit drug abuse. On admission, vital signs at the time of presentation were BP 154/82, HR 114, RR 26, Tmax 104 F, and saturating 94% on 2 liters oxygen via nasal cannula.

Upon physical exam, a pulmonary exam revealed rhonchi in the left lung and decreased air entry to the left lung bases. Neurological exam shows dysarthric speech, generalized weakness, ataxia, but no facial droop. On labs, arterial blood gas showed pH 7.55, pCO2 24.3, PO2 58.2, and HCO3 20.7. Complete blood count showed a white blood cell count of 14,900 with 81% segmented cells and a platelet count of 124,000. The comprehensive metabolic panel showed sodium 121, potassium 3.2, chloride 87, blood urea nitrogen 25, creatinine 1.58, glucose 113, aspartate aminotransferase (AST) 828, alanine aminotransferase (ALT) 255, and creatinine kinase 15,468. Procalcitonin was elevated at 5.3. Lactic acid was within normal limits. CRP was >190. Influenza A and B testing was negative. Initial imaging included CT head which was unremarkable for acute pathology. Chest x-ray (Fig-1) showed extensive consolidation at the left lower lobe indicating pneumonia.

The initial empiric antibiotic regimen was Vancomycin, Cefepime, and Azithromycin, but narrowed to azithromycin after a positive *Legionella* urine antigen test. Urine *Streptococcus pneumoniae* antigen was negative.

On day 3 of hospitalization, the patient was transferred to the intensive care units after requiring...
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Fig-2:
CT thorax without contrast: lung views. Figure A: Consolidation in the left middle and lower lobe with air bronchograms indicating pneumonia. Figure B: Pleural effusion visible in the left lower lobe.

Fig-3:
MRI of the brain without contrast showing no acute findings. Figure A: T2. Figure B: T1. Figure C: Diffusion weighted imaging.

intubation for worsening respiratory status. He exhibited dysarthria and altered mental status while on vancomycin, cefepime, and azithromycin. Repeat blood and urine cultures showed no growth. MRI of the brain (Fig-3) was normal and no acute abnormality was demonstrated. Lumbar puncture showed 10 WBCs with normal glucose and protein levels. CSF culture showed no growth. CSF immunology testing was negative. The patient was then started on dexamethasone for possible Immune-mediated encephalopathy due to Legionella infection.

With the steroid therapy and antibiotic regimen narrowed to Azithromycin, the patient showed remarkable improvement. He was extubated and transferred out of the intensive care unit. His labs including creatinine and abnormal liver tests showed improvement. His respiratory status also improved and he was weaned off of supplemental oxygen to room air. He completed a 14-day course of Azithromycin.

Discussion
This is a case of a 53-year-old male who was diagnosed and treated for immune-mediated encephalopathy in the setting of Legionnaires’ disease. The challenge persists as there is rarely any evidence of the infection on neuroimaging, CSF analysis, or pathology as reported by Robbins et al [7]. The most distinct and common clinical condition of Legionnaires disease is pneumonia, which presents similar clinically and radiographically to community-acquired pneumonia. Due to the rarity of Legionnaires disease and its nonspecific presentation, most patients will often initially be misdiagnosed with community-acquired pneumonia. In this case study, the patient presented with symptoms suggestive of pneumonia but several days later presented with neurological abnormalities, necessitating a re-evaluation of the diagnosis. Central nervous system abnormalities such
as confusion, obtundation, dysarthria, and cerebellar dysfunction appear to be involved in almost half of all patients with Legionnaires’ disease. It is common to test for Legionella in patients with severe pneumonia, exposure to contaminated water in large facilities, and immunodeficiencies. This case demonstrates that for patients with severe pneumonia with neurological abnormalities or failure to respond to beta-lactam monotherapy, Legionella infection should be considered and tested.

The mechanism by which Legionella is able to produce encephalopathic manifestations is unknown. Raff et al report autopsies of 183 patients with Legionnaires disease where CNS findings of 158 subjects (86.3%) were normal, unremarkable, or nonspecific [10]. Encephalitis, an inflammatory process of the brain, is a process that can potentially be a cause for neurological dysfunction but has only been one documented case of meningoencephalitis with a confirmed positive Legionella PCR derived from lumbar puncture [8]. Standard CT and MRI are often normal concerning neuroimaging findings in neurologically complicated Legionella infection [8]. Recently, there have been rare cases in which Legionnaires disease can have abnormalities on neuroimaging. Halperin JJ reported hyperdensities in the corpus callosum in a patient with Legionella infection who presented with encephalopathy [9]. Shibue et al also presented a case of Legionella pneumonia in which initial MRI revealed a corpus callosum lesion on admission [10]. All in all, neuroimaging has largely been nonspecific or unrevealing of Legionella pathology or infection. Our patient had symptoms of fever, altered mental status, dysarthria with unremarkable neuroimaging.

Neurological involvement in Legionnaires disease is unknown. Lumbar puncture, in addition to neuroimaging, is largely normal or nonspecific. Immune-mediated mechanisms of toxins may be responsible for the findings indicative of encephalopathy [11]. Molecular mimicry has also been suggested as a possible cause as one study suggests [12]. Imai et al suggested a vascular cause as an etiology to the neurological abnormalities. She reports a single-photon emission computed tomography (SPECT) of the brain demonstrating hypoperfusion to the frontal lobe and cerebellum to explain memory deficits, slurred speech, and ataxia in a patient with Legionnaires’ disease [13]. The standard neuroimaging and lumbar puncture was unrevealing for the etiology of the abnormal neurologic manifestations of our patient, which is consistent with the literature.

Since Legionella is an intracellular bacterium, it can replicate inside phagocytic cells such as macrophages and microglia and can activate inflammasome pathways [14]. Inflammasome pathways act to remove intracellular pathogens and this might be the cause of the CNS dysfunction in Legionella infections [14]. Pattern recognition receptors (PRRs) are found on host cell membranes and cytoplasms and recognize infections caused by microorganisms. The different types of PRRs including toll-like receptors (TLRs), nod-like receptors (NLRs), and RIG-I-Like receptors (RLRs) which effectively recognize L. pneumophila and trigger an immune cascade [15]. This response by the immune system may be a huge factor to the predominance of sterile findings for Legionella PCR or culture in patients with encephalopathic manifestations of Legionnaires’ disease.

Our patient presented with encephalopathy felt to be immune-mediated. He was treated mainly with azithromycin and dexamethasone. This treatment regimen is also supported in the literature [16]. Mortality for patients with Legionnaires disease ranges from 1 to 10 percent. Early diagnosis and administration of appropriate medications and antibiotic therapy is essential for improved outcomes. Prompt testing for Legionella is recommended for patients with severe pneumonia with atypical features of gastrointestinal symptoms, severe hyponatremia, failure to respond to beta-lactam monotherapy, and central nervous system involvement. In summary, a large percentage of patients with Legionnaires’ disease will present or develop CNS abnormalities. Immune-mediated mechanisms by Legionella infection may be responsible for encephalopathy in patients with Legionnaires’ disease presenting with CNS involvement. Neuroimaging is not reliable in detecting Legionella-induced CNS pathology. The patient will require a full evaluation to assess other medical
conditions that can cause encephalopathy.

**Conclusion**

We present a case of Legionnaires disease in a patient with clinical features of pneumonia who was found to develop signs and symptoms of encephalopathy. Neuroimaging and lumbar puncture was negative for an identifiable cause of encephalopathy. CNS involvement by *Legionella* may be due to immune-mediated mechanisms and thus, adjunctive corticosteroids can be considered in therapeutic management.

**Conflict of Interest**

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

**Author Contribution**

The corresponding author for this submission is Dr. Mohammed Abdel-Rahim. This manuscript was done in collaboration with the co-authors Dr. Jeffrey Chow and Dr. Mayank Singhal. The manuscript was performed equally by Dr.’s Mohammed Abdel-Rahim and Jeffrey Chow with review by Dr. Mayank Singhal.

**Ethics Approval**

Patient consent was signed by the patient allowing for publication of this case report. Ethics approval was obtained by the Campbell University School of Osteopathic Medicine as well as Cape Fear Valley Medical Center.

**Funding Information**

No funding was provided for this Case Report.

**Acknowledgments**

Campbell University School of Osteopathic Medicine and Cape Fear Valley Medical Center.

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