Fatal Mycoplasma pneumoniae pneumonia in a previously healthy 18-year-old girl

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Summary. A case of fatal Mycoplasma pneumoniae pneumonia in a previously healthy 18-year-old girl is reported. On hospital day 9, the antibody titer to M. pneumoniae was 1:512 in the complement fixation test and 1:5120 in the microparticle agglutination assay. After five weeks in the intensive care unit, the patient died from necrotizing hemorrhagic pneumonia with multi-organ failure. No significant superinfections occurred during ICU treatment. Corticosteroids (hospital day 8 onward) did not influence the course of the disease. It is noteworthy that, as in some previously reported cases, the clinical state deteriorated during presumably adequate antibiotic treatment (2 days before admission onward), and despite documented eradication of the pathogen from the respiratory tract (PCR from bronchoalveolar fluid on hospital day 22 was negative). However, the illness had lasted for several days before admission to the hospital, therefore the potentially beneficial effect of antibiotic treatment at an early stage of the disease cannot be assessed. Clearly, in default of other treatment options, correct diagnosis and early treatment of mycoplasma community-acquired pneumonia seems mandatory. This is the third case of fatal mycoplasma pneumonia reported from Austria in recent years, making this topic worthy of further scientific attention.

Key words: Mycoplasma pneumoniae, necrotizing pneumonia, multi-organ failure.

Introduction

Mycoplasma pneumoniae is a frequent cause of respiratory tract disease. The infection shows important epidemiological fluctuations, with peak incidences every four to seven years [1, 2]. A minority of M. pneumoniae infections (around 3%) lead to community-acquired pneumonia, the mycoplasma-associated disease of greatest clin-
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Fig. 1. Spiral-CT scan (hospital day 8) demonstrates bilateral upper lobe consolidation with air bronchograms and a large amount of pleural effusion.

Fig. 2. Transverse thin-section CT scans of the chest (hospital day 17) show ground-glass opacities associated with smooth interlobular and intralobular septal thickening, with predominantly reticular pattern in lower lobes.

Case report

An 18-year-old previously healthy girl was admitted to a hospital in southern Austria with fever up to 40 °C and cough with yellowish expectoration. Significant laboratory values were an elevated serum level of C-reactive protein (CRP; 22.3 mg/dl, reference range: <1.1 mg/dl), a mild leucocytosis (15.4 G/l, reference range: 3.8–11 G/l), and an elevated serum level of alanine aminotransferase (ALT 63 U/l; reference range: <31 U/l). Two days before admission the patient had been prescribed moxifloxacin by her physician. Chest X-ray revealed pericardial patchy attenuation of the right lower lobe. A CT scan of the thorax showed a hazy consolidation that appeared more solid than on radiography. The diagnosis of community-acquired pneumonia was made and treatment with roxithromycin and ceftriaxone was initiated. During the next days, the patient showed undulating fever with no improvement of the general condition. On hospital day 6 the patient showed a Quick prothrombin time of 48%, which was considered as a sign of developing sepsis. The patient was therefore transferred to the local ICU. Antibiotic treatment was changed from roxithromycin to clarithromycin (plus cefepime). At that time the leucocyte count was 17.27 G/ml and serum CRP 33.9 mg/dl. A control CT scan of the thorax revealed progression of the pneumonic infiltrate with consolidation involving the posterior basal right lower lobe, but the patient still showed sufficient oxygenation with spontaneous respiration. On hospital day 7, the patient had respiratory failure and required intubation for mechanical ventilation. Acute renal failure with anuria developed, therefore hemodialysis was initiated. A pericardial effusion had developed between hospital days 4 and 7, and a discrete exanthema on the right arm, which had been visible at admission, had progressed to the trunk.

On hospital day 8 the patient was transferred to Vienna General Hospital. On admission, a CT scan of the thorax showed progression of the pulmonary infiltrates, a large amount of bilateral pleural effusion and areas of hazy consolidation with air bronchograms, which now also included the apical part of both upper lobes (Fig. 1). In addition to respiratory failure, liver failure became evident, so that extracorporeal liver support with a molecular adsorption recirculating system (MARS) had to be initiated shortly after admission. Antimicrobial treatment with clarithromycin and cefepime was continued. Through the next four weeks anti-mycoplasma treatment was continued with alternating clarithromycin, azithromycin, ciprofloxacin, amikacin, and trimethoprim-sulfamethoxazole. From admission to Vienna General Hospital onward, the patient received hydrocortisone via a perfusor up to 30 mg/h (mostly 8 mg/h) throughout the hospital stay.

The pulmonary infiltrates were increasing and the CT scan showed areas of diffuse ground-glass attenuation and acinar attenuation of both lungs after hospital day 17 (Fig. 2). On hospital day 34 extracorporeal membrane oxygenation (ECMO) was initiated. On hospital day 35 the patient died from progressive hemorrhagic pneumonia and multi-organ failure. Pathological examination revealed septic dystrophy of the parenchy-
matous organs and fibrinous pericarditis. Cerebral bleeding of the parietal-temporal lobe and subpleural, pulmonary and diffuse gastrointestinal bleeding as a sign of hemorrhagic diathesis were also observed.

**Microbiological investigations**

Comprehensive investigations of the etiology of the pneumonia were performed. The results of serological tests are shown in Table 1. PCR assays for detection of CMV (serum, day 16) and *Chlamydia pneumoniae* (bronchoalveolar lavage, day 24) were negative.

Conventional bacteriological cultures were performed from blood (days 9, 14, 15, 26, 28, 29, 36), pleural fluid (d 9 and 13), pericardial fluid (d 35), ascites (d 15), urine (d 11), intravascular catheter tips (d 10, 24, 28, 29) and bronchial secretions (d 11, 14, 16, 18, 24, 36). All cultures remained nega-

| Pathogen                                      | Day | Result | Assay               |
|----------------------------------------------|-----|--------|---------------------|
| *Legionella pneumophila*                     | 9   | neg    | Antigen/urine       |
| *Legionella* spp. IgG                        | 11  | neg    | ELISA               |
| *Legionella* spp. IgM                        | 11  | neg    | ELISA               |
| *Chlamydia psittaci* IgG                     | 11  | neg    | ELISA               |
| *Chlamydia psittaci* IgA                     | 11  | neg    | ELISA               |
| *Chlamydia pneumoniae* IgM                   | 23  | neg    | CF                  |
| *Chlamydia pneumoniae* IgM                   | 9   | neg    | ELISA               |
| *Chlamydia pneumoniae* IgG                   | 9   | neg    | ELISA               |
| *Chlamydia pneumoniae* IgA                   | 18  | neg    | ELISA               |
| *Chlamydia pneumoniae* IgA                   | 18  | neg    | ELISA               |
| *Chlamydia pneumoniae* IgG                   | 23  | 55 AU  | ELISA               |
| *Chlamydia pneumoniae* IgG                   | 23  | 125 AU | ELISA               |
| *Chlamydia pneumoniae* IgG                   | 23  | 115 AU | ELISA               |
| Bordetella pertussis IgA                     | 11  | neg    | ELISA               |
| Bordetella pertussis IgM                     | 11  | neg    | ELISA               |
| Pneumocystis jiroveci                        | 24  | neg    | Antigen/BAL         |
| Streptococcus pneumoniae                     | 9   | neg    | Antigen/urine       |
| Haemophilus influenzae                       | 9   | neg    | Antigen/urine       |
| *Brucella abortus*                           | 9   | <1:20  | MAG                 |
| *Brucella melitensis*                        | 9   | <1:20  | MAG                 |
| *Francisella tularensis*                     | 9   | <1:20  | MAG                 |
| *Weil Felix* (OX-19, OX-2, OX-K)             | 9   | <1:20  | MAG                 |
| Leptospira spp.                              | 9   | <1:50  | MAG                 |
| *Borrelia burgdorferi* IgG                   | 11  | neg    | ELISA               |
| *Borrelia burgdorferi* IgM                   | 11  | neg    | ELISA               |
| *Salmonella* spp. (OD, OA, OB, OC)           | 9   | ≤1:20  | MAG                 |
| Hantaan virus IgG                            | 16  | neg    | ELISA               |
| Hantaan virus IgM                            | 16  | neg    | ELISA               |
| Adenovirus                                   | 9   | neg    | CF                  |
| CMV                                         | 9   | 1:16   | CF<sup>a</sup>      |
| CMV IgG                                      | 9   | neg    | ELISA               |
| CMV IgM                                      | 9   | neg    | ELISA               |
| CMV (serum)                                  | 16  | neg    | PCR                 |
| Enterovirus                                  | 9   | 1:8    | CF                  |
| HSV                                         | 9   | 1:8    | CF<sup>a</sup>      |
| HSV IgM                                      | 9   | neg    | ELISA               |
| Influenza A                                  | 9   | 1:8    | CF<sup>a</sup>      |
| Influenza B                                  | 9   | 1:4    | CF<sup>a</sup>      |
| Parainfluenza virus                          | 9   | 1:4    | CF<sup>a</sup>      |
| VZV                                         | 9   | 1:8    | CF<sup>a</sup>      |
| VZV IgM                                      | 9   | neg    | ELISA               |
| EBV IgM                                      | 9   | neg    | ELISA               |
| Coxiella burnetii                            | 23  | neg    | CF                  |
| RSV                                         | 23  | neg    | CF                  |
| HIV                                         | 9   | neg    | ELISA               |
| HAV                                         | 9   | neg    | ELISA               |
| HBV (Hbs-Ag)                                 | 9   | neg    | ELISA               |
| HCV                                         | 9   | neg    | ELISA               |
| Anti-A60-AK IgG to mycobacteria              | 24  | neg    | ELISA               |

<sup>a</sup>Repeated on hospital day 23 without significant change of the result; <sup>b</sup>*Chlamydia pneumoniae* ELISA plus, Medac, Wedel, Germany; cut-off value: 29 AU.
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dequate antibiotic treatment [10, 13]. Clearly, from some of the existing reports, the theoretic possibility of a con-infection including M. pneumoniae and an additional pathogen cannot be ruled out completely.

Both in the present case and in some previously reported cases of M. pneumoniae-associated ARDS, deterioration of the clinical state took place during presumably adequate antibiotic treatment [10, 13]. Clearly, from some stage of illness onward, the clinical course can no longer be influenced by antibiotics. However, in the present case, as well in previously described cases, the illness had lasted for several days before admission to hospital, therefore the effect of antibiotic treatment at an early stage of the illness cannot be assessed from the existing reports. Animal experiments have shown that significant inflammatory changes develop very early in the course of M. pneumoniae infection [28].

The development of pulmonary infiltrates in mycoplasma pneumonia is initially related to migration of mononuclear cells into the airways. Following cytokine release by macrophages, a mononuclear cell inflammatory response including mainly CD4+ T cells, but also B cells and plasmocytes, contributes to infiltrate formation [29–31]. In human infection, lymphoplasmacytic bronchiolar wall infiltrates (cellular bronchiolitis) and bronchiolitis obliterans with organizing pneumonia (BOOP) have been described in open lung biopsy specimens from patients with nonfatal respiratory failure [8, 13]. There are data supporting the hypothesis that the severity of the disease and pulmonary infiltrates may be directly correlated with the strength of the individual immune response [20, 33]. There is also evidence that immunosuppressed patients with M. pneumoniae infection may lack pulmonary infiltrates [34]. In this context, corticosteroids, which down-regulate the cell-mediated immune response, may reduce immune-mediated pulmonary injury and may therefore be beneficial in extraordinarily severe mycoplasma pneumonia [10, 13]. The beneficial effect of corticosteroids has been described in some cases, although treatment failures have been reported in others. Previously published experiences with corticosteroid treatment of severe mycoplasma pneumonia have been summarized by Chan and Welsh [13]. In the present case the patient received corticosteroids from hospital day 8

tive except an intravascular catheter tip removed on day 28, which yielded <100 colony forming units of Staphylococcus epidermidis. Bronchial secretions yielded low quantities of C. albicans (d 11, 14, 16, 18, 36).

Diagnosis of M. pneumoniae infection

On hospital day 9, antibody titers to M. pneumoniae were positive at 1:512 in the complement fixation (CF) test and 1:5120 in the microparticle agglutination (MAG) assay (Serodia Myco II, Fujirebio). These values were considered diagnostic for acute M. pneumoniae infection [14]. Two weeks later, the anti-M. pneumoniae titers had decreased to 1:128 in the CF test (day 23) and 1:640 in the MAG assay (day 24). PCR for detection of M. pneumoniae from bronchoalveolar lavage on hospital day 24 (after a total of 22 days of anti-mycoplasma therapy) was negative.

Discussion

There are several descriptions of severe cases of Mycoplasma pneumoniae pneumonia with and without associated multi-organ failure [15–19]. Clinically severe cases of M. pneumoniae pneumonia published before 1995 have been reviewed by Chan and Welsh [13]. In Austria, two cases of fatal mycoplasma pneumonia have been reported during recent years [12, 19].

Extremely severe or fatal cases of mycoplasma pneumonia may be underdiagnosed, because at the time of admission the patients are mostly critically ill, which does not raise suspicion of a mycoplasma etiology of pneumonia [20]. Furthermore, the possibility of comprehensive microbiological investigations, not only to diagnose M. pneumoniae infection but also to rule out other potential etiologies of pneumonia, may not be available in all healthcare settings. Nevertheless, clinically severe cases represent only a small minority of all cases of mycoplasma pneumonia.

In contrast to some published cases of severe M. pneumoniae pneumonia, the patient showed mild leucocytosis on admission [6, 10, 13]. However, it has been shown that leucocytosis is not uncommon in mycoplasma pneumonia [21]. CRP values have not been reported in most previous cases of severe mycoplasma pneumonia. The CRP serum level in the present case was considerably higher than in a patient collective from our institution [22] but lower than in our previously published case of fatal mycoplasma pneumonia with multi-organ failure [12].

In the present case, diagnosis of M. pneumoniae pneumonia was made from the results of serological tests. The patient showed highly elevated and diagnostic antibody titers in two different tests [14]. In addition to the high single titers, the fourfold decrease in titer between hospital days 9 and 23 is indicative of acute mycoplasma infection at the time of admission, because both tests mainly detect ‘early’ IgM antibodies [21, 22]. The negative PCR result on hospital day 24 after a total of 22 days of antimycoplasma therapy is not surprising. It is a shortcoming of the present report that no attempt was made to detect M. pneumoniae in the respiratory tract during an early stage of disease. However, it has been shown that the correlation between serology and PCR may be poor [25, 26]. One of the explanations for this finding may be a decrease of the bacterial load in the throat during the course of the illness [27]. With regard to moxifloxacin treatment from 2 days after admission onward, even a negative PCR result on admission would not have unambiguously ruled out a M. pneumoniae infection.

The urine antigen tests for detection of S. pneumoniae and H. influenzae were performed relatively late in the course of the illness, after 11 days of potentially active antimicrobial treatment. IgG antibodies to C. pneumoniae in the medac ELISA plus were considerably elevated, but IgM and IgA antibodies were below the cut-off level for positivity. No evidence of Legionella sp. infection was obtained from the urine antigen test, or by antibody determination on hospital days 9 and 11. However, the antigen test enables the detection of exclusively L. pneumophila serogroup 1, and antibody determination within the first 11 days of hospitalization is quite early with regard to the slow mounting of Legionella-specific antibodies in the course of the illness. No anamnestic data on potential exposure to Legionella sp. were available. In the light of these considerations, the theoretic possibility of a co-infection including M. pneumoniae and an additional pathogen cannot be ruled out completely.

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onward, with progression of the pulmonary infiltrates despite presumable eradication of the pathogen itself.

To date, none of the potential treatment options for severe *M. pneumoniae* pneumonia has been evaluated in controlled clinical trials. Nevertheless, in default of other options, early diagnosis and treatment of community-acquired mycoplasma pneumonia seems mandatory. At present, one recommendable tool, among others, for the diagnosis of acute *M. pneumoniae* infection is ELISA detection of specific IgM and IgA antibodies [14]. If no rapid access to a well equipped laboratory is available, the bedside test Immunocard Mycoplasma (Meridian Bioscience, Cincinnati, OH, USA) for detection of specific IgM is a feasible though less sensitive alternative [35]. Studies on the pathogenesis of severe *M. pneumoniae* infections, which would enable conclusions on possible treatment options, are warranted.

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