Severe Acute Lung Injury Caused by Mycoplasma pneumoniae: Potential Role for Steroid Pulses in Treatment

Published evidence of pathogenetic mechanisms of acute respiratory distress syndrome (ARDS) in mycoplasmal lung infections suggests that the pulmonary injury is related to a cell-mediated immune response. Therefore, steroids may play a role in the treatment of severe cases. We describe a patient who had Mycoplasma pneumoniae pneumonia that progressed to severe ARDS requiring mechanical ventilation and who had improvement with prednisolone pulses.

Severe pulmonary injury due to Mycoplasma pneumoniae is extremely unusual, and there are only scarce descriptions of patients who needed invasive ventilatory support [1]. In this report, we describe a previously healthy young man who, while receiving effective antibiotic treatment, developed adult respiratory distress syndrome (ARDS) related to M. pneumoniae infection. He was treated with high doses of corticosteroids. After he received treatment, his condition improved radiologically and clinically, and gasometric parameters improved in a temporal pattern consistent with a causal relation between this improvement and the administration of pulses of methylprednisolone. A review of the literature on the subject supports the idea that lung injury in mycoplasmal infections is the result of an excessively vigorous cell-mediated immune response. The down-regulation of this response would be the pathophysiological substrate for corticosteroid usefulness.

A 24-year-old man was admitted to the hospital with fever, toxic appearance, chills, abdominal pain, and diarrhea. He had experienced acute fever (temperature, >39°C) and rigors 48 h before admission, followed by nausea, diffuse colicky abdominal pain, and diarrhea (without blood, mucus, or pus in the stools) 12 h later. The next day, pollakiuria, urinary tenesmus, and myalgias developed, with persistence of high-grade fever and pyrogenemia.

The patient was evaluated in the emergency department and was admitted with an initial diagnosis of enteric infection. He was heterosexual and monogamous and had no history of injection drug abuse. He denied having any significant epidemiological exposure, including contact with birds or persons with active tuberculosis. He worked as a technician in a telecommunications company.

The results of physical examination were unremarkable. The only symptoms present were fever and myalgias. No abnormalities were found by abdominopelvic ultrasonography. Results of laboratory studies at admission were also unremarkable; his WBC count was 5300 cells/mm³ (89% neutrophils), and the erythrocyte sedimentation rate was 23 mm/h. Cultures of blood, stool, and urine samples were performed, and therapy with iv ciprofloxacin (400 mg b.i.d.) was started. During the following 24 h, dry cough and signs of condensation in the left lower lobe were noted during physical examination. A chest radiograph showed a homogeneous left lower-lobe opacity with a tenuous interstitial bilateral infiltrate.

On the second day after admission, the patient had a minimally productive cough and retrosternal pain. A sputum sample was sent for microbiological direct examination and culture. Pleural ultrasonography showed a minimal amount of pleural effusion and consolidation of subjacent lung parenchyma; the possibility of typical bacterial pneumonia was considered, and iv ceftriaxone (1 g b.i.d.) was added to his treatment. The possibility of an atypical pneumonia agent was considered unlikely at that time; however, high doses of ciprofloxacin were deemed adequate empirical coverage for those agents.

On the third day after admission, the patient’s clinical condition clearly worsened. The sputum turned hemoptic; a new chest radiograph confirmed bilateral airspace disease. Determination of arterial blood gas levels showed severe hypoxemia (PO₂, 48.7 mm Hg; fraction of inspired oxygen [FiO₂], 21%), and leukopenia developed (WBC count, 3900 cells/mm³ [90% neutrophils]). Blood samples were sent for serological investigation of M. pneumoniae, Chlamydia psittaci, Chlamydia pneu-
Moniae, Coxiella burnetii, Legionella species, and Leptospira species. Bronchoalveolar lavage was considered but was not performed because of critical hypoxemia. Treatment with ceftriaxone and ciprofloxacin was switched to iv imipenem (500 mg q.i.d.) and clarithromycin (500 mg b.i.d.), and the patient was transferred to the intensive care unit.

On day 4 after admission, the patient became critically ill with refractory hypoxemia. A chest radiograph demonstrated worsening of his condition, and dense bilateral infiltrates were observed (figure 1). Repeated pleural ultrasonography showed only a minimal bilateral pleural effusion. A trial of noninvasive ventilation with bilevel positive pressure was unsuccessful at restoration of an acceptable PO2. The patient underwent intubation, and mechanical ventilation was established (FiO2, 100%; positive end-expiratory pressure [PEEP], 10 cm H2O). In spite of these high ventilator settings, severe hypoxemia continued (PO2, 45 mm Hg). Static lung compliance was 33.4 mL/cm H2O.

In spite of these high ventilator settings, severe hypoxemia continued (PO2, 45 mm Hg). Static lung compliance was 33.4 mL/cm H2O. On day 4 after admission, the patient became critically ill with refractory hypoxemia. A chest radiograph demonstrated worsening of his condition, and dense bilateral infiltrates were observed (figure 1). Repeated pleural ultrasonography showed only a minimal bilateral pleural effusion. A trial of noninvasive ventilation with bilevel positive pressure was unsuccessful at restoration of an acceptable PO2. The patient underwent intubation, and mechanical ventilation was established (FiO2, 100%; positive end-expiratory pressure [PEEP], 10 cm H2O).

A Swan-Ganz catheter was inserted. Measurements were consistent with a hyperdynamic state with normal pulmonary capillary wedge pressure (mean arterial pressure, 77 mm Hg; pulmonary capillary wedge pressure, 11 mm Hg; cardiac index, 6.54 L/[min/m2]; systemic vascular resistance, 436 dyne/[s/cm5]; oxygen delivery, 2.37 mL/[kg/min]; and oxygen consumption, 9.8 mL/[kg/min]). Acute lung injury was diagnosed. The lung injury score was 3.25, which is consistent with ARDS [2]. Short attempts at inverse-ratio ventilation, ventilating the patient in Trendelenburg’s position at 60°, and use of a high level of PEEP (up to 25 cm H2O) for short periods were unsuccessful in achieving an improvement in the gas exchange. A transthoracic Doppler echocardiogram showed no abnormalities.

On day 5, the patient became afebrile. There was no improvement in gas exchange. The decision was made to start treatment with high doses of corticosteroids. The patient received 1 g of iv methylprednisolone sodium succinate. Ciprofloxacin therapy was reinitiated for a synergistic effect against atypical pneumonia agents. Twelve hours after the steroid pulse, significant improvement in gas-exchange parameters was also noted (figure 2). This improvement was not associated with negative fluid balance.

On day 6, treatment with iv trovafloxacin (300 mg/d) was substituted for ciprofloxacin therapy because of its better activity against atypical pneumonia agents. Another 1-g bolus of methylprednisolone was administered. A chest radiograph revealed significant resolution of opacities (figure 3), and significant improvement in gas exchange (figure 2) was noted. Static lung compliance increased to 39.3 mL/cm H2O; on day 7, it further increased to 79 mL/cm H2O. On the same day, results of the serological survey were available: IgM antibody to M. pneumoniae was positive, and the titer of IgG antibody was positive (>1:256). Cold agglutinins with anti-I specificity were positive at a 1:32 dilution; these results were considered diagnostic of severe M. pneumoniae infection. There were no other reports consistent with an alternative etiologic diagnosis that could explain the patient’s clinical presentation (table 1).

On the following days, gas exchange continuously improved, chest radiographs revealed resolution of opacities, and parameters of pulmonary mechanics improved. On day 11, he successfully underwent extubation. Clarithromycin therapy was changed to oral administration, and imipenem treatment was discontinued on day 13. The patient was discharged on day 16 after admission. He completed a 4-week course of oral clarithromycin and trovafloxacin, and recovered uneventfully from his disease. He remained in good health at a 12-month follow-up.

M. pneumoniae usually causes mild respiratory disease. It has been reported that only 2% of all patients with M. pneumoniae pneumonia require hospitalization [3]. Of patients who are admitted to the hospital, between 0.5% [4] and 10.9% [5] require mechanical ventilation. Information about the pathophysiology of human ARDS in mycoplasmal pneumonia is scarce because of its relative infrequency. The patient described here had an unusual clinical presentation with worsening respiratory failure in spite of appropriate empirical antibiotic treatment. The clinical sequence suggested an atypical pneumonia agent, and because of their relative frequency, the more probable agents were M. pneumoniae and C. pneumoniae. There were no reported local cases of infection caused by Legionella species, and the epidemiological background made C. psittaci unlikely. Although the first choices for treatment of infections due to atypical agents are macrolides or tetracyclines, we believe that deterioration of the patient’s clinical presentation was not due to antibiotic failure.

The usual MIC90 of ciprofloxacin against M. pneumoniae is
1 µg/mL (although it can be up to 8 µg/mL). The peak serum concentration of ciprofloxacin after iv infusion of 400 mg is 4.6 µg/mL, and the pulmonary concentration is 1.6- to 4-fold greater than the serum concentration, which is well above the usual MIC₉₀ for these pathogens. In addition to these pharmacokinetic and microbiological considerations, small numbers of patients with mycoplasmal pneumonia have responded to ciprofloxacin treatment [6]. Although our patient’s treatment was changed to imipenem/clarithromycin, in accordance with the accepted management guidelines for severe community-acquired pneumonia [7], we considered that deterioration was taking place during presumably effective antibiotic therapy, which suggested an inappropriate inflammatory response as the cause for this deterioration. It was then decided that the patient should be treated with corticosteroids in an attempt to modulate this response. The improvement in gas exchange was dramatic, concomitant in time with the onset of action of corticosteroids.

The role of corticosteroids in the treatment of early ARDS is clearly controversial. Prospective, multicenter, placebo-controlled studies have shown that patients with ARDS do not benefit from the use of high doses of corticosteroids early in the course of the disease [8–10]. These studies demonstrated the lack of usefulness of corticosteroid treatment for a population of patients who mainly had sepsis due to typical bacterial pathogens. In these infections, the inflammatory response leading to ARDS is primarily centered on neutrophil migration into the airway. The precise mechanism of damage to the pulmonary endothelium and epithelium is not exactly known. Nevertheless, the most likely agents of damage are reactive oxygen species and proteases, with the activated neutrophil as their most likely source [11]. This type of immune response is clearly different from the one observed in mycoplasmal infections, and the aforementioned conclusions regarding the lack of effectiveness of steroids in the treatment of early ARDS may not be applicable to Mycoplasma-associated ARDS.

There is substantial evidence (from animal models and human cases) that pulmonary infiltrates in mycoplasmal pneumonia are related to mononuclear cell migration into the airway. After Mycoplasma species enter the respiratory tract, alveolar macrophages become locally attracted in response to mycoplasmal infection. Following opsonization of bacteria by complement or
suggests that individual immune responses to failure [1, 16]. There is experimental and clinical evidence that lung-biopsy specimens from patients with nonfatal respiratory organizing pneumonia (BOOP) have been described in open ®ltrates (cellular bronchiolitis) and bronchiolitis obliterans with immunosuppressed humans with mycoplasmal infection attenuate or do not develop lung lesions [20], and [18]. Accordingly, immunosuppressed animals with mycoplasmal infections mimicked by the macroscopic pathological lesions found in IL-correlated with a nodular pattern [19]. This nodular pattern is reaction within 7 days of onset of mycoplasmal pneumonia) level of cell-mediated immunity (measured as a positive PPD reaction within 7 days of onset of mycoplasmal pneumonia) correlated with a nodular pattern [19]. This nodular pattern is mimicked by the macroscopic pathological lesions found in IL-2–immunoinactivated mice infected with Mycoplasma pulmonis [18]. Accordingly, immunosuppressed animals with mycoplasmal infection attenuate or do not develop lung lesions [20], and immunosuppressed humans with M. pneumoniae infection may lack pulmonary in®ltrates [21]. Thus, the host level of cell-mediated immunity might alter the pathological pattern of pneumonia.

Corticosteroids down-regulate the cell-mediated immune response [22–24] and therefore may have a profound effect by reducing immune-mediated pulmonary injury seen in mycoplasmal infections. Clinical evidence supporting this concept was reported by Chan and Welsh [1], who reviewed cases of severe M. pneumoniae infections that were reported in the English-language medical literature from 1966 through 1991. They found that, of 8 patients with nonfatal respiratory failure who received corticosteroid therapy, 6 responded favorably to steroid treatment. They pointed out that given the frequent recognition of bronchiolitis and BOOP in their series, and given the fact that these conditions are responsive to corticosteroids, they may well be the underlying substrate for corticosteroid usefulness.

Four additional cases of M. pneumoniae–associated bronchiolitis and BOOP with marked hypoxemia were later reported [16, 25]. Two patients with BOOP and one with acute inflammatory bronchiolitis required treatment with corticosteroids, and their conditions improved thereafter; none of these patients required mechanical ventilation. Although administration of steroids may be associated with an increased risk of new infections and adverse effects on metabolism, their use seems to be justi®ed for patients who are developing respiratory failure.

It is interesting that the use of corticosteroids is clearly indicated for the treatment of severe pneumonia caused by another pathogen (Pneumocystis carinii) for which cell-mediated immunity is crucial for the control of the infection. For patients with severe hypoxemia, the use of corticosteroids has demonstrated clinical benefits that prevent the deterioration of gas exchange that occurs after initiation of antibiotic treatment. There is also evidence that, in other infections in which a cell-mediated immune response is needed for their control, corticosteroids might be bene®cial. Corticosteroid treatment is indicated for patients who are critically ill with typhoid fever and

<table>
<thead>
<tr>
<th>Variable (test)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycoplasma pneumonia</td>
<td>IgM, positive; IgG, 1:256</td>
</tr>
<tr>
<td>Chlamydia pneumonia</td>
<td>IgM, negative; IgG, 1:32</td>
</tr>
<tr>
<td>Chlamydia psittaci</td>
<td>IgM, negative; IgG, 1:16</td>
</tr>
<tr>
<td>Legioella species</td>
<td>IgM, negative; IgG, negative</td>
</tr>
<tr>
<td>Leptospira species</td>
<td>Total antibodies, negative</td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>Not done</td>
</tr>
<tr>
<td>Influenza A and B viruses</td>
<td>Total antibodies, 1:16</td>
</tr>
<tr>
<td>Parainfluenza virus types 1±3</td>
<td>Total antibodies, negative</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Total antibodies, negative</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Total antibodies, negative</td>
</tr>
<tr>
<td>HIV (ELISA)</td>
<td>Negative</td>
</tr>
<tr>
<td>Blood, stool, and urine (culture)</td>
<td>Negative, with inflammatory</td>
</tr>
<tr>
<td>Sputum (direct examination and culture)</td>
<td>Negative, with inflammatory</td>
</tr>
<tr>
<td>Pneumocystis carinii (IF with monoclonal antibodies of tracheal aspirate)</td>
<td>Negative</td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibodies</td>
<td>Negative</td>
</tr>
<tr>
<td>C3, C4, and CH50</td>
<td>Normal values</td>
</tr>
<tr>
<td>Antinuclear antibodies and rheumatoid factor</td>
<td>Negative</td>
</tr>
</tbody>
</table>

NOTE. IF, immunofluorescence.
tuberculous pericarditis, and it might be useful for patients with tuberculous meningitis and ARDS associated with acute miliary tuberculosis or for those with unusually severe Epstein-Barr virus infections [26].

In conclusion, the aforementioned evidence strongly suggests that ARDS secondary to mycoplasmal infection is a lymphoid cellularity ARDS caused by a harmful, “overreacting” cell-mediated immune response that could potentially be tapered by the use of steroids. It is unclear whether ARDS associated with mycoplasmal infection could be a fulminant and life-threatening variant of BOOP [27], a condition also immunologically mediated and responsive to steroids. This seems unlikely in our study, because our patient did not have a relapse (as would have been expected in a case of BOOP) after discontinuation of corticosteroid treatment [28]. The successful outcome for our patient suggests that corticosteroids may play an important role in the treatment of ARDS in pulmonary infections due to Mycoplasma species.

Acknowledgments

We thank Dr. Corina González, for her helpful suggestions; Dr. Roberto Bitton, for his assistance in reviewing the manuscript; and Mrs. Brenda Koliren (Medical English Center, Buenos Aires, Argentina), who kindly assisted us in preparing the English version of the article.

Marcelo Radisic, Andrés Torn, Pablo Gutierrez, Héctor A. Defranchi, and Pablo Pardo

1 Internal Medicine Department, 2 Intensive Care Unit, and 3 Respiratory Diseases Unit, Sanatorio de la Trinidad, Capital Federal, Argentina

References