Two Cases of Acute Respiratory Distress Syndrome with High Values of Chlamyophila pneumoniae-Specific Antibodies

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Abstract

We herein report two cases of acute respiratory distress syndrome (ARDS) with high values of Chlamydia pneumoniae-specific antibodies. In the first case (a 65-year-old man), high levels of anti-C. pneumoniae antibodies (IgG and IgA) were detected on admission, and the anti-C. pneumoniae IgA level rose by Day 30. The patient was successfully treated with quinolone and steroids. In the second case (an 85-year-old man), abnormally high levels of anti-C. pneumoniae IgM were detected on admission. The patient did not recover, despite receiving treatment with several antibiotics and anti-inflammatory agents. Neither of the patients displayed other pathogen-specific antigens or antibodies. Chlamydophila pneumonia is usually mild, although it can cause severe interstitial pneumonia and ARDS in reinfected patients and the elderly.

Key words: Chlamydia pneumoniae, pneumonia, ARDS

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Introduction

Chlamydia pneumoniae is now recognized to be a common source of respiratory infection (1-3). Diagnosing C. pneumoniae infection is often difficult because antibody assays are the only effective diagnostic methods (1, 2, 4). In Japan, ELISA-based detection of C. pneumoniae-specific immunoglobulin A, G and M antibodies (Ab-IgA, Ab-IgG and Ab-IgM) is generally used to identify this pathogen (5, 6). Pneumonia caused by C. pneumoniae usually has a prolonged but mild clinical course (1-3). We herein report two cases of severe interstitial pneumonia with high levels of C. pneumoniae-specific antibodies.

Case Reports

Case 1

The patient was a 65-year-old man with hypertension and hyperlipidemia who did not suffer from any other chronic diseases. He presented with fever and chills, followed by a severe cough and shortness of breath on the 5th day before hospitalization on our unit. At the time of the clinic visit, he was already in hypoxia; a chest X-ray showed diffuse infiltration. He was referred to our hospital and immediately transferred to the ICU due to acute respiratory distress syndrome (ARDS). The physical findings were as follows: body temperature, 39.0°C; blood pressure, 140/84 mmHg; heart rate, 113 beats/min; respiratory rate, 40 breaths/min; oxygen saturation, 78% on 100% oxygen; fine crackles in all lung zones on both sides. The leukocyte count was 22,720/mm³. The blood chemistry analysis data were within the normal limits, with the exception of the levels of lactate dehydrogenase (512 IU/L), alkaline phosphatase (493 IU/L) and C-reactive protein (19.13 mg/dL). The results of an arterial gas analysis performed on 100% oxygen were as follows: pH=7.459, pO₂=45.9 mmHg, pCO₂=30.7 mmHg, HCO₃=21.5 mmol/L. A chest X-ray and computed tomography (CT) scan of the chest showed bilateral diffuse consolidation and...
ground glass opacity (Fig. 1A). Other pertinent laboratory tests provided negative results, including blood cultures, sputum cultures (including acid-fast bacilli), the procalcitonin level and urinary Legionella pneumophila and Streptococcus pneumoniae antigens. Autoantibodies were negative, except for antinuclear antibodies, which were positive at a titer of 1:80. A cytological examination of the bronchoalveolar lavage (BAL) fluid revealed the presence of multiple neutrophils and lymphocytes, consistent with a diagnosis of ARDS. Culturing of the BAL fluid was negative.

The patient was placed on a mechanical ventilator due to ARDS of an unknown cause. He was treated with ceftriaxone sodium (2.0 g/day) and pazufloxacin mesilate (1,000 mg/day) antibiotics, and methylprednisolone pulse and sivelestat sodium (2.0 g/day) and pazufloxacin mesilate (1,000 mg/day) antibiotics, and methylprednisolone pulse and sivelestat sodium were administered for the ARDS (Fig. 2A). Acute-phase serum samples (obtained on the 10th day of hospitalization) showed the following values for HITAZYME C. pneumoniae-specific antibodies: Ab-IgM=1.35 index (ID); Ab-IgG=2.45 ID; and Ab-IgA=1.82 ID. The values of anti-Mycoplasma pneumoniae and anti-C. psittaci antibodies were negative. These results strongly suggested infection with C. pneumoniae. Therefore, the ceftriaxone sodium was discontinued, and pazufloxacin mesilate was administered as the sole antibiotic. Approximately 30 days after admission, the serum samples showed that the values of anti-C. pneumoniae antibodies were 1.21 ID (Ab-IgM), 2.64 ID (Ab-IgG) and 3.45 ID (Ab-IgA), that is, the Ab-IgA value had risen by 1.63 ID (Fig. 3). The patient’s respiratory condition subsequently improved (as shown on an X-ray and CT scan in Fig. 1B), and he was discharged from the hospital.

**Case 2**

The patient, an 85-year-old man, who was largely bedridden as a result of the sequelae of a cerebral infarction and ischemic heart disease, although he was still able to feed himself. Approximately one week before admission, he developed a common cold-like illness with shortness of breath and loss of appetite. His respiratory condition worsened, and he was referred to our hospital and immediately transferred to the ICU due to ARDS. The physical findings on admission were as follows: body temperature, 37.0°C; blood pressure, 131/83 mmHg; heart rate, 80 beats/min; respiratory rate, 23 breaths/min; oxygen saturation, 78% on room air; coarse crackles in all lung zones on both sides. The leukocyte count was 7,690/mm³. The blood chemistry analysis data were within the normal limits, except for the levels of lactate dehydrogenase (437 IU/L) and C-reactive protein (19.31 mg/dL). The results of an arterial gas analysis performed on 100% oxygen were as follows: pH=7.428, pO₂=105 mmHg, pCO₂=31 mmHg, HCO₃⁻=20.1 mmol/L. A chest X-ray and CT scan of the chest showed diffuse consolidation, primarily over the right lung field (Fig. 4). Other pertinent laboratory tests provided negative results, including blood cultures, sputum cultures (including acid-fast bacilli), urinary cultures and urinary L. pneumophila and S. pneu-
The patient was administered tazobactam sodium/piperacillin sodium (13.5 g/day) and azithromycin (500 mg/day) antibiotics. Methylprednisolone pulse, sivelestat sodium and direct hemoperfusion using a polymyxin B immobilized fiber column (PMX-DHP) were used to treat the ARDS. The BAL fluid revealed the presence of multiple neutrophils and lymphocytes.

(niae) antigens. All autoantibodies were negative. Culturing of BAL fluid was negative. A cytological examination of the BAL fluid revealed the presence of multiple neutrophils and lymphocytes.

Figure 2. Clinical courses of the two cases. The ratio of \(\text{PaO}_2\) to \(\text{FiO}_2\) (denoted as \(P/F\); left y-axis) and the level of CRP (mg/dL; right y-axis) are plotted as a function of the number of days after admission (x-axis). A and B show the clinical courses of cases 1 and 2, respectively. mPSL: methylprednisolone, PSL: prednisolone, PMX: direct hemoperfusion using a polymyxin B immobilized fiber column (PMX-DHP); CTRX: ceftriaxone, PZFX: pefacoxfacin mesilate, AZM: azithromycin, TAZ/PIPC: tazobactam sodium/piperacillin sodium, LVFX: levofloxacin, Mino: minocycline hydrochloride.
patient’s respiratory condition worsened (Fig. 2B), and the antibiotic treatment was changed to levofloxacin (500 mg/day). Serum samples obtained on the 7th day of hospitalization showed the values of C. pneumoniae-specific antibodies to be as follows: Ab-IgM=2.91 ID; Ab-IgG=1.46 ID; and Ab-IgA=0.88 ID. Subsequent serum samples obtained on the 18th day of hospitalization revealed an Ab-IgM level of 2.09 ID and an Ab-IgG level of 1.68 ID. These results strongly suggested infection with C. pneumoniae. Inflammatory data (such as the CRP level) demonstrated a remarkable recovery, presumably due to the administration of levofloxacin. However, the patient’s respiratory condition did not improve, and the fibrin deposits in the lungs progressed. Ultimately, the patient died due to respiratory failure.

**Discussion**

C. pneumoniae is the third species of human disease-causing Chlamydia (Chlamydiophila). This species corresponds to approximately 5-10% of the pathogens identified in cases of community-acquired pneumonia (1-3). However, a laboratory diagnosis of C. pneumoniae infection is difficult to obtain (2, 4). This fastidious pathogen grows poorly on cell cultures, antigen detection methods exhibit low sensitivity and nucleic acid amplification techniques are not widely available or standardized (2, 4). The only sensitive and specific method for detecting this bacterium is assays for C. pneumoniae-specific IgG, IgA and IgM antibodies. Notably, antibody detection also allows the clinician to discriminate between primary infection, reinfection and past exposure (4-6).

In Japan, the ELISA-based detection of C. pneumoniae-specific immunoglobulin G, A and M antibodies (Ab-IgG, Ab-IgA and Ab-IgM) is generally used to identify this pathogen (5, 6). In the HITAZYME assay, C. pneumoniae infection is strongly suggested by a value of>3.0 ID for C. pneumoniae Ab-IgG or Ab-IgA in a single serum sample (6). A diagnosis of current infection is defined by a rise of at least 1.35 ID in the Ab-IgG level or 1.0 ID in the Ab-IgA level upon comparison of pairs of serum samples (6). However, since the levels of C. pneumoniae-specific IgG and IgA do not increase during the early stages of infection, making an early diagnosis of primary infection with C. pneumoniae is difficult (2, 5, 6). More recently, it has become possible to identify early-stage infections (before the rise of the IgG and IgA levels) based on the detection of C. pneumoniae-specific Ab-IgM. Specifically, the diagnosis of current infection is defined as an anti-C. pneumoniae Ab-IgM level of >2.0 ID in a single serum sample (5). Many people exposed to C. pneumoniae are not symptomatic. Indeed, approximately 70% of otherwise asymptomatic elderly individuals are antibody-positive (1, 2), and false-positive results have been reported (5-7). Therefore, it is difficult to diagnose C. pneumoniae infection solely on the basis of antibody tests, and the diagnosis typically requires the exclusion of other diseases.

Continuously high values of C. pneumoniae-specific Ab-IgA imply a continuous infection with C. pneumoniae (8). In case 1, the level of C. pneumoniae-specific Ab-IgA exceeded the diagnostic threshold (>3.0 ID) 30 days after admission. The Ab-IgA level subsequently exhibited a slow decrease along with a complementary slow rise in the level of C. pneumoniae-specific Ab-IgG by the fourth month. The initial level of C. pneumoniae-specific Ab-IgA and subsequent slow rise of the level of C. pneumoniae-specific Ab-IgG together suggest that the patient harbored an ongoing infection. In case 2, infection with C. pneumoniae was determined based on the IgM diagnostic criteria. The level of C. pneumoniae-specific Ab-IgG rose slightly by the 18th day of admission. The patient’s clinical pathology did not suggest medications as a possible cause of the ARDS, and (with the exception of the C. pneumoniae-specific antibodies) no pathogen-specific antigens or antibodies were detected. Therefore, we consider it likely that these two patients suffered from ARDS due to a C. pneumoniae infection.

C. pneumoniae infection usually exhibits a prolonged but mild clinical course (1-4). However, in elderly individuals or patients with chronic disease, severe life-threatening pneumonia has been reported (9-12). Such cases of severe pneumonia often appear as interstitial shadows and present as ARDS (9-12). Notably, the occurrence of interstitial pneumonia is considered to be evidence of reinfection with this pathogen (13). It has been reported that the 60-kDa protein of C. pneumoniae represents an antigen for delayed-type hypersensitivity, the presumptive cause of interstitial pneumonia and ARDS (13). In case 1, the nature of the antibody profile indicated a significant possibility of C. pneumoniae reinfection. We hypothesize that the patient was suffering from pneumonia resulting from delayed-type hypersensitivity following reinfection with C. pneumoniae. In contrast to that observed in case 1, the patient in case 2 exhibited elevation of the Ab-IgM level but not the Ab-IgG or Ab-IgA levels. These results suggest that the patient was suffering from a first infection by C. pneumoniae, which in turn led to serious pneumonia and ARDS. To our knowledge, there are few reports of C. pneumoniae infection leading to serious pneumonia in elderly or immunocompromised patients (9, 10). The clinical courses of the two cases described here strongly suggest that C. pneumoniae can cause severe pneumonia and ARDS in the elderly, not only by reinfection, but also by first-time primary infection.

The recommended treatment for C. pneumoniae includes the new quinolones, macrolides or minocycline hydrochloride, as these medications are well taken up by infected cells (2, 4). Although mild C. pneumoniae infection can be cured with antibiotic treatment alone, severe C. pneumoniae infection must be treated with antibiotics in combination with steroid therapy, the latter for the purpose of suppressing immune overreaction (9-12). In the present study, the patient in case 1 recovered successfully following treatment with a combination of antibiotics and steroid medications. In
case 2, the patient’s inflammatory symptoms were successfully addressed by combination treatment. However, the patient’s respiratory condition did not recover, despite the administration of several aggressive treatments for ARDS. Prior to the hospitalization described here, this individual was already largely bedridden and in poor general condition. Presumably, this preexisting condition contributed to the difficulty in treating the ARDS.

In summary, we herein reported two cases of severe acute interstitial pneumonia with high values of *C. pneumoniae*-specific antibodies. One patient successfully recovered following treatment with antibiotics and steroids, while the other did not. As noted by others, making an early diagnosis of *C. pneumoniae* infection is difficult because antibody assays are the only effective diagnostic method. Although *C. pneumoniae* is usually associated with mild pneumonia, infection with this bacterium can cause severe life-threatening pneumonia in elderly patients and those with reinfection. Our experience strongly suggests that *C. pneumoniae* infection should therefore be considered in elderly patients presenting with severe interstitial pneumonia.

The authors state that they have no Conflict of Interest (COI).

References


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