

# Severe Peripheral Neuropathy With Areflexic and Flaccid Quadriplegia Complicating Legionnaires' Disease in an Adult Patient

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Legionnaires' disease is an acute systemic bacterial infection that generally occurs as a severe lobar pneumonia associated with multisystemic extrapulmonary manifestations. Any species of the *Legionellaceae* family may cause this form of pneumonia in both normal and compromised hosts, but the most frequently pathogenic species is *Legionella pneumophila* that accounts for about 90% of all human infection.<sup>1,2</sup>

Ubiquitous in aquatic environments, the gram-negative *Legionella* organism is a facultative, intracellular parasite of freshwater protozoa such as the amoebae. The prevailing mode of transmission is probably by direct inhalation of aerosols that come from a water source (including air-conditioning cooling towers, water mains, showers, and swimming pools) contaminated with *Legionella* bacteria.<sup>3,4</sup>

Patients with Legionnaires' disease usually have fever, chills, systemic symptoms, and diarrhea, in association with cough that may be dry or may produce sputum. Chest x-ray generally shows a lobar pneumonia, while laboratory tests may demonstrate a concomitant renal and hepatic involvement.<sup>2–4</sup> Several neurologic manifestations are frequently observed in subjects with legionellosis and are represented by a reversible encephalopathy with headache and abnormal mentation in the majority of cases. Other neurologic ab-

normalities, including brainstem and cerebellar dysfunction or peripheral nerve involvement, are relatively infrequent and tend to persist beyond resolution of acute clinical manifestation.<sup>5–7</sup>

An exceptional case of severe peripheral neuropathy with areflexic and flaccid quadriplegia in a middle-aged woman with Legionnaires' disease is described.

## CASE REPORT

A 48-year-old Caucasian female patient, who smoked about 30 cigarettes daily, was hospitalized owing to persisting hyperpyrexia, chills, asthenia, anorexia, and dry cough for about 5 days.

Physical examination at the time of admission showed peripheral cyanosis, tachypnea, dyspnea, and a high body temperature (39°C). Pulmonary auscultation revealed a respiratory silence at the right lung basis and diffuse, bilateral rales at the upper lobes. The laboratory workout demonstrated severe hypoxia (arterial oxygen pressure, 48 mm Hg; arterial oxygen saturation, 84%), with remarkable leukocytosis and neutrophilia (white blood cell count, 25,740/mm<sup>3</sup>; absolute neutrophil count, 24,970/mm<sup>3</sup>), hyponatremia (133 mEq/L), and increased plasma levels of transaminases (alanine aminotransferase, 56 U/L), and lactic dehydrogenase (664 U/L), in association with an elevated erythrocyte sedimentation rate (67 mm/h).

Chest x-ray and contrast-enhanced computed tomographic scan disclosed bilateral, diffuse, alveolar pulmonary infiltrates, associated with moderate pleural effusion at the right lung basis (Fig. 1). Culture of urine, sputum, and bronchoalveolar lavage tested negative, while blood cultures yielded *Staphylococcus aureus*. Search of autoantibodies and serology for *Mycoplasma pneumoniae*, *Coxiella burnetii*, *Chlamydia psittaci*, *Chlamydia pneumoniae*, *L. pneumophila*, and human immunodeficiency virus (HIV) were negative.

Our patient underwent mechanical ventilation in an intensive care unit because of concomitant severe respiratory failure, while antimicrobial chemotherapy was immediately started with intravenous amoxicillin-clavulanate (2.2 g thrice daily), ciprofloxacin (500 mg twice daily), in association with methyl-prednisolone (20 mg thrice daily).

A week later, the antimicrobial regimen was changed owing to persisting hyperpyrexia and distress respiratory syndrome, and

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**FIGURE 1.** Contrast-enhanced computed tomographic scan of patient's chest showing bilateral, diffuse, alveolar pulmonary infiltrates, consistent with *L. pneumophila* pneumonia.

amoxicillin-clavulanate was replaced with intravenous imipenem (500 mg thrice daily). At the same time, urinary antigen testing (by immunoenzymatic assay) for *L. pneumophila* was requested.

Ten days after the admission, neurologic examination showed a complete flaccid quadriplegia with areflexia, while sensation was lightly reduced in hands and feet, and cranial nerves were intact. The patient was alert and oriented, speaking was unaltered, mentation appeared normal, and nuchal rigidity was not observed. Brain contrast-enhanced computed tomographic scan and electroencephalogram did not show any significant abnormality. Cerebrospinal fluid was at normal pressure and contained 2 leukocytes per  $\text{mm}^3$ , and protein (49 mg/dL) and glucose (99 mg/dL) levels proved within normal limits. Electromyography revealed a severe axonal sensory-motor polyneuropathy with diffuse denervation involving both arms and legs, and a treatment with 4 consequent plasmapheresis and daily physiotherapy were started.

Eleven days after the hospitalization, the positive result of urinary antigen testing for *L. pneumophila* was received, and prompted administration of intravenous clarithromycin (500 mg twice daily), always in association with imipenem and ciprofloxacin, for further 28 days.

The patient became afebrile 2 days after the start of last antibiotic treatment. A week later, respiratory failure regressed, and laboratory workout did not show any abnormality, except for a persisting, moderate increase of erythrocyte sedimentation rate (38 mm/h). Chest x-ray revealed a remarkable reduction of pleural effusion and pulmonary infiltrates, and mechanical ventilation was not further needed.

At the end of this 4-week antibiotic therapy, chest x-ray disclosed a complete resolution of *Legionella* pneumonia, and serologic tests for *L. pneumophila* serogroup 1 (by indirect immunofluorescent assay) became positive, with a titer of 1:512. Two months after the onset, our patient had persisting paralysis of her proximal muscles in both arms and legs, but was able to move

the digits of all her extremities, although only minimally. A new electromyography confirmed the severe sensory-motor axonal polyneuropathy, with slight signs of reinnervation. Four months after hospitalization, the patient showed a remarkable neurologic improvement and was able to move all her limbs, with the persistence of a moderate hyposthenia. Six months later, a moderate peripheral hyposthenia was also observed.

## DISCUSSION

An estimated 8000 to 18,000 people get Legionnaires' disease in the United States every year, and this infection represents 15% of nosocomial pneumonia in European countries.

Some people can be infected with the *Legionella* bacterium and have mild symptoms (such as fever, asthenia, and muscle aches, known as Pontiac fever) or a completely silent illness. Legionellosis may be diagnosed as outbreak after persons have breathed mists that come from a water source contaminated with *Legionella*, but it often occurs as a single, isolated case not associated with any recognized epidemic. The 3 commonly observed forms of legionellosis are nosocomial, community-acquired, and European hotel-acquired.<sup>2-4</sup>

People of any age may get Legionnaires' disease, but this pneumonia most often affects middle-aged and older persons, particularly cigarette smokers. In addition, patients with an impaired immune defense, especially when the deficiency involves the cell-mediated immunity (HIV infection, corticosteroid therapy, myeloma, acute or chronic lymphocytic leukemia, lymphoma), may be at increased risk. Other favoring concomitant conditions include organ transplants, solid malignancies, renal failure, alcoholism, and diabetes.<sup>3,4,8</sup>

The pathogenesis of legionellosis is largely due to the ability of *Legionella* species to invade and grow within alveolar macrophages—intracellular legionellae display a remarkable capacity to avoid endosomal and lysosomal bactericidal activities—and to establish a unique replicative phagosome. Moreover, the *Legionella* bacterium has several cell-associated and extracellular factors that may favor its pathogenicity, including flagella, fimbria, and degradative enzymes. The pulmonary histopathologic lesions of legionellosis are predominantly located in alveolar ducts and alveoli, which contain a mixture of neutrophils, macrophages, fibrin, and cellular debris.<sup>4,9</sup>

The central nervous system involvement is common during the Legionnaires' disease and is usually represented by a reversible, diffuse encephalopathy, which clinically occurs with headache, abnormal mentation (including mild confusion, delirium, hallucinations, drowsiness, or coma), memory disturbances, personality changes, or seizures. This encephalopathy is observed in about 30% to 50% of patients with Legionnaires' disease and generally tends to resolve

with the regression of acute illness.<sup>5,10,11</sup> On the other hand, encephalitis with prominent brainstem signs, cerebellar dysfunction, myelopathy, and cranial nerve paralysis are more rarely described and clinically present disturbances of gait, ataxia, tremor, dysarthria, increased muscle tone, hyperactive reflexes, neck stiffness, facial or ocular palsies, or nystagmus.<sup>12–20</sup>

Finally, peripheral nerve involvement with sensory-motor polyneuropathy, leading to hyposthenia or paralysis in both arms and legs, is exceptionally reported in association with Legionnaires' disease. These uncommon, peripheral neurologic abnormalities tend to persist beyond regression of acute clinical manifestation.<sup>21–24</sup>

The pathogenesis of neurologic complications related to legionellosis remains uncertain still today. Cerebrospinal fluid examination is usually normal, suggesting that a bacterial meningoencephalitis with a direct invasion of central nervous system by the legionellae does not occur. Other possible explanations include the action of bacterial toxins (such as the lipopolysaccharide antigen) of concurrent vasculitis, metabolic disturbances, autoimmune mechanisms, or a combination of multiple pathogenetic mechanisms.<sup>12,21,22</sup>

The most useful routine tests for diagnosis of Legionnaires' disease are urinary antigen detection and sputum or bronchoalveolar lavage culture. Urinary antigen testing is carried out by immunoenzymatic or radioimmunologic assay, may rapidly detect antigens of *L. pneumophila* serogroup 1 (which is responsible for 70% of cases of this pneumonia), and is 60% to 80% sensitive during the early phase of the infection. Culture of sputum or bronchoalveolar lavage may directly show the presence of legionellae in pathologic samples, but several days are required for growth, and its diagnostic sensitivity is lower (50%–60%).

Serological studies performed by indirect immunofluorescent assay are also helpful for diagnosis when convalescent-phase antibody titers can be compared with acute-phase ones. However, they cannot be employed for clinical decision making because of the low positive predictive value of commercially available acute-phase serologic tests and the slow antibody appearance. Therefore, failure of seroconversion is common for legionellosis, particularly when non-*pneumophila* species are involved, and seroconversion may also take much longer than 4 weeks.<sup>2,25,26</sup>

Macrolides and fluoroquinolones are currently considered the first-choice drugs for the antimicrobial treatment of persons with Legionnaires' disease. Oral erythromycin, intravenous azithromycin, and oral or intravenous levofloxacin, gatifloxacin, and moxifloxacin have been approved by the US Food and Drug Administration as first-line antimicrobial therapy for this infection.<sup>27</sup> However, clarithromycin and several other fluoroquinolones (such as ciprofloxacin and moxifloxacin) are highly active against *Legionella* bacterium and may provide an effective antibiotic

treatment. Other antimicrobial compounds (such as rifampicin, streptogramins, and ketolides) may also prove useful in the therapy for legionellosis, although they seem less active than macrolides and quinolones.<sup>27–30</sup>

To conclude, our patient represents the fifth described case, to the best of our knowledge, of Legionnaires' disease complicated by a severe polyneuropathy with paralysis of the limbs. Particularly, she is the first reported case of *Legionella* pneumonia with severe respiratory failure rapidly followed by a complete flaccid and areflexic quadriplegia. Diagnosis of legionellosis was made by urinary antigen testing and confirmed by serologic tests, while axonal polyneuropathy was demonstrated by electromyography and neurophysiological investigations.

Prolonged antimicrobial therapy for 39-day duration with ciprofloxacin and clarithromycin, associated with plasmapheresis and physical therapy, lead to a remarkable improvement of the sensory-motor neuropathy after a 4-month duration follow-up.

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