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ORIGINAL ARTICLE

Necrotizing pneumonia caused by refractory *Mycoplasma pneumonia* pneumonia in children

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Abstract

Background To investigate the clinical features of necrotizing pneumonia (NP) caused by refractory *Mycoplasma pneumoniae* pneumonia (RMPP).

Methods A retrospective observational study was carried out in patients with NP caused by RMPP who were admitted to our hospital from January 2008 to December 2015, and the clinical manifestations, laboratory data, imaging performances, hospital courses and outcomes were analyzed.

Results Twenty-five patients with NP caused by RMPP were collected, with a median age of 5.1 (4.0–7.9) years. The mean duration of fever and hospital stay was 21.0 ± 8.9 and 19.9 ± 9.9 days, respectively. The levels of lactate dehydrogenase (LDH), C-reactive protein, interleukin (IL)-6, IL-10 and interferon-gamma were elevated. Meanwhile, the pleural fluid cell count, LDH and protein were also increased. 80.0% of the patients had pleural effusion; and a high incidence of lobar atelectasis and pulmonary consolidation was found the patients. The mean duration from the onset of symptoms to the discovery of necrotic lesions was 21.0 ± 6.9 days. 80.0% of the patients were administrated corticosteroids, and bronchoalveolar lavage was extracted separately from all patients. Of the 20 patients who presented with pleural effusion, 11 underwent thoracocentesis alone and 2 underwent chest drainage. All patients received prolonged courses of antibiotics (32.2 ± 8.7 days). All patients were dischaged home and recovered without surgical intervention; and chest lesions were resolved or only minimal residual fibrotic changes were residual within 3.0 (2.0–6.0) months.

Conclusions Necrotizing pneumonia caused by RMPP is severe, however, self-limiting and reversible. Good outcomes can be achieved with appropriate management.

Keywords Children · *Mycoplasma pneumoniae* · Necrotizing pneumonia · Refractory

Introduction

Mycoplasma pneumoniae (MP) is the common pathogens leading to community-acquired pneumonia (CAP) in children [1, 2]. *M. pneumoniae* pneumonia (MPP) is generally recognized as a self-limiting illness, but sometimes it will develop into refractory *M. pneumoniae* pneumonia (RMPP), with deterioration of conditions though after a regular macrolide antibiotic therapy for 7 days or longer [3, 4]. RMPP can lead to various pulmonary and extrapulmonary complications [5] and may develop under some situations into necrotizing pneumonitis [6]. Necrotizing pneumonia (NP), sometimes called cavitary pneumonia or cavitary necrosis, is commonly caused by *Streptococcus pneumoniae* (SP) in children [7–9]. There is scant literature focused on NP caused by RMPP in children. In the present study, we reviewed 25 patients with NP caused by RMPP who were admitted to our hospital, and we analyzed the clinical characteristics of these patients.

Methods

Case inclusion

Twenty-five patients with NP caused by RMPP admitted to Children's hospital, Zhejiang University School of Medicine from January 1, 2008 to December 31, 2015

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were identified. We diagnosed MPP based on the signs and symptoms of pneumonia [10], including fever, cough, abnormal lung auscultation and a new infiltrate on chest radiograph, as well as positive laboratory results, including serologic test (MP IgM, EUROIMMUN, Lübeck, Germany) positive and antibody titer ≥ 1:160 (FUJIREBIO INC., Tokyo, Japan) and MP polymerase chain reaction (PCR) tests (DaAnGene Co., Ltd., Guangzhou, China) from the nasopharyngeal aspirate and BAL and/or pleural effusion. RMPP was diagnosed according to the *Guidelines for management of community acquired pneumonia in children* [3, 4], which describes how the clinical characteristics of MPP deteriorate despite regular macrolide antibiotic therapy for 7 days or longer. The diagnostic criteria for NP were based on the clinical characteristics of pneumonia and characteristics revealed by chest computed tomography (CT). CT manifestations of NP are the destruction of normal lung parenchymal structure and a decrease in the parenchymal enhancement, which are gradually replaced by multiple small air or fluid-filled cavities [11–13]. Meanwhile, we excluded a lung abscess with solitary cavitation surrounded by an enhancing rim in the imaging. To exclude the possibility of co-infection, additional items were examined, as we previously described [5], including blood, pleural effusion (BD Diagnostics, Franklin Lakes, NJ, USA) and nasopharyngeal aspirate/broncho-alveolar lavage (BAL) cultures (Biomerieux, Lyons, France), protein purified derivative (PPD), nasopharyngeal aspirate for virus antigen detection (Diagnostic Hybrias, Webster, TX, USA) (respiratory syncytial viruses, metapneumovirus, adenovirus, influenza viruses, and parainfluenza virus), and serology for *Chlamydia trachomatis* (CT), *Chlamydia pneumoniae* (CP) and *Legionella pneumophila* (LG) (EUROIMMUN, Lübeck, Germany).

This study was approved by the Ethics Committee of Children's Hospital, Zhejiang University School of Medicine (no. 2012121). The legal guardians of each patient provided written informed consent.

BAL under flexible bronchoscopy

We choose different types of fiberoptic bronchoscopes, such as Olympus BFXP40 (2.8 mm external diameter and 1.2 mm working channel), BF-3C30 (3.6, 1.2 mm) and BF-P40 (4.9, 2.2 mm), according to the age and body weight of patients. Patients were sedated with intravenous midazolam (0.1–0.15 mg/kg) after more than 6 h fasting, and the nose and vocal cords were anesthetized topically with 1% lidocaine. Then the bronchoscope was inserted in the orifice of lobar bronchia, where the lesion located on CT scanning. According to the different body weight (weight < 20 kg: 1 mL/kg/time, 3 times; weight > 20 kg: 20 mL/time, 3 times), BAL with normal saline was conducted with − 25 to about − 100 mmHg (− 3.3 to − 13.3 kPa) suction. At the same time, we collected the BAL fluid from patients for microbiological determination. We monitored the heart rate, pulse oxygen saturation (SpO_2) and respiratory rate of the patients during the procedure. If the patient had sign and symptom of hypoxia (cyanosis, low SpO_2 and/or high heart rate), we would give them oxygen at once, and stopped the procedure temporarily as necessary.

Data collection

The demographics, clinical information, laboratory results, imaging performance and outcomes were gathered from the medical information on our patients. Samples of nasopharyngeal aspirate were routinely detected for bacteria, viruses and MP on the day of admission. Blood specimens were also tested for routine blood examination, cytokines, lactate dehydrogenase (LDH), procalcitonin (PCT), subpopulations of T lymphocytes, immunoglobulins and specific antibody to atypical pathogens. A chest CT scan was carried out during hospitalization and within the follow-up period. Pleural effusion was diagnosed by ultrasound and patients were administrated thoracentesis when necessary. Patients received flexible bronchoscopy (FOB) with bronchoalveolar lavage according to the *Guide to pediatric bronchoscopy* [14]. Routine blood examination was performed every 2–3 days if it was abnormal. Patients who were administrated oxygen therapy and mechanical ventilation were assessed by the Guidelines [3]. All patients were followed up until the necrotic lesions were absorbed. Body temperature, respiratory tract signs and symptoms, and extrapulmonary complications [15] of the patients were examined and recorded at study entry and every 8 hours thereafter.

Measurement of serum cytokines

The concentrations of cytokines in serum, including interleukin(IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α and interferon (IFN)-γ were detected using a CBA HumanTh1/Th2 Cytokine Kit II (BD Biosciences, San Diego, CA, USA). Using FACSCalibur flow cytometer (BD Biosciences), we acquired the data of serum samples, and then generated the results using BD CBA Software (BD Biosciences, San Jose, CA, USA). Then the standard curve was established. The lowest detection limit of cytokines was 1.0 pg/mL, while the highest was 5000 pg/mL.

Statistical analysis

Statistical analyses were carried out using SPSS software (version 20.0) (IBM Corp., Armonk, NY, USA). Data

representing the normal distribution were expressed as mean ± standard deviation, while data showing a skewed distribution were exhibited as median values (interquartile range).

Results

Clinical features

All patients were identified with MP infection and had negative results for other pathogenic infections. This study enrolled 8 boys and 17 girls. The median age was 5.1 (4.0–7.9) years. All the patients were previously healthy and had no underlying diseases except a history of fever for a mean of 13.2 ± 6.8 days before hospitalization. The mean duration of fever and hospital stay was 21.0 ± 8.9 and 19.9 ± 9.9 days, respectively. All the patients presented fever and cough, 8.0% suffered chest pain and chill, and 16.0% suffered tachypnea. Of the 25 patients, 16 had extrapulmonary complications, including 7 with myocarditis, 1 with proteinuria, 6 with liver function abnormalities, 4 with rash, and 1 induced by with hemolytic anemia. Physical examination showed that 76.0% of the patients presented a decrease of in breath sounds on one side and 44.0% had rales (Table 1).

Laboratory data

The laboratory data are exhibited in Table 2. These results showed that the mean values for CRP and LDH increased significantly compared with those of the normal values. The serum cytokines of these patients were also detected in the patients. The median values for interleukin 2 (IL-2), IL-4, IL-6, IL-10, TNF-α and IFN-γ were 3.4 (2.8–5.6) pg/mL, 3.7 (2.3–4.7) pg/mL, 50.1 (28.4–129.7) pg/mL, 5.1 (3.9–11.5) pg/mL, 2.8 (2.5–3.4) pg/mL, and 12.8 (6.1–74.9) pg/mL, respectively. Meanwhile, the pleural fluid values were analyzed in all patients. Interestingly, the median value of the pleural fluid cell count, and LDH and protein were obviously elevated.

Radiologic findings

A chest high-resolution CT scan was performed if patients suffered constant fever despite antibiotic therapy, or were suspected with cavity formation on the chest radiograph. Representative CT images from two patients with NP are shown in Fig. 1. Table 3 shows the details of pulmonary complications occurring in our patients. According to the CT scan, the mean time from the onset of symptoms to the discovery of necrotic lesions was 21.0 ± 6.9 days.

Treatment and outcome

Before admission, all patients had received at least one type of antibiotics. After admission, all patients were administrated with macrolides and at least another kind

Table 1 Clinical characteristics of 25 NP patients caused by RMPP

Clinical information	Total subjects ($n=25$)
Age, y	5.1 (4.0–7.9)
Male/female, *n*	8/17
Clinical presentation, % (*n*/*N*)	
Fever	100 (25/25)
Cough	100 (25/25)
Chest pain	8.0 (2/25)
Chill	8.0 (2/25)
Tachypnea	16.0 (4/25)
Patients with extrapulmonary complications, % (*n*/*N*)	64.0 (16/25)
Physical examination, % (*n*/*N*)	
Rales	44.0 (11/25)
Decreased unilateral lung sound	76.0 (19/25)
Duration of fever before admission, d	13.2 ± 6.8
Total duration of fever, d	21.0 ± 8.9
Length of stay, d	19.9 ± 9.9

Data are presented as mean ± SD, median (25th–75th percentile) or *n* (%)

Table 2 Laboratory findings of 25 NP patients caused by RMPP

White blood cell ($\times 10^9$/L)	11.13 ± 3.20
Neutrophil (%)	76.5 ± 11.7
C-reactive protein (CRP), mg/L	87 ± 51
Lactatedehydrogenase (LDH), IU/L	685 ± 316
Procalcitonin (PCT), ng/mL	0.317 (0.091–0.966)
Cytokines, pg/mL	
Interleukin 2 (IL-2)	3.4 (2.8–5.6)
IL-4	3.7 (2.3–4.7)
IL-6	50.1 (28.4–129.7)
IL-10	5.1 (3.9–11.5)
Tumor necrosis factor alpha (TNF-α)	2.8 (2.5–3.4)
Interferon gamma (IFN-γ)	12.8 (6.1–74.9)
Pleural fluid values	
Cell count ($\times 10^6$/L)	760 (277–1250)
N (%)	56.8 ± 22.9
Glucose (mmol/L)	5.78 ± 1.35
LDH (U/L)	2685 ± 943
Protein (g/L)	44.8 ± 5.9

Data are presented as mean ± SD, median (25th–75th percentile). The normal range of laboratory indices: PCT, 0–0.460 ng/mL; CRP, < 8 mg/L; LDH, 110–295 U/L; IL-2, 1.1–9.8 pg/mL; IL-4, 0.1–3.0 pg/mL; IL-6, 1.7–16.6 pg/mL; IL-10, 2.6–4.9 pg/mL; TNF-α, 0.1–5.2 pg/mL; IFN-γ, 1.6–17.3 pg/mL

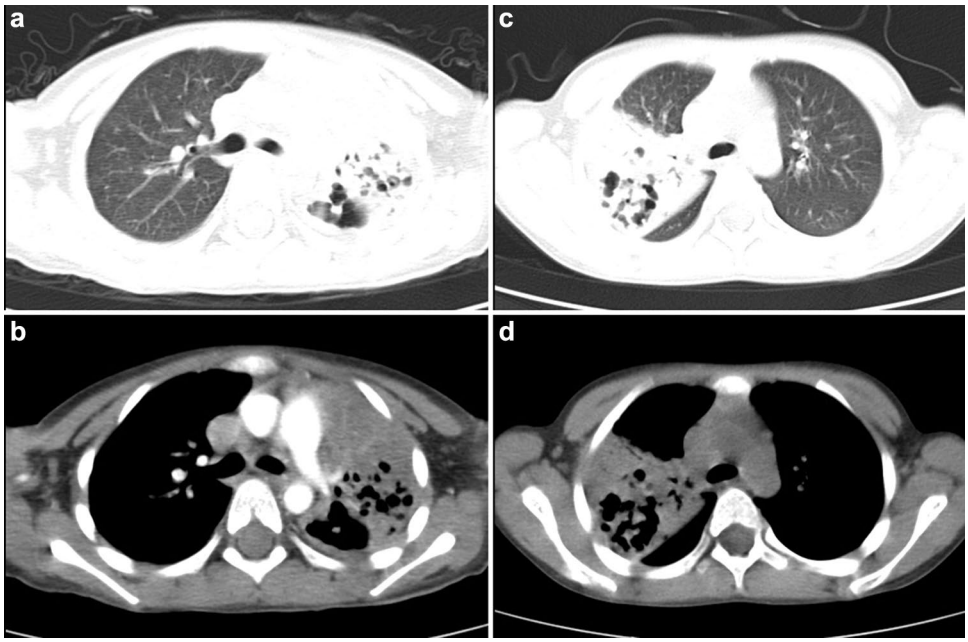

Fig. 1 Representative chest computed tomography (CT) images from a 4-year-old boy (**a**, **b**) and a 4-year 3-month-old girl (**c**, **d**) hospitalized with necrotising pneumonia (NP). The lung (**a**, **c**) and mediastinum (**b**, **d**) CT windows are shown at the same anatomic level. CT findings of NP including multiple air-filled cavities within the lung parenchyma

of antibiotics, such as penicillin, cephalosporins, imipenem or vancomycin. These patients were also administered antibiotics after hospital discharge, with the total course of antibiotics including hospitalization and discharge being 32.2 ± 8.7 days. Ten patients needed oxygen therapy, 20 were administrated corticosteroids, 25 received flexible bronchoscopy (FOB) with bronchoalveolar lavage, and no patients required mechanical ventilation. Under FOB, three patients were found to have local bronchial stenosis and four had bronchial epidermal exfoliation and a mucous plug. All patients were discharged when they were afebrile, signs and symptoms had disappeared, and laboratory results and radiological imaging indicated no further symptomatic deterioration. No deaths occurred in the study. Follow-up studies were carried out for all patients with chest X-ray and chest CT scans taken, occasionally. The chest radiology of all the patients revealed absolute resolution and only minimal fibrotic residues over the previous area of consolidation (detailed data are shown in Table 3).

Discussion

For children, MP is one of the main pathogens causing CAP. MPP was generally thought to be a self-limiting disease, but increasingly, RMPP, which causes various pulmonary and extrapulmonary complications, such as NP, has been researched and published in recent years [4–6, 16, 17]. NP is indicated when there is liquefaction and cavitation of pulmonary tissue, which is thought to be caused by several pathogens, such as SP, MP, *Staphylococcus aureus* and so on [11, 18–20].

All patients included into this study were previously healthy. The median age of these NP patients was 5.1 (4.0–7.9) years, which was similar to other reported studies with MP-associated NP in children [6, 9]. Most patients presented extrapulmonary complications (64%) and decreased unilateral lung sound (76%). All patients had developed fever before admission, with a mean duration of 13.2 ± 6.8 fever days before admission. After hospitalization, fever persisted in the patients and the mean total length of fever days was 21.0 ± 8.9 days, which leading to prolonged hospital stay. The prolonged course was related to radiography of significantly severe lung damage and refractory treatment of RMPP.

Regarding the laboratory examinations, CRP levels were increased markedly in the NP patients, which was consistent with previous articles [6, 21]. Meanwhile, the abnormal laboratory findings of elevated LDH, IL-6, IL-10 and IFN-γ observed in many of our patients were possibly caused by the excessive inflammatory response to RMPP. The pleural fluid features involved with NP in our study, particularly the high values of the pleural fluid cell count, LDH and protein were also observed. These observations presumed that the reason for the progress of NP was not associated with an inadequate therapy but rather with the presence of the pyrogenic products of inflammation and tissue damage [22].

Pleural effusion often occurred with NP, and 80.0% with NP caused by RMPP in the study were associated with pleural effusion, which was in accordance with other reports [23–25]. A high incidence of lobar atelectasis and pulmonary consolidation were found in the patients (44.0 and 76.0%, respectively). The diversification of radiological manifestations may be due to direct organismic impact

Table 3 Radiology findings, treatments and outcomes of 25 NP patients caused by RMPP

Radiology findings	
Patients with pulmonary complications, % (*n*/*N*)	
Pleural effusion	80.0 (20/25)
Lobar atelectasis	44.0 (11/25)
Pulmonary consolidation	76.0 (19/25)
Pleural thickening	20.0 (5/25)
Pleural effusion septation	0.0 (0/25)
Mean time for finding necrotic lesions, d	21.0 ± 6.9
Endoscopic manifestation, % (*n*/*N*)	
Local bronchial stenosis	12.0 (3/25)
Bronchial epidermal exfoliation and mucous plug	16.0 (4/25)
Only mucous congestion and edema	72.0 (18/25)
Treatments	
Antibiotic therapy days before admission	10.8 ± 5.2
Antibiotic therapy days after admission	21.4 ± 9.2
Total antibiotic therapy days	32.2 ± 8.7
Oxygen therapy, % (*n*/*N*)	40.0 (10/25)
Mechanical ventilation, % (*n*/*N*)	0.0 (0/25)
Use of corticosteroids, % (*n*/*N*)	80.0 (20/25)
Bronchoalveolar lavage, % (*n*/*N*)	100.0 (25/25)
Thoracocentesis, % (*n*/*N*)	55.0 (11/20)
Chest drainage, % (*n*/*N*)	10.0 (2/20)
Outcomes	
Median time for WBC count recovered, d	0 (0–3)
Mean time for CRP normalized, d	14.4 ± 8.7
Median time for PCT normalized, d	0 (0–6)
Median time for necrotic lesions absorbed, mon	3.0 (2.0–6.0)

Data are presented as *n* (%), or mean ± SD, or median (25th–75th percentile)

and host hyper-responsiveness of immunology. These meaningful radiographical manifestations of lung destruction were in accordance with the complex course. Interestingly, in patients with NP caused by RMPP, the mean time from the onset of symptoms to the discovery of necrotic lesions was 21.0 ± 6.9 days, which was a little longer than that in other reports [21]. The cause for delayed diagnosis was likely due to a delay in performing a CT scan. Thus, in patients with RMPP presenting persistent fever or symptomatic deterioration, severe complications, such as NP, should be considered and CT should be performed as soon as possible.

Because of a longer duration of fever, a prolonged course of antimicrobial agents was administered to the patients. The mean total length of antibiotic therapy was 32.2 ± 8.7 days. The period of therapy was as long as that of other reports [11, 19]. Most patients were prescribed with corticosteroids because a cell-mediated strong immune response plays an important role in the development of RMPP [4, 26], and it was discovered that corticosteroids were of great benefit in improving conditions. In addition, Barreira et al. [27] had reported a successful case of treating MP associated with NP using corticosteroids. FOB with BAL has now become an important method for diagnosis and therapy for respiratory diseases [28, 29]. We performed BAL in all the patients and found that BAL could remove respiratory tract secretions, and release obstruction of the respiratory tract. Thoracocentesis and chest drainage can be performed for identification of pathogens and symptomatic relief in necrotizing pneumonia with pleural fluid collections. Of this series, 55.0% of the patients underwent thoracocentesis and 10.0% of them experienced chest drainage.

Despite the severe and prolonged process, the long-term outcomes for the patients with NP have been reported to be good. All the patients were discharged without mortality. NP recovery without surgical intervention, and the chest radiographs in the follow-up illustrated almost full resolution or only minimal residual fibrotic change within 3.0 (2.0–6.0) months of hospitalization. The outcomes of the study were consistent with earlier reports of NP [1]. Thus, when NP caused by RMPP is diagnosed in children, it can be recognized as a severe, but, self-limiting and reversible disease.

The present study had several limitations. First, it was a retrospective observational study, and the patients enrolled were from a single center. Second, there may have been several patients who were co-infected with other pathogens, which could not be detected through our methods.

In conclusion, NP may not be considered a rare complication of RMPP in children given the increasing use of CT scans, and it can have a severe, prolonged clinical course and radiological manifestations. However, good outcomes can be expected with appropriate management including antibiotics, corticosteroids, BAL and other strategies, such as chest drainage for pleural effusions.

Author contributions WX was responsible for the literature search and manuscript preparation. ZLJ and ZYL participated in the data collection. CZM was responsible for improving the manuscript. ZYY was responsible for the study design and revision of the manuscript.

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Compliance with ethical standards

Ethical approval This study was approved by the ethics committee of the Children's Hospital, Zhejiang University School of Medicine (IRB no. 2012.121).

Conflict of interest The authors declare that they have no competing interests.

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