Lethal *Legionella* infection in an immunocompromised child: first reported case in the Middle East

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Legionnaires disease continues to be underreported in the Middle East — a reflection of underdiagnosis, both clinically and by laboratory investigations. We draw the attention to this unusual cause of occasionally fatal, yet severe, pneumonia by reporting an immunocompromised infant who succumbed to *Legionella pneumophila* pneumonia. The urinary test for *Legionella* antigen was positive, and this was then confirmed by a bronchoalveolar fluid culture. Moreover we have reviewed the incidence, pathophysiology, association with immunodeficiency, diagnostic tools, and treatment in this case report.

**Case**

A 13-month-old girl was admitted to our hospital with a high-grade fever and difficulty in breathing for a few hours previously. The chest radiograph (Figure 1) showed the presence of air-space disease affecting the upper zone of the right lung. The past medical history revealed a diagnosis of infantile spasm at the age of 11 months, and she had been on the ACTH therapy for the previous 6 weeks. The adverse effect of the ACTH therapy was apparent with a cushingoid appearance and high cortisol levels in the blood (7460 mmol/L). The patient was admitted to the pediatric ward with the impression of aspiration pneumonia and was started on empirical antibiotic treatment (intravenous ceftriaxone and clindamycin). Initially, the patient was normoxemic on room air; however, after 2 days of hospitalization, respiratory distress progressed with an increase in oxygen requirement. As a result of clinical deterioration, antimicrobial treatment was intensified that included intravenous vancomycin, meropenem, fluconazole, and erythromycin.

Pulmonary infections are common among patients with altered host immunity. In addition to the common bacterial, fungal, and viral infections, *Legionella* is a well-recognized causative agent. An outbreak of an unusual organism in 1976 resulted in the death of 29 participants (16%) of the annual convention of the American Legion in Philadelphia.1 About 6 months later, a new fastidious gram-negative bacillus was isolated from the pulmonary tissue of some of those who died. In recognition of the historical association with the American Legion Convention, this disease was named legionnaires disease (LD).

In retrospect, several prior unsolved outbreaks of pneumonia were soon learned to be LD, including outbreaks in the 1950s and 1960s. In addition, an unidentified organism isolated from a patient’s blood in 1947 was shown to be *Legionella bozemanii* many years later.2 Since then, the *Legionella* is a well-established etiologic agent of both community and hospital-acquired pneumonias. Currently, more than fifty species of the family Legionellaceae have been identified. *Legionella pneumophila* alone causes approximately 90% of human infections. *Legionella micdadei* and *Legionella dumoffii* are the second and third most common species to cause LD in children, respectively.3 Risk factors for LD in children following exposure include immunocompromised status, especially, corticosteroid treatment and chronic pulmonary disease. In this report, we describe a case of a 13-month-old girl who was on adrenocorticotropic hormone (ACTH) treatment for infantile spasms. She developed severe *L pneumophila* pneumonia that lead to respiratory failure, severe acute respiratory distress syndrome (ARDS), and death.
As the patient continued to deteriorate, she was transferred to the pediatric intensive care unit, where a hypoxemic respiratory failure resulted in intubation and mechanical ventilation. A bronchoalveolar lavage (BAL) effluent was clear in color, and special stains for acid-fast bacilli, fungi, and *Pneumocystis carinii* were negative, with no evidence of viral cytopathy. BAL fluid multiplex polymerase chain reaction (PCR) detected *L. pneumophila*. This was confirmed by *Legionella* culture specimens. A *Legionella* urine antigen enzyme immunoassay (EIA) test was also positive. Accordingly, her antibiotics were changed to azithromycin, rifampicin, and ciprofloxacin. The patient progressed to ARDS, and she had failure of ventilation on conventional mechanical ventilator. A high frequency oscillatory ventilation (HFOV) was initiated and nitric oxide was added. She also developed a severe hemodynamic instability that required escalating doses of dopamine and epinephrine. The patient continued to deteriorate in the form of hypoxemia and severe respiratory failure not responding to high settings of HFOV, prone positioning, and nitric oxide. Her ARDS continued to worsen (Figure 2) and eventually led to her death.

**DISCUSSION**

In adults, LD accounts for 2% to 9% of community-acquired pneumonias. The true incidence of this disease in children is unknown, as most of the infections have been reported as scattered case reports.

The environmental reservoir of *Legionella* in nature is fresh water. The growth of *Legionella* occurs more readily in warm water. Air conditioned and cooling towers continue to be the most frequently suspected sources in reported community-acquired outbreaks. Modes of transmission of *Legionella* to humans include inhalation of aerosols containing *Legionella*, and aspiration of water contaminated with the organism.

The primary host defense mechanism against *Legionella* is the cell-mediated immunity. Similar to other intracellular pathogens, depression of cell-mediated immunity by glucocorticoids and immunosuppressive drugs poses a high risk for infection by interfering with T cells and macrophage functions. Glucocorticoids have known suppressive effects on the immune system. They alter the population of circulating leukocytes and decrease the number of lymphocytes and monocytes. In addition to affecting cell numbers, steroids also reduce cellular functions. Glucocorticoids inhibit the system of multiple cytokines including interferon gamma and interleukin-2 that may lead to subsequent inhibition of activation and proliferation of T lymphocytes. Thus, the use of glucocorticoids has long been suspected to predispose patients to unusual infections.

Many case reports in the published studies addressed the link between glucocorticoid therapy and *Legionella* pneumonia. Garcia et al., in 2004, reported a fatal case of *Legionella* pneumonia in a case of systemic lupus erythematosus treated with steroids. Abernathy-Carver et al described two cases of *Legionella* pneumonia (L pneumohilia and L micdadei) occurring in children with bronchial asthma receiving high-dose systemic steroids. The only similar case to that of ours was described by Le Francois et al, in 1989, when they reported a case of infantile spasms in an infant aged 8 months who was treated with ACTH for 4 weeks and then died because of severe *L. pneumohilia* pneumonia.

Isolation of *Legionella* species by culture is considered the gold standard for the diagnosis of LD with a
specificity of 100%. Recently, there has been a significant increase in the proportion of cases diagnosed by the urinary antigen test. The test format is an EIA. It is only specific for \textit{L. pneumophila} serogroup 1, which causes the vast majority of LD cases from the community. The average sensitivity of this test is in the range of 70% to 80%.

Deoxyribonucleic acid (DNA) amplification by PCR using swab specimens, BAL, urine, and serum enables the specific amplification of minute amounts of \textit{Legionella} DNA and can provide results within a short time frame. It also has the potential to detect infections caused by any \textit{Legionella} species and serogroups.

The effective treatment of LD is based, in part, on the intracellular concentration of antibiotics. Erythromycin, with or without rifampicin, was considered an effective therapy many years ago. Azithromycin, clarithromycin, and the quinolones have replaced erythromycin as a therapy for patients with LD. Usually, 7 to 14 days of therapy is sufficient to cure most patients. However, the therapy duration may need to be considerably longer for patients with lung abscesses, empyema, endocarditis, or extrathoracic infection.

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