Case Report

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Legionnaires' disease in immunocompromised patients: a case report of *Legionella longbeachae* pneumonia and review of the literature

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In addition to *Legionella pneumophila*, about 20 *Legionella* species have been documented as human pathogens. The majority of infections by non-*pneumophila* *Legionella* species occur in immunocompromised and splenectomized patients. Here, we report a case of 'classical' lobar pneumonia caused by *Legionella longbeachae* in a splenectomized patient receiving corticosteroids for chronic immune thrombocytopenia. Tests for *Legionella* antigen were negative. *L. longbeachae* was immediately detected in bronchoalveolar fluid by PCR and subsequently confirmed by culture on legionella-selective media. The features of Legionnaires' disease in immunocompromised patients with special emphasis on significance and detection of non-*pneumophila* species are reviewed.

Introduction

Legionella is consistently reported among the most commonly identified pathogens in community- and hospital-acquired pneumonia (Stout & Yu, 1997). About 20 different pathogenic species have been reported, with *Legionella pneumophila* accounting for more than 80% of human infections. The most commonly isolated non-*pneumophila* *Legionella* spp. are *Legionella longbeachae* (3.2%), *Legionella bozemanii* (2.4%), *Legionella micdadei*, *Legionella dumoffii* and *Legionella feeleii* (2.2% combined) (Yu *et al.*, 2002). *L. longbeachae* is far more common in Australia (30.4%), where infection has been associated with exposure to potting mixes (Yu *et al.*, 2002; O'Connor *et al.*, 2007).

Legionnaires' disease can be acquired by the inhalation of contaminated aerosols or by microaspiration of contaminated water (Stout & Yu, 1997). Domestic aquatic reservoirs have been described as a source both in nosocomial and community-acquired infections (Pedro-Botet *et al.*, 2002).

The clinical features of pneumonia caused by *Legionella* spp. are diverse. Early symptoms include fever, malaise, myalgia, anorexia and headache. Cough is only slightly productive. During the course of illness, fever exceeding 40 °C, stupor, and respiratory and even multiorgan failure may develop. Elevation of creatinine kinase and diarrhoea have been reported as disease-specific symptoms for legionellosis in a comparative study (Sopena *et al.*, 1998).

The incidence of community-acquired pneumonia caused by *Legionella* is probably underestimated as many species

and serogroups are not properly detected by commercially available tests (Roig & Rello, 2003). This issue is of importance as patients with community-acquired legionellosis are more likely to require admission to the hospital and the intensive care unit compared to patients with pneumonia of other causes (Sopena *et al.*, 1998).

Legionnaires' disease has been historically referred to as 'atypical' pneumonia, based on its clinical presentation and the notion that chest radiographic findings are neither lobar nor consolidating, as seen in the 'classical' pyogenic pneumonia (Tan *et al.*, 2000). We report the case of a patient with unilateral lobar cavitating pneumonia in which *L. longbeachae* was the only aetiological agent. In addition, we summarize the special features of Legionnaires' disease in immunocompromised patients.

Case report

A 69-year-old man presented to the emergency room in October 2006 with complaints of dyspnoea on effort, somnolence, a non-productive cough, fever and night sweats. History was significant for chronic idiopathic thrombocytopenic purpura for which he underwent splenectomy in 2002 and relapsed thereafter. Three weeks prior to admission, he experienced fatigue and a new episode of severe thrombocytopenia, for which he had received dexamethasone at a dose of 40 mg per day for 3 days.

On admission, his temperature was 39.4 °C, heart rate was 117 beats min⁻¹, blood pressure was 115/72 mmHg and respiratory rate was 26 min⁻¹. Physical examination

Abbreviation: BAL, bronchoalveolar lavage.

revealed fine crackles and marked dullness of the right middle lobe. Petechiae and multiple ecchymoses were present on the lower extremities, trunk and oral mucosa.

Laboratory testing was remarkable for leukocytosis (13.4 nl^{-1}), thrombocytopenia (3 nl^{-1}) and elevated C-reactive protein (CRP, 392 mg l^{-1} , normal $<5 \text{ mg l}^{-1}$). Hepatic, pancreatic and renal parameters as well as urinalysis were normal. Capillary blood gas analysis confirmed moderate hypoxia and respiratory alkalosis due to hyperventilation (pO_2 66 mmHg, pCO_2 26 mmHg, pH 7.51, HCO_3 21.1 mmol l^{-1}).

Chest radiograph and computed tomography revealed a distinct confluent infiltration of the right middle lobe including two small cavitations. Pleural effusions were absent. Bronchial obstruction or external compression could be excluded (Fig. 1).

Microbiology

Gram and acid-fast stains of bronchoalveolar lavage (BAL) fluid were negative. A *Legionella*-genus specific PCR detected *L. longbeachae* DNA in the BAL fluid within 18 h [nucleic acids extracted from an equivalent of 25 μl BAL fluid (QIAamp DNA Mini kit; Qiagen) were used in a PCR (40 cycles with primers U24 (5'-CGC CTT CGC CAC TGG TGT TGT T-3') and L65 (5'-AAC GCG TAG GAA TAT GCC TT AGA-3'))]. Identification was enabled by sequence determination of the amplified 16S rDNA fragment (capillary electrophoresis GeneticAnalyser; Applied Biosystems).

Colonies typical for *Legionella* grew on a *Legionella* medium (*Legionella*-BCYE; Becton Dickinson) after several days of incubation, and were identified as *L. longbeachae* by partial sequencing of the 16S rRNA gene (Bottger, 1989). *Legionella* urine antigen enzyme immunoassay (Biotest) tested negative. Cultures for other bacteria (including mycobacteria), fungi and respiratory viruses were negative. All blood cultures remained negative. On the basis of these results, we made a definitive diagnosis of *L. longbeachae* pneumonia.

Management and clinical course

During initial antibiotic therapy with intravenous piperacillin/tazobactam for 24 h, the clinical symptoms worsened markedly. Identification of *L. longbeachae* in BAL fluid prompted a change of antibiotic therapy to intravenous moxifloxacin. The patient recovered quickly and was switched to oral moxifloxacin for a total of 12 days. Thrombocytopenia markedly improved as the patient recovered.

Discussion

In the case reported here, a clinical presentation with high fever, markedly elevated CRP and the radiographic presentation of cavitating pneumonia in a splenectomized patient was suggestive of classical pneumonia caused by

Fig. 1. (a, b) Chest radiograph on admission showing airspace consolidation of the right middle lobe. (c) Chest-CT additionally revealed two small cavitations ($\sim 10 \times 10 \text{ mm}$, black arrows) and excluded bronchial obstruction or external compression. Pleural effusions were absent.

Streptococcus pneumoniae. In contrast, Legionnaires' disease has been historically referred to as 'atypical'

pneumonia based on its clinical presentation and the long-held belief that chest radiographic findings are neither lobar nor consolidating (Tan *et al.*, 2000). Three-quarters of patients with *L. pneumophila* pneumonia present with an abnormal chest X-ray. Patchy pneumonic infiltrates, predominantly of the lower lobes, but also circumscribed or even lobar consolidations are observed. Cavitations are rather uncommon (Tan *et al.*, 2000). No study has addressed the radiographic manifestations of legionellosis in the immunocompromised host, but cavitations are probably more common than in immunocompetent patients (Di Stefano *et al.*, 2007; Muder *et al.*, 1987; Tan *et al.*, 2000; Fraser *et al.*, 2004; Dowling *et al.*, 1983; Senecal *et al.*, 1987). In conclusion, *Legionella* spp., like other causes of 'atypical' pneumonia, cannot be confirmed or excluded by distinct radiographic patterns.

Clinical practice guidelines recommend testing for *Legionella* in selected patients, including seriously ill patients without an alternative diagnosis, older and immunocompromised patients, as well as patients non-responsive to beta-lactam antibiotics (British Thoracic Society Standards of Care Committee, 2001; Mandell *et al.*, 2007). *Legionella* spp. do not grow on standard microbiology media, and are usually not detected by blood culture or Gram stain or culture of sputum. Culture isolation from BAL fluid is considered the gold standard of diagnosis, but may not always be helpful for the clinician because it takes 4–10 days. Moreover, currently available selective media are probably suboptimal for the isolation of non-*pneumophila* *Legionella* spp. (Muder & Yu, 2002). The availability of tests for *Legionella* antigen in the urine resulted in a decreasing use of cultures and serological studies (Benin *et al.*, 2002). The major drawback is that urinary antigen tests are virtually limited to *L. pneumophila* (Roig & Rello, 2003). Due to the shortcomings of culture and urinary antigen tests, PCR appears to be a promising tool for the simultaneous, rapid and reliable detection of many different *Legionella* species. Most of the commercially available assays target species-specific regions within the 16S and 5S rRNA genes and in the macrophage inhibitor potentiator (*mip*) gene. PCR techniques using ribosomal genes as target have the potential to provide a rapid diagnosis of several *Legionella* spp. with the use of readily obtainable respiratory tract specimens (Bencini *et al.*, 2007; Diederer *et al.*, 2006).

Numerous case reports suggest a higher rate of non-*pneumophila* *Legionella* spp. among immunocompromised and splenectomized patients than in immunocompetent hosts (Jaeger *et al.*, 1988; Jernigan *et al.*, 1994; Korman *et al.*, 1998; McClelland *et al.*, 2004; Schwebke *et al.*, 1990; Wilkinson *et al.*, 1987; Fang *et al.*, 1990; Garcia *et al.*, 2004; Lang *et al.*, 1990; Radaelli *et al.*, 1991; Singh *et al.*, 2002). *L. longbeachae* was first described as a cause of pneumonia in two Californian patients (McKinney *et al.*, 1981). Since then, only nine cases have been reported outside Australia. Interestingly, three of those patients were splenectomized (Gorelik *et al.*, 2004; Lang *et al.*, 1990), and three others

received immunosuppressive drugs because of systemic lupus erythematosus (Garcia *et al.*, 2004; McClelland *et al.*, 2004) or heart transplantation (Korman *et al.*, 1998).

The primary host defence mechanism against *Legionella* is cell-mediated immunity, similar to other intracellular pathogens. Depression of cell-mediated immunity by glucocorticoids and immunosuppressive drugs may predispose the host to Legionnaires' disease (Schlossberg & Bonoan, 1998). Transplant recipients carry the highest risk (Singh *et al.*, 2002). Corticosteroids and disorders associated with immunosuppression, e.g. cancer, are independent risk factors (Poupard *et al.*, 2007). Hairy cell leukaemia also increases the risk of *Legionella* infection because of monocyte deficiency and dysfunction (Fang *et al.*, 1990; Radaelli *et al.*, 1991). In contrast, the incidence of Legionnaires' disease is not higher in neutropenia, acute leukaemia and HIV infection (Schlossberg & Bonoan, 1998).

Loss of the spleen due to splenectomy, spleen irradiation, infarction or sickle cell disease increases the risk of infection with *S. pneumoniae*, *Streptococcus meningitidis* and *Haemophilus influenzae*. An increased risk of legionellosis has not been recognized. However, there is a striking coincidence of splenectomy and infections with non-*pneumophila* *Legionella* spp., as reported here and in previous reports by Gorelik *et al.* (2004) and Lang *et al.* (1990). The spleen, by delivery of antigen, regulation of lymphocyte traffic, opsonization, phagocytosis and as a site of lymphocyte priming, plays an important role during any bacterial infection. Accumulating reports of infection with non-*pneumophila* spp. in splenectomized patients suggest that spleen-related factors might be especially important in the defence against these species.

Different *Legionella* species must be considered as causal agents of pneumonia in immunocompromised hosts, even if radiographic appearance suggests pneumococcal pneumonia. Antigen assays and serology can fail to detect non-*pneumophila* *Legionella* species. PCR testing of BAL fluid should be considered in high-risk patients.

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