Case Report

Acute respiratory distress syndrome caused by *Mycoplasma pneumoniae* without elevated pulmonary vascular permeability: a case report

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Abstract: Sporadic patients with acute respiratory distress syndrome (ARDS) caused by *Mycoplasma pneumoniae* have been reported. However, knowledge about the pathophysiology and pharmacological treatment of this condition is insufficient. Moreover, the pulmonary vascular permeability in ARDS related to *M. pneumoniae* infection has not been reported. We report a case of ARDS caused by *Mycoplasma pneumoniae* without elevated pulmonary vascular permeability, which was successfully treated using low-dose short-term hydrocortisone, suggesting that pulmonary infiltration in ARDS caused by *Mycoplasma pneumoniae* does not match the criteria of permeability edema observed in typical ARDS.

Keywords: *Mycoplasma pneumoniae*; acute respiratory distress syndrome (ARDS); transpulmonary thermodilution technique; pulmonary vascular permeability index (PVPI); corticosteroid treatment

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Introduction

Mycoplasma pneumoniae is one of the most common pathogens in young adult cases of community-acquired pneumonia (CAP). *M. pneumoniae* pneumonia (MPP) manifests non-specific symptoms and findings such as fever, sore throat, persistent dry cough, weakness and hepatic disorder, which are sometimes self-limiting (1,2). However, life-threatening cases of MPP including acute respiratory distress syndrome (ARDS) as a clinical presentation have been reported (2,3). Although systemic steroid therapy with appropriate anti-mycoplasmal drugs may be successful for these cases (2,3), their pathophysiology has not been fully elucidated.

The pulmonary vascular permeability index (PVPI), the ratio of the extravascular lung water (EVLW) to the pulmonary blood volume, reflects alveolar-capillary barrier permeability and is now regarded as a useful marker to differentiate ARDS from hydrostatic edema, with high specificity. In ARDS patients, EVLW increases with elevated PVPI, while in hydrostatic edema, EVLW increases without elevated PVPI (4). However, to the best of our knowledge, EVLW and PVPI in ARDS related to *M. pneumoniae* infection have not been reported. We herein describe a patient with MPP who progressed to severe ARDS, prompting the need for mechanical ventilation without elevated pulmonary vascular permeability, who was successfully treated with low-dose short-term hydrocortisone and levofloxacin.

Case presentation

A 31-year-old male who was previously in good health was admitted to a local hospital with fever and nonproductive cough. Although he was treated for bacterial pneumonia with cefotiam and piperacillin for the first 3 days, and subsequently with meropenem (MEPM) and micafungin for 1 day, his clinical condition changed rapidly for the worse and progressive dyspnea was observed. Then, he

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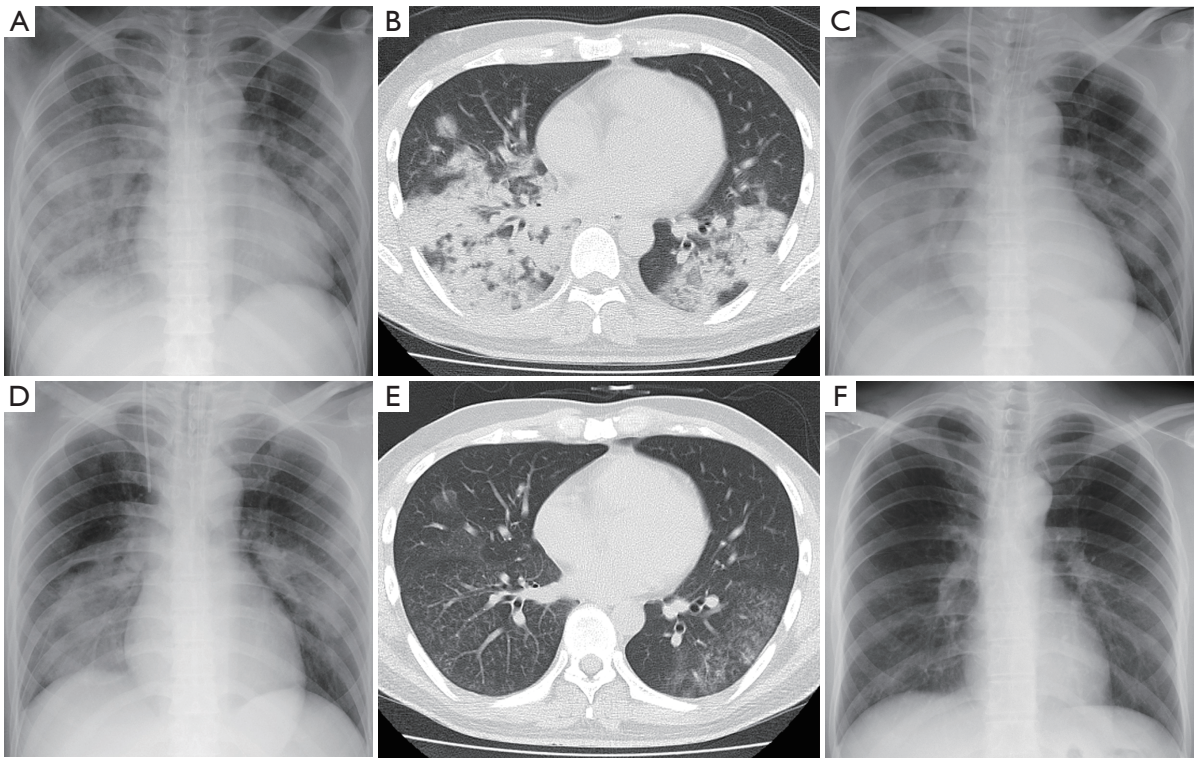

Figure 1 Chest X-ray (A, C and D: antero-posterior; F: postero-anterior) and computed tomography (CT) (B and E) findings. (A) and (B): Diffuse air-space consolidation predominantly in the right lung on admission to our hospital (day 1); (C) Worsening of pre-existing lung infiltration one day after initiation of the treatment using levofloxacin (LVFX) (750 mg/day) with meropenem (3 g/day) (day 2); (D) Marked improvement during corticosteroid treatment (day 5). (E) and (F): Further improvements after administration of LVFX in a total period of two weeks (day 22). CT (E), but not X-ray (F), detected only indistinct micronodular infiltration.

was transferred to our hospital with oxygen inhalation. On physical examination, his temperature was 38.8 ℃, pulse 100/min, blood pressure 120/70 mmHg and respiratory rate 24/min. Lung auscultation revealed decreased breath sounds in both lungs.

Laboratory data were as follows: white blood cell count, 4,320/μL (neutrophils, 89.4%; lymphocytes, 8.6%; eosinophils, 0.2%; monocytes, 1.6%; basophils, 0.2%); hemoglobin, 12.2 g/dL; platelet count, 12.2×10^4/μL; C-reactive protein, 19.55 mg/dL; AST, 59 IU/L; ALT, 60 IU/L; LDH, 412 IU/L; (1-3)-β-d-glucan, 8.3 pg/mL (<20); and KL-6, 141 U/mL (<500). Serum anti-*M. pneumoniae*, *Chlamydophila pneumonia*, human immunodeficiency virus antibodies, serum *Aspergillus* galactomannan and *Cryptococcus neoformans* antigens, and *Streptococcus pneumoniae* and *Legionella pneumophila* urinary antigens were all negative. Arterial blood gas values when oxygen was supplied at 8 L/min by a non-rebreather mask were pH 7.500, $PaCO_2$ 40.3 mmHg, PaO_2 52.5 mmHg and oxygen saturation of 89.0%. Chest X-ray (*Figure 1A*) and computed tomography (CT) (*Figure 1B*) showed diffuse air-space consolidation predominantly in the right lung. Although treatment using levofloxacin (LVFX) (750 mg/day) with MEPM (3 g/day) was initiated for severe CAP of unknown origin, dyspnea and pulmonary infiltration developed, necessitating mechanical ventilation on the second hospital day (*Figure 1C*). The PaO_2/FiO_2 ratio at 10 cmH_2O positive end-expiratory pressure (PEEP) was 89.4 (89.4/1.0) mmHg. A continuous cardiac output (CCO) monitoring system (VolumeView^{TM}/EV1000^{TM}, Edwards Lifesciences, Irvine, CA, USA) used for evaluation of the patient's hemodynamic status revealed a preserved cardiac index (4.4 L/min/m^2) with elevated EVLW indexed for body weight (EVLWi) (12.1 mL/kg), leading to a diagnosis of ARDS. Nevertheless, PVPI (2.1) was not elevated as in ARDS (4).

Blood and sputum cultures ordered on admission were negative. However, *M. pneumoniae* DNA was detected in a bronchial lavage specimen obtained just after intubation by

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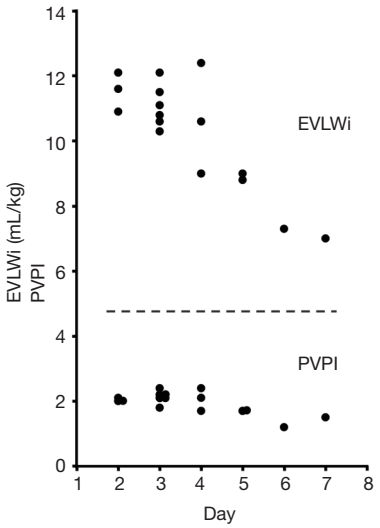

Figure 2 Time course of extravascular lung water indexed for body weight (EVLWi) and pulmonary vascular permeability index (PVPI) values. Until day 6, all values were measured using a continuous cardiac output monitoring system (VolumeViewTM/EV1000TM, Edwards Lifesciences, Irvine, CA, USA) at 10 cmH2O positive end-expiratory pressure (PEEP), whereas values of day 7 were measured during spontaneous respiration. EVLWi values decreased in response to treatments, while PVPI values were 2.4 or less over the entire measurement period.

loop-mediated isothermal amplification assay. The patient was diagnosed with severe ARDS accompanied by mild hepatic disorder as a clinical presentation of fulminant MPP, and low-dose hydrocortisone infusion (300 mg/day) was started with the continuation of LVFX. MEPM was tapered and then stopped. After the initiation of corticosteroid treatment, the clinical course rapidly turned favorable. Pulmonary infiltration (*Figure 1D*) and oxygenation status improved in response to treatments. Hydrocortisone dose was tapered to 0 mg for 4 days (300 mg, 200 mg, 150 mg and 75 mg) and the endotracheal tube was removed after 4 days of mechanical ventilation (day 6). Then, oxygen therapy was stopped at day 12. After the administration of LVFX for a total period of two weeks, chest CT (*Figure 1E*), but not chest X-ray (*Figure 1F*), detected only indistinct micronodular infiltration, and hepatic disorder was not observed. EVLWi values declined with the improvement of the clinical course (*Figure 2*). However, PVPI values were 2.4 or less over the measurement period (*Figure 2*). The particle agglutination titer for *M. pneumoniae* rose from <1:40 to 1:2,560 during two weeks.

Discussion

MMP usually follows a favorable clinical course and only a few percent of all patients with MPP need hospitalization (5). However, about 6% of inpatients with MPP require ventilatory support (2). Although the prognosis of MPP with hypoxia is not always poor (6,7), knowledge of the pathophysiology and pharmacological treatment of ARDS in MPP is insufficient due to its rarity.

ARDS is a condition designated with clinical diagnostic criteria and alveolocapillary hyperpermeability is regarded as its physiological hallmark. However, a clinical diagnosis of ARDS does not necessarily coincide with the presence of DAD, the histological hallmark of the syndrome, suggesting the heterogeneity of this clinical condition (8,9).

Sepsis due to common bacterial pathogens is a leading cause of ARDS and the inflammatory response under this condition that leads to ARDS mainly results from marked accumulation of neutrophils in the lung. It was thought that activated neutrophils induce an increase of pulmonary vascular permeability through the release of reactive oxygen species, proteases, leukotrienes and other molecules (10,11). Recently, the CCO monitoring system, which combines a transpulmonary thermodilution (TPTD) technique and continuous pulse contour analysis, has enabled the real-time evaluation of patients' hemodynamic status including pulmonary vascular permeability, and been used for fluid management in critical care settings (12).

In contrast, pulmonary infiltration in MPP is considered to be associated with excessive cell-mediated immunity. After *M. pneumoniae* infection, alveolar macrophages and T cells synergistically induce the cellular immune response by the release of proinflammatory cytokines leading to ARDS in individuals with hyperresponsiveness (13-15). Although open lung biopsy in ARDS is impracticable, autopsy cases of MPP with fatal respiratory failure have shown that mycoplasma organisms localized on the surface of bronchiolar epithelium, whereas the tissue inflammation and damage extended into deeper parts of the lungs (16), suggesting host immune responses to highly immunogenic molecules associated with *M. pneumoniae*. However, in spite of the above-mentioned differences of pathophysiology, the pulmonary vascular permeability in ARDS related to *M. pneumoniae* infection has not been reported, except for this manuscript.

The characteristics of our patient at the beginning of ventilatory support represented severe ARDS as described by the Berlin definition (PaO_2/FiO_2 <100 mmHg with

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PEEP ≥5 cmH_2O) (17). Concerning the CCO monitoring system, previous studies have suggested that EVLWi (>10 mL/kg) should be included in the definition of ARDS (18). Moreover, PVPI was higher in ARDS patients than in patients with hydrostatic pulmonary edema (4.7±1.8 *vs.* 2.1±0.5) (4). A PVPI of 3.0 was proposed as the cut-off value to allow the diagnosis of ARDS with sensitivity of 85% and specificity of 100% (4). The EVLWi value of our patient was more than 10 mL/kg, which was consistent with ARDS, and decreased in response to treatments. However, PVPI values were not equivalent to those of ARDS patients over the measurement period. Although there is no report regarding a correlation in clinical course between improvements of PVPI values and those of pulmonary infiltrations, we thought it was unlikely that PVPI was initially at a high value and had returned to normal by the time the patient was monitored because dyspnea and pulmonary infiltration kept getting worse until the initiation of PVPI monitoring. These data suggest that pulmonary infiltration caused by *M. pneumoniae* does not match the criteria of permeability edema observed in typical ARDS, reflecting the differences of pathophysiology.

Randomized controlled studies have revealed that high-dose short-term corticosteroid is ineffective for patients with sepsis-related ARDS, suggesting that neutrophilic lung inflammation with increased pulmonary vascular permeability is steroid-resistant (19-21). However, corticosteroids may have a desirable effect on MPP by down-regulating cell-mediated immunity. Clinical evidence supporting this hypothesis has been reported by several groups (2,3,6,7). Although about half of previously reported patients with fulminant MPP were treated with methylprednisolone pulse therapy probably following typical ARDS (6), the optimal dose and duration of steroid therapy remain unclear.

Besides *M. pneumoniae* infection, excessive cell-mediated immunity is observed upon immune reconstitution after the initiation of anti-HIV therapy, pregnancy, withdrawal from immunosuppressive agents and the initiation of antimicrobial treatment for patients with pathogen-induced immunosuppression resulting in various infectious diseases, such as *Pneumocystis jirovecii* pneumonia, cryptococcal disease and active tuberculosis (22-24). Generally speaking, the therapeutic dose of corticosteroids (prednisolone) for the treatment of these diseases is 0.5-1.5 mg/kg/day or less (25-27). Moreover, a recent study has shown that low-dose hydrocortisone treatment (10 mg/hour for 7 days) for severe CAP was related to decreased durations of mechanical ventilation and hospital stay, as well as risk of mortality (28). For these reasons, low-dose hydrocortisone infusion was introduced for our patient, and resulted in prompt clinical improvement. The hydrocortisone dose could be decreased from 300 mg to 0 mg for 4 days. The requirement for a sufficient dose and duration of corticosteroid treatment of ARDS in MPP may differ from that of sepsis-related ARDS.

Our data from previous reports indicate that the presence of alveolocapillary hyperpermeability or DAD is not a requirement for the diagnosis of a clinical syndrome of ARDS. The accumulation of data from the CCO monitoring system may contribute to narrowing down the heterogeneous conditions clinically diagnosed with ARDS to a typical phenotype. However, this system requires specialized devices and invasive procedures. More research is needed to find serum markers that can reflect alveolocapillary hyperpermeability or DAD.

Conclusions

In summary, our patient with MPP presented severe ARDS without elevated pulmonary vascular permeability, and was successfully treated with low-dose short-term hydrocortisone and anti-mycoplasmal drug. These facts suggested that the real-time monitoring of PVPI in ARDS related to *M. pneumoniae* infection may provide useful information about the pathophysiology and pharmacological treatment of individual patients. Further clinical studies on PVPI in ARDS related to *M. pneumoniae* infection are needed in order to establish the standard treatment of this rare condition.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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