Case report

Legionnaire’s disease presenting with encephalitis, myoclonus, and seizures: Successful treatment with doxycycline

Burke A. Cunha,a,b,* Bertamaria Dieguez,a,b Nonso Osakwea,b

a Infectious Disease Division, NYU Winthrop Hospital, Mineola, New York, United States
b State University of New York, School of Medicine, Stony Brook, New York, United States

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ABSTRACT

Legionnaire’s disease (LD) is a non-zoonotic atypical community acquired pneumonia (CAP) with several characteristic extra-pulmonary findings. Pending diagnostic test results, selected characteristic findings when considered together are the basis of clinical syndromic diagnosis and the basis of empiric antimicrobial therapy. Of the extra-pulmonary manifestation of LD, neurologic findings are among the most common, e.g., headache, mental confusion. In LD, encephalitis is rare as are myoclonus and seizures. This is a most interesting case of LD that presented with encephalitis, myoclonus, and seizures. Pulmonary infiltrates developed early after admission. LD was suspected on the basis of otherwise unexplained characteristic findings, e.g., hypophosphatemia, elevated serum transaminases, microscopic hematuria, elevated ferritin, and empiric doxycycline therapy was started. The diagnosis of LD was further supported by prominent and persistent myoclonus and seizures, rare but characteristic neurologic findings in LD.

On week 12 of hospitalization, he finally seroconverted with negative urinary antigen tests indicating his LD was due to a non-L. pneumophila (serotype 01) strain. On doxycycline, he made a slow but complete recovery. We believe this is the first reported case of LD presenting with encephalitis, myoclonus, and seizures successfully treated with doxycycline.

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Introduction

Legionnaire’s disease (LD) most commonly presents as a non-zoonotic atypical community pneumonia (CAP) with multisystem extra-pulmonary manifestations. While no individual clinical finding is diagnostic of LD, the presence of several otherwise unexplained characteristic findings, when considered in concert, are the basis for a clinical syndromic diagnosis [1–6] (Table 1).

Of the extra-pulmonary manifestations of LD, neurologic findings are among the most common, e.g., headache, mental confusion, [7–15]. As with other non-specific findings, the diagnostic significance of neurologic abnormalities depends on the associated clinical context. Otherwise unexplained mental confusion in a patient with CAP suggests possible LD [16,17]. Clinicians should endeavor to recognize characteristic diagnostic findings, e.g., hypophosphatemia, not only those findings consistent with the diagnosis, e.g., hyponatremia [5,6]. Among the neurologic manifestations of LD, myoclonus is rare, but characteristic of LD. Therefore, in a CAP patient, otherwise unexplained myoclonus is a diagnostic clue pointing to LD as the diagnosis. Seizures are also a rare manifestation of LD [14,15]. When both myoclonus and seizures occur with CAP, LD is the most probable diagnosis. Except for LD, no other cause of CAP is accompanied by both myoclonus and seizures. If other characteristic clinical features of LD are present in a CAP patient, then the added presence of myoclonus and seizures further supports the clinical syndromic diagnosis [5,14,15].

We describe a case of LD, that presented with prominent neurologic manifestations, e.g., encephalitis, myoclonus, seizures.

Case

The patient was a 41 year old healthy male who ten days prior to admission complained of fever, and headache. He visited multiple emergency departments, but routine laboratory tests and CT scans of the chest were negative and he was discharged home. Subsequently, following a generalized seizure he was admitted to the hospital and was intubated.

Physical examination was unremarkable except for obtundation. His temperature was 101.7°F with a heart rate of 86 bpm.
Table 1
Legionnaire’s disease: Clinical Predictors and Diagnostic Eliminators in Admitted Adults with Pneumonia.*

| Clinical Predictors | Diagnostic Eliminators |
|---------------------|------------------------|
| • Fever (> 102°F) with relative bradycardia | • Fever (> 102°F) without relative bradycardia |
| • Highly elevated ESR (> 90 mm/h) or highly elevated CRP (> 35 mg/L) | • Severe myalgias |
| • Highly elevated serum ferritin levels (> 2 x normal) | • Negative chest radiograph (no infiltrates) |
| • Hypophosphatemia (on admission/early) or hyponatremia | • No relative lymphopenia |
| • Elevated CK (> 2 x normal) | • Leukopenia |
| • Microscopic hematuria (on admission) | • Thrombocytopenia |
| Legionario’s disease very likely if > 3 predictors present | Levels of ferritin minimal or not elevated |
| | Legionario’s disease very unlikely if < 3 predictors or any diagnostic eliminators present |

Adapted from: Cunha BA, Cunha CB (Ed.) Legionnaire’s disease: A Clinical Diagnostic Approach. Infectious Disease Clin North Am 2017;31:81-93.
* Otherwise unexplained. If finding is due to an existing disorder, it should not be used as a clinical predictor.

Discussion

LD was suspected on the basis of relative bradycardia, relative lymphopenia, elevated serum transaminases, hyponatremia, hypophosphatemia, elevated ferritin and microscopic hematuria and he was empirically treated with doxycycline. He remained obtunded and his myoclonus continued. Repeat EEG again showed global slowing diagnostic of encephalitis. The neurointensive care unit (NICU) staff ordered a scrotal ultrasound which showed left hydrocele and small calcifications in the right testicle. Scrotal calcifications suggested paraneoplastic disorder to the NICU staff. Paraneoplastic panel (included anti-Hu, anti Yo, anti-NMDA, NMO IgG, anti-Ma2, and anti-glutamic acid decarboxylase (GAD) 65 antibodies) was negative. Flow cytometry was normal. His PET scan was negative for malignancy. On HD #22, GAD 65 serum antibody was positive. The NICU staff interpreted the GAD 65 antibody titer as indicative of an autoimmune encephalitis (ADEM) and plasmapheresis, IVIG, and rituximab were given, but without effect. His fever resolved after 29 days. Repeat head MRI on HD #48 remained normal. Serial Legionella sp. titers and Legionella urine antigen tests remained negative. Repeat EEG on HD # 83 again showed global slowing diagnostic of encephalitis. After 12 weeks, on HD # 84, his Legionella sp. EIA titer was elevated at 1.17 (n = < 0.90) while his Legionella urine antigen remained negative indicating his Legionnaire’s disease was due to a non-L. pneumophila (serogroup 01) species. His mental confusion and myoclonus slowly resolved and he had no further seizures and was discharged.

Conclusion

This case of LD is unique in several aspects. A clinical syndromic diagnosis of LD was made early in hospital admission, but seroconversion occurred 12 weeks later [5,6]. Serial Legionella urinary antigen tests over weeks of hospitalization remained negative. It is known, but often forgotten, that titer elevations may, in some cases, occur as late as 6–12 weeks after infection. If not elevated early, most clinicians stop ordering titers. Legionella urinary antigenuria occurs early after infection, but persists for weeks/months following LD. In this case, the repeatedly negative Legionella urinary antigen tests together with an elevated Legionella sp. (serotype 01) titer at 12 weeks, indicated that the LD of this patient was due to a non-L. pneumophila (serotype 01) sp. In this clinical context, the elevated Legionella sp. titer was diagnostic of LD [2,6]. Importantly, in CAP, on the basis of neurologic findings alone, with prominent and persistent myoclonus and seizures LD is the most likely diagnosis. The elevated Legionella sp. titer was not needed to establish a clinical syndromic diagnosis, but was important in identifying the causative Legionella sp. as a non-L. pneumophila (serotype 01) species.

The NICU staff thought the diagnosis of acute disseminated encephalomyelitis (ADEM) explained the patient's neurologic findings, i.e., the testicular calcifications may have indicated a paraneoplastic syndrome [18-20]. However, the paraneoplastic panel was negative. The presence of GAD antibodies resulted in treatment of “possible ADEM,” which had no effect on his encephalitis, myoclonus, or seizures. ADEM may follow infection,
usually viral (3 reported cases following LD) usually > 2 weeks after infection. Against the diagnosis of ADEM was myoclonus which is not a feature of ADEM [18–20]. Also importantly, in ruling out ADEM were negative head MRI scans which showed no white or gray matter abnormalities which are characteristic of ADEM [16,17]. Also with ADEM, demyelination a constant feature, but was not present here [19,20]. Even though GAD antibody titer was unexplained, negative head MRI scans, lack of malignancy, timing of onset all effectively ruled out ADEM clinically.

We believe this to be the first reported case of LD due to a non-
Legionella pneumophilia (serotype 01) species presenting with encephalitis, myoclonus, and seizures. His encephalitis, myoclonus and seizures continued for months even though his pulmonary infiltrates due to LD cleared with doxycycline therapy. He gradually improved slowly and was discharged with a normal neurologic examination.

Ethical approval

n/a.

Conflict of interest

All authors have no conflict of interest

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