Pediatrics and Neonatology (2013) 54, 402—405

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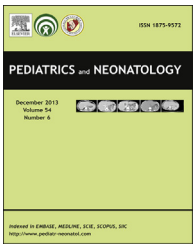

CASE REPORT

Clinical Features of *Mycoplasma pneumoniae* Infections in the 2010 Epidemic Season: Report of Two Cases with Unusual Presentations

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Received Nov 10, 2011; received in revised form Feb 9, 2012; accepted Oct 17, 2012

Key Words
cytokine;
drug resistance;
Mycoplasma pneumoniae;
myocarditis;
steroid

Mycoplasma pneumoniae (Mp) is one of the main pathogens causing community-acquired pneumonia, particularly in young individuals. Host immune response appears to play an important role in prolonged symptoms, as well as in the recent increasing prevalence of drug-resistant Mp isolated from patients. Case 1 had a prolonged clinical course caused by drug-resistant Mp and received steroid therapy despite Mp susceptibility to some antimicrobial agents. Serum cytokine profiles revealed elevation of interleukin-6/-10 and interferon-γ in acute phase. Case 2 had mycoplasmal myocarditis without any respiratory symptoms, which resolved spontaneously without the administration of any antimicrobial agent. These observations suggest that host immune response probably contributes to the etiology of Mp-associated complications.

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1875-9572/$36
http://dx.doi.org/10.1016/j.pedneo.2012.11.016

1. Introduction

Mycoplasma pneumoniae (Mp) is one of the main pathogens causing community-acquired pneumonia in children, especially in those of school age. Macrolide (ML) antibiotics are usually considered to be the first choice for the treatment of Mp infections. However, the prevalence of ML-resistant Mp isolates in pediatric patients has been increasing rapidly, with a confirmed 23S rRNA mutation. In 2008, the prevalence was reportedly 30.0% in Japan[1] and 70% in China.[2] Although no significant differences between prolonged clinical symptoms and drug resistance have been reported previously, host immune response has been recognized as contributing to severity. Serum cytokine profiles revealed high levels of inflammatory cytokines such as interleukin (IL)-6/-10 and interferon (IFN)-γ,[3,4] with a study including the finding of a significant association between serum level of IL-18 and severity of Mp pneumonia in children.[5]

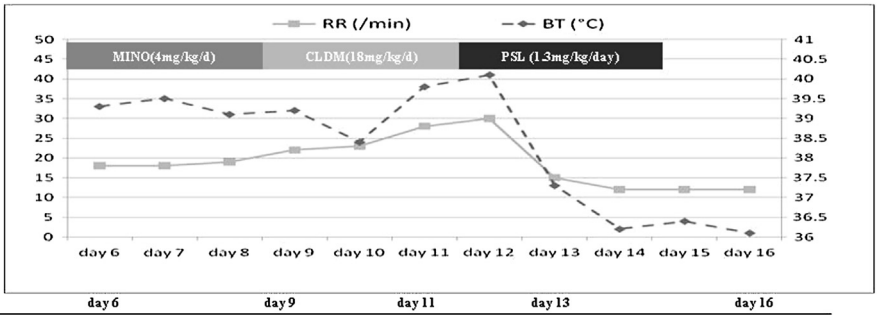
Herein, we present two patients with interesting characteristics to report clinical aspects of Mp-associated complications in the 2010 epidemic season.

2. Case Reports

2.1. Case 1

A previously healthy 9-year-old boy, with a 6-day history of high fever and dry cough, was brought to our department and admitted in December 2010. He had received clarithromycin (CAM, 10 mg/kg/d) 2 days prior to hospitalization. Physical examination on admission revealed fever (37.8°C), but no rales in either lung on auscultation. Respiratory distress was not evident from his respiratory rate (RR, 18/min) or percutaneously measured oxygen saturation (SpO_2, 97%) on room air. A chest roentgenogram on admission indicated consolidation in the right middle lobe. A nasopharyngeal swab (NPS) sample was collected on admission and sent for comprehensive rapid analysis using real-time polymerase chain reaction (PCR) to determine the causative pathogen.[6] This assay detected Mp DNA, but no other respiratory bacterial or viral DNA. Bacterial culture of the same specimen yielded no causative pathogens.

Vital signs, treatments, and laboratory data during the clinical course are shown in Figure 1. The patient was treated with antibiotics [minocycline (MINO), 4 mg/kg/d for 3 days, and clindamycin, 18 mg/kg/d for 3 days]. Clinical symptoms, including fever, continuous dry cough, and respiratory conditions, persisted despite the administration of these antibacterial agents. The chest radiographic abnormality had not resolved by Day 11 after the onset. Blood tests revealed increases in aspartate aminotransferase and lactate dehydrogenase (LDH) together with elevations in ferritin and soluble IL-2 receptor (sIL-2R), without significant hepatic and renal dysfunctions. These findings and the clinical course suggest that Mp infection induced host immune response. Intravenous administration of prednisolone (1.3 mg/kg/d) for 3 days was initiated on Day 12 after the onset. The patient recovered rapidly after steroid administration and was discharged on Day 16 after the onset. No recurrence was evident at follow-up assessment on Day 20.



	day 6	day 9	day 11	day 13	day 16
IL-2 (pg/mL)	NP	NP	0	0	0
IL-4 (pg/mL)	NP	NP	0	0	0
IL-6 (pg/mL)	NP	NP	17.56	0	0
IL-10 (pg/mL)	NP	NP	16.11	8.91	0
TNF-α (pg/mL)	NP	NP	0	0	0
IFN-γ (pg/mL)	NP	NP	5.37	0	0
IL-17A (pg/mL)	NP	NP	0	0	0
AST (IU/L)	30	67	63	35	28
LDH (IU/L)	293	567	541	432	260
Ferittin (ng/mL)	NP	NP	602	NP	109
sIL-2R (U/mL)	NP	NP	1960	NP	1380
WBC ($x10^2/\mu L$)	44	28	52	69	71
CRP (mg/dL)	3.0	1.5	0.8	0.3	0.1

Figure 1 Clinical course in Case 1. Laboratory data revealed that elevations of serum IFN-γ and IL-6/-10 concentrations resolved after the initiation of steroid therapy. AST = aspartate aminotransferase; BT = body temperature; CLDM = clindamycin; CRP = C-reactive protein; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MINO = minocycline; NP = not performed; PSL = prednisolone; RR = respiratory rate; sIL-2R = soluble interleukin-2 receptor; TNF = tumor necrosis factor; WBC = white blood cell counts.

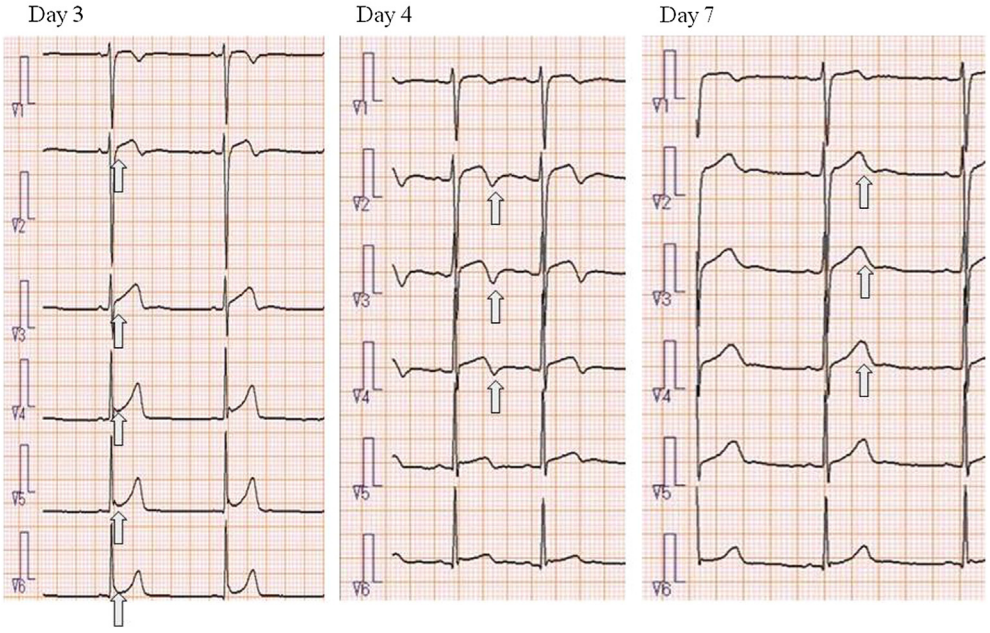


Figure 2 Electrocardiographic changes in Case 2. Arrows indicate elevation of ST wave (V2—6) on Day 3, negative T wave (V2—4) on Day 4, and positive T wave (V2—4) on Day 7 after onset of symptoms, respectively. Decrease of T wave (V5 and V6) on Day 7 also was observed.

On Day 19 after the onset, the MP strain was isolated from the NPS sample obtained on admission for the determination of minimal inhibitory concentrations (MICs). Susceptibility tests using microdilution methods with pleuropneumonia-like organism broth, as previously described,[7] showed MICs of MINO and levofloxacin of 0.25 and 0.5 μg/mL, respectively, suggesting the absence of drug resistance. On the other hand, MICs of erythromycin, CAM, azithromycin, telithromycin, and rokitamycin were >64, >64, 32, 64, and 0.125 μg/mL, respectively. Genetic analysis data for the strain indicated amino acid substitution A2063G in domain V of 23S rRNA. In this case, we confirmed that the causative pathogen was ML-resistant Mp.

Serum samples were obtained on Days 11, 13, and 16 after the onset. Circulating levels of seven inflammatory cytokines were measured using a BD CBA kit (Becton-Dickinson Biosciences, San Diego, CA, USA), together with a BD cytometric bead array system (Becton-Dickinson Biosciences). Serum concentrations of IFN-γ, IL-6, and IL-10 were increased on Day 11 and decreased after steroid administration.

2.2. Case 2

In December 2010, a previously healthy 13-year-old girl was brought to our department with a 3-day history of fever and chest pain. Vital signs were as follows: body temperature, 37.7°C; heart rate, 88/min, regular; RR, 18/min; SpO_2, 97% on room air; and blood pressure, 113/70 mmHg. Physical examination revealed neither any significant cardiac murmurs nor any pericardiac rubs. A chest roentgenogram on admission indicated no significant cardiomegaly and consolidations in the lung. Laboratory findings included elevated serum concentrations of creatine kinase (CK, 398 IU/L and CK-MB 34 IU/L) and C-reactive protein (CRP, 4.9 mg/dL), and a positive troponin-T reaction, all suggesting cardiac involvement. Elevation of S—T waves in leads V2—6 also suggested cardiac involvement. Echocardiography showed mild left ventricular hypertrophy and mitral valve regurgitation (Grade I), but no significant pericardial effusion or coronary dilation. The patient was diagnosed as having myocarditis and was admitted to our department immediately. The chest pain and fever resolved spontaneously, with improvements in laboratory findings (e.g., serum levels of CK and CRP decreased). Mp infection was diagnosed with a four-fold elevation of antibody titers against Mp (particle agglutination method) on Days 3 and 7. At discharge, echocardiography showed no effusions or regurgitation involving the left ventricle. Figure 2 summarizes the electrocardiographic changes.

We analyzed changes of viral antibodies in both acute and convalescent phases. These analyses included antibodies against coxsackie virus A type (2—7, 9, and 10) and B type (1—5), cytomegalovirus, and influenza virus (H1N1, H3N2, and B), but no significant elevations were observed.

3. Discussion

ML-resistant Mp infection in Case 1 induced prolonged clinical course even though a drug to which the organism was susceptible had been administered. Amino acid substitution (A2063G) of 23Sr rRNA in the isolate is the most prevalent pattern, and its prevalence is increasing. In 2011, the prevalence of ML-resistant Mp strain among children with community-acquired pneumonia in Japan was reported to be 89.5% (68 of 76 strains).[8] The rapidly increasing prevalence seems to be due to transport of the resistant strains from

Asian countries, including China, to Japan via travel and/or business. This strain was resistant to CAM but susceptible to MINO. However, an antimicrobial therapy did not ameliorate symptoms. We speculate that the immune response might have contributed to this patient's prolonged clinical course. It was reported that inflammatory cytokines including IL-8/-18 and IFN-γ play important etiological roles.[4,5,9] High serum levels of sIL-2R, IL-6, and IL-10 were reported in severe Mp infection, presenting as hemophagocytic syndrome.[3] We confirmed elevations of serum cytokines, together with high serum concentrations of ferritin, sIL-2R, and LDH, which also suggested host immune response. Oishi et al[5] reported a relationship between IL-18 and LDH in Mp pneumonia: the LDH value of 480 IU/L corresponds to the IL-18 value of 1000 pg/mL, which is an appropriate level to begin steroid administration for Mp pneumonia. We could not measure serum IL-18 levels in Case 1. However, a maximum LDH value of 561 IU/L may reflect elevation of serum IL-18 level, which is a reasonable criterion for starting steroid administration. In fact, Case 1 responded well to the steroid treatment. These findings suggest that prolonged Mp infection did not result from drug resistance, but rather from host immune response. The treatment option for ML-resistant Mp pneumonia appears to be MINO, but it is not recommended for pediatric patients aged 8 years or younger.[8] Definitive proof of efficacy and safety of steroid administration to ML-resistant Mp-infected children when treating the prolonged symptoms will require a randomized trial.

Myocarditis caused by Mp infection in Case 2 improved spontaneously without any respiratory tract infectious symptoms. The symptoms in this case were similar to those of viral myocarditis such as coxsackie virus B type infection. However, Case 2 did not progress to a severe state with arrhythmias or acute cardiac failure. Izumi[10] reported that coxsackie B viruses were the most common causative pathogens, while only 4% of myocarditis cases were caused by Mp infection. Morimoto et al[11] reported 24 cases of myocarditis caused by Mp infection, 13 (54.2%) of whom were 15 years and younger. They reported myocarditis, which was caused by Mp infection, to have a good prognosis because only one patient died. Only two cases (8.3%) developed grade III atrioventricular block or abnormal Q waves, suggesting relatively mild cardiac injuries as compared to viral infections.

Case 2 showed spontaneous recovery and mild clinical features, including mild hypertrophy involving the left ventricular muscle and mild mitral valve regurgitation. Furthermore, she did not develop severe heart failure despite not receiving an antimicrobial agent. It seemed that host immune response occurred against Mp infection.

Of 24 patients with Mp-associated myocarditis, 23 showed rhinitis and 12 had pneumonia.[11] We did not perform real-time PCR assay for the detection of Mp DNA, instead of evidence concerning the four-fold elevation of antibody titers. The respiratory tract is considered to be the transmission pathway of Mp. If the patient shows symptoms related to myocarditis during the Mp epidemic season, collecting nasopharyngeal samples is useful to clarify the causative pathogen by real-time PCR assay.

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