Clinical features, risk factors and treatment of fulminant Mycoplasma pneumoniae pneumonia: A review of the Japanese literature

[1, 2]Koichi Izumikawa, [3]Kinichi Izumikawa, [1]Takahiro Takazono, [2]Kosuke Kosai, [4]Yoshitomo Morinaga, [1]Shigeki Nakamura, [1,2]Shintaro Kurihara, [1]Yoshifumi Imamura, [1]Taiga Miyazaki, [2]Misuzu Tsukamoto, [4]Katsunori Yanagihara, [2]Kohei Hara and [1]Shigeru Kohno

[1]Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

[2]Nagasaki University Infection Control and Education Center, Nagasaki University Hospitals, Nagasaki, Japan

[3]Department of Internal Medicine, Izumikawa Hospitals, Nagasaki, Japan

[4]Department of Laboratory Medicine, Nagasaki University Hospitals, Nagasaki, Japan

Corresponding author:

Koichi IZUMIKAWA, M.D., Ph.D.

Department of Molecular Microbiology and Immunology,

Nagasaki University Graduate School of Biomedical Sciences

1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Phone: +81-95-819-7273, Fax: +81-95-849-7285

E-mail: koizumik@nagasaki-u.ac.jp

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ABSTRACT

Mycoplasma pneumoniae (MP) is one of the most common causes of community-acquired pneumonia in children and young adults. Although MP sometimes causes self-limiting pneumonia, severe and fulminant cases with hypoxia occur, but their clinical features have rarely been reported. This study aimed to reveal the clinical manifestations, risk factors, and treatment of fulminant MP pneumonia (MPP). Using PubMed and abstracts from the proceedings of several domestic Japanese academic societies, we reviewed the Japanese and English literature for cases of fulminant or severe MPP reported in Japan. All clinical information such as sex, age, underlying diseases, clinical symptoms, clinical course, laboratory and radiological findings, and treatment was collected and analyzed. In total, 52 fulminant MPP cases were reported between September, 1979 and February, 2010. The dominant population of fulminant MPP was young adults without severe underlying diseases. Cough (97.3%), fever (100.0%), and dyspnea (83.3%) with diffuse abnormal findings in radiological examinations were noted. Antibiotics without anti-mycoplasmal activity were used in 32 cases (61.5%) as initial treatment prior to the onset of hypoxia. Anti-mycoplasmal drugs were appropriately used in 41 cases (78.8%) after onset of respiratory failure with steroids (23 cases, 45.1%) and effective. The majority of patients improved within 3–5

days after steroid administration. There were only 2 fatal cases. Although this small retrospective study did not reveal the apparent risk factors of fulminant MPP, initial inappropriate use of antibiotics may be a risk factor, and early administration of appropriate anti-mycoplasmal drugs with steroids as a cellular immune suppressor is required.

INTRODUCTION

Mycoplasma pneumoniae is one of the most common causes of atypical pneumonia worldwide occurring in all populations especially youths. Transmission of *M. pneumoniae* occurs via infected respiratory droplets during close contact between the source and the recipient. Atypical pneumonia is considered to account for 7-20% of community-acquired pneumonia (CAP) [1,2]. Previous Japanese epidemiological studies of CAP have also indicated a prevalence of 5.2-15.4%, which does not differ from the data of studies carried out in other countries [3-5]. The actual incidence of *M. pneumoniae* pneumonia (MPP), however, may be higher in patients with mild symptoms that can be managed without hospital admission. Commonly, patients with mycoplasma respiratory infection may have nonproductive, persistent cough, pharyngitis, rhinorrhea, and occasional extrapulmonary manifestations such as hemolysis, skin reactions (e.g.. the Stevens-Johnson syndrome), and central nervous system complications. Although MPP is sometimes self-limiting, and macrolides are effective against it, numerous fulminant cases of MPP, including that of acute respiratory distress syndrome (ARDS), have been reported to date [6,7]. The major clinical manifestation of fulminant MPP is respiratory failure with diffuse consolidation or an abnormal interstitial pattern that can be observed on a chest radiograph. The

incidence of fulminant MPP is relatively rare despite the high prevalence of *M. pneumoniae* infection, and its etiology has not been fully described. The clinical features of fulminant MPP have not been clearly elucidated either.

We reviewed 52 cases of fulminant MPP with respiratory failure; we obtained their reports from multiple institutes and clinics in Japan and analyzed their clinical characteristics, risk factors, and treatment.

MATERIAL & METHODS

Case collection

Using PubMed and abstracts from the proceedings of several domestic Japanese academic societies, we searched the Japanese and English literature for cases of fulminant or severe MPP reported in Japan before February, 2010. Fulminant MPP was defined as the apparent presence of MP infection with hypoxia. All cases must ful1filled following conditions; (1) the patients should be diagnosed with MPP after obtaining positive findings from any of microbiological laboratory tests such as culturing or serological antibody tests including the passive agglutination (PA) test, complement fixation (CF) test, or indirect hemagglutinin (IHA) test in either single titer (titers of $\geq$ 64, $\geq$320 and $\geq$320 were considered positive for CF and IHA, and PA, respectively) or

elevated paired titer (a 4-fold increase in paired serum was considered positive), immunochromatography (IgM), or PCR; and (2) the patient should present no evidence of causative agents other than MP; and (3) the patient should have experienced acute onset of hypoxia with no previous history of respiratory failure (PaO_2 < 80.0 torr or arterial oxygen saturation < 95.0% at room air). All information in the acquired literature, such as sex, age, underlying diseases, clinical symptoms, clinical course, laboratory and radiological findings, and treatment, was collected and analyzed. We acquired permission to use the data in the literature from the corresponding author of each report.

Statistical analysis

Correlation of the radiological findings and severity of inflammation using inflammation markers such as white blood cell (WBC) count, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR) were analyzed by Kruskal-Wallis test. Risk factor of mechanical ventilation was evaluated in the multivariate analysis. Values of $p < 0.05$ were considered statistically significant. The statistical analysis was made using the SPSS V20 FOR WINDOWS (SPSS Inc., Chicago, IL, USA) and PRISM software (GraphPad Software, Inc., La Jolla, CA, USA).

RESULTS

Patient characteristics

We found and analyzed 52 cases in the literature between September, 1979 and February, 2010. All cases involved Japanese patients and MP infection was diagnosed by serological antibody tests such as PA, CF, and IHA. PA, CF, and IHA diagnosed 15, 27, and 20 cases, respectively, and confirmed single titer elevation in 2, 3, and 4 cases, respectively. The remaining cases were diagnosed by paired titer elevation in serum samples. MP was isolated in 2 of 3 cases in which culture was attempted. No case diagnosed by PCR or IgM immunochromatography was confirmed. The incidence of MPP was predominant among men (29 cases). Almost 50% of fulminant MPP cases (44.2%) occurred in patients aged 20–49 years (mean age, 42.3 years). Fourteen cases (26.9%) were reported among patients aged 30–39 years. There were 7 cases (13.5%) of fulminant MPP in the elderly (age > 70 years). Four cases were found among younger patients (age <20 years). Table 1 indicates the patients' underlying diseases. The majority of fulminant MPP patients (72.5%) had no underlying diseases, and 14 patients were current smokers.

The average PaO_2 of all patients was 52.3 torr, and 16 cases (30.1%) had severe hypoxia, with PaO_2 <50 torr. Mechanical ventilation was carried out in 15 patients

(28.8%). An extremely high $PaCO_2$ (>100 torr) was observed in 3 cases, chronic bronchitis was the underlying disease in 2 cases, and 1 case had no underlying disease. The reason for the patients' high $PaCO_2$ was unclear.

Clinical features of fulminant MPP

All patients (100%) presented with fever (>37.0°C) at their first visit to the hospital. The distribution of fever is shown in Table 2. A relatively high fever (>38.0°C) was observed in 46 cases (88.5%). Respiratory symptoms such as cough and dyspnea were observed on admission in 51 (97.3%) and 43 (83.3%) cases, respectively. The frequency of other upper respiratory symptoms and sputum production was lower (26.9% had sputum production). The average WBC count, CRP level, and ESR on admission were 10,486/μL (51 cases), 19.1 mg/dL (41 cases), and 70.4 mm/h (41 cases), respectively. The majority of severe MPP cases exhibited a relatively moderate inflammation response. Elevated serum aspartate amino transferase (AST) and alanine transaminase (ALT) levels (>40 IU) at the onset of respiratory failure was observed in 28 (60.9%) of 46 cases. All abnormal findings disappeared within 7–10 days of the onset of respiratory failure. The average serum total protein and albumin were 6.4 g/dL and 3.0 g/dL, respectively, among 34 cases; 11 cases (32.3%) exhibited low serum protein and

albumin levels. Sputum culture was performed for 35 cases, and normal flora were detected in 33 cases (94.3%). *Klebsiella pneumoniae* was detected in 2 cases but not considered a causative agent together with MP. The tuberculin reaction test was performed in 34 cases, and 32 cases (94.1%) produced a negative reaction. The average duration from onset of infection to the development of respiratory failure was 11.2 days in 51 cases (range, 5–21 days).

Radiological features of fulminant MPP

Analysis of chest radiography findings, including computed tomography scans, was performed in all 52 cases. A diffuse interstitial pattern (e.g., reticular, nodular, linear) was observed in 32 cases (61.5%). A diffuse alveolar pattern with or without air bronchogram was observed in 13 cases (25.0%). A mixed interstitial and alveolar pattern was observed in 7 cases (13.5%). Pleural effusion was noted in 7 cases, and these cases were categorized as either alveolar or mixed pattern cases. Correlation of the radiological findings and severity of inflammation using inflammation markers indicated that mixed pattern cases had higher CRP (n = 5, 28.7 mg/dL) compared to that of interstitial (n = 26, 17.2 mg/dL) or alveolar pattern (n = 10, 19.1 mg/dL) cases, however, there was no statistical different (p = 0.143). No such trend was identified

when comparing the findings of WBC counts and ESR, either.

Pathological features of fulminant MPP

Pathological investigation was performed in 24 cases: transbronchial lung biopsy (20 cases), open lung biopsy (3 cases), and autopsy (1 case). Table 3 lists the pathological findings and the average duration (days) from onset of infection to the pathological examinations being performed. Acute bronchiolitis was identified in the early phase of infection, followed by organizing pneumonia and alveolitis with or without granuloma formation at the recovery phase. These findings, however, were acquired from different cases. Diffuse alveolar damage was reported in 1 of the fatal cases.

Treatment of fulminant MPP

The initial treatment prior to respiratory failure is summarized in Table 4. Appropriate anti-mycoplasmal drugs such as macrolides (erythromycin, clarithromycin, and azithromycin) were used as primary treatment for MPP in only 6 of 52 cases. Beta-lactams and aminoglycosides, which have no potent activity against MP infection, were used as initial treatment in 32 cases (61.5%). The total rate of both inappropriate treatment and no-treatment cases was 78.8% (41 cases). No patients were treated with

quinolones or tetracyclines. The treatment after onset of respiratory failure is summarized in Table 5. Anti-mycoplasmal drugs with steroids were used in 23 cases (45.1%), and minocycline was used in almost half of these cases. Single administration of anti-mycoplasmal drugs without steroids were used in 18 cases (35.2%). No patients were administered antimicrobial agents without anti-mycoplasmal activity.

The efficacy of the steroids was assessed; Table 6 summarizes the dose, duration, and efficacy of steroids for fulminant MPP. Methylprednisolone was administered at over 500 mg/day to almost half of the patients, and the majority of these patients showed improvement within 3–5 days of steroid treatment. Prednisolone dosage was gradually tapered within a week for almost all cases. There were 4 patients who remained unresponsive after a week of steroid treatment; however, all patients showed improvement in 14 days.

Outcome of fulminant MPP

Only 2 deaths were reported among the 52 reviewed cases; the remaining 50 patients recovered. Fulminant MPP occurred in a 64-year-old apparently healthy woman who died from multiple organ failure although she was administered with a combination of erythromycin and steroids 2 days after admission. The patient received her first dose of

anti-mycoplasmal drugs only 17 days after the first appearance of respiratory symptoms; only beta-lactams were used before admission [8]. In another case, an 18-year-old man died due to Stevens-Johnson syndrome, which occurred as a complication of MP infection. The autopsy revealed apparent diffuse alveolar damage. Minocycline was administered only 7 days after the onset of MP infection. Although steroid therapy was initiated on day 4, the patient's condition did not improve.

DISCUSSION

The incidence of respiratory failure in cases of fulminant MPP has rarely been reported despite the high prevalence of MPP [6]. Among 295 MPP cases, we have encountered only 3 patients (1.0%), which presented respiratory failure (data not published).

MPP is sometimes a self-limiting disease; however, the following are considered virulence-associated factors of MP: 1) direct interaction between human host cells caused by toxicity (e.g., adherence to bronchoepithelial cells, toxin production, reactive oxygen species, and cytokines), and 2) indirect interaction of immunological or allergic reaction to MP infection [9,10]. Although the apparent mechanism and etiology of fulminant MPP have not been revealed, there are at least 3 possible hypotheses: 1) hyperimmune response originating in the lung due to repeated childhood MP infections,

2) loss of the ability to eradicate MP from the lung in primary infection resulting in longer-lasting MP infection in the lung, which may cause a hyperimmune response, and 3) overactive innate immune response such as macrophage activation via heterodimerization of Toll-like receptors 2 and 6 of the bronchoepithelial cells to MP lipoproteins [11]. Thus, the immunological hyper-reaction in the lung may induce lymphocyte activation, resulting in systemic impairment of cellular immunity and progression to fulminant status.

In this literature review, the majority of patients with fulminant MPP did not have underlying diseases, and very few patients were malnutritioned or had a history of smoking. Although the dominant population of fulminant MPP cases was young and healthy adults, MPP may become severe in elderly patients (age >70 years) (13%). All cases were confirmed as MPP infection with serological tests, the gold standard for diagnosis of MP infections. Although all cases were reported as *M. pneumoniae* single infection, it is possible that respiratory pathogens other than *M. pneumoniae* may have been involved. Since this was not a prospective study, the diagnostic methods for causative agents of pneumonia other than *M. pneumoniae*, such as culturing, serological tests, antigen detection, and PCR varied with each report.

The clinical manifestations of fulminant MPP were cough, high fever, and hypoxia

with diffuse abnormal findings on radiologic examination. Varied chest radiographic patterns were recognized in patients with fulminant MPP, and these findings may reflect the difference in the immunological response (e.g., difference in cytokine production) [10]. Liver dysfunction such as ALT and AST elevation were common in fulminant MPP. This may not have been caused by the direct invasion of MP to liver tissue, and an indirect immunological response to MP in liver tissue is considered to have played an important role. There were 15 cases required mechanical ventilation (37 cases not) in this review, we compared following factors such as sex, average age, existence of underlying diseases, appropriateness of initial treatment, and radiological patterns to estimate the risk factors for requirement of mechanical ventilation. No significant factors were associated for the requirement of mechanical ventilation (data not shown).

Cellular immunity is considered important in the etiology of MP infection, as described above. Since the Bacille Calmette-Guérin vaccination is common and adopted for routine childhood immunization in Japan, we consider negative tuberculin test results to be indicative of cellular immunity impairment in the Japanese population. The tuberculin test was negative in 94.1% of all cases. Data in our analysis supported the premise that early-phase impairment of cellular immunity may be correlated to the etiology of fulminant MPP.

The pathological findings demonstrated that acute bronchiolitis followed by organizing pneumonia, alveolitis, and granuloma formation were observed sequentially. Although this transitional change was not proved in one patient with several sequential tissue biopsy, the transition of the pathological findings was well-matched compared to that in a previous report [6].

The onset of respiratory failure was between 5 and 21 days (average, 11 days) from the appearance of symptoms; beta-lactams, but not tetracyclines or macrolides, were used as initial treatment prior to the development of respiratory failure in the majority of cases. Eighteen and 7 days, respectively, had elapsed until the first administration of anti-mycoplasmal drugs in the 2 fatal cases in this study. Other fatal MP cases have been published recently [12,13], and 14 days had elapsed until the first administration of anti-mycoplasmal drugs in 1 case. On the other hand, we found that anti-mycoplasmal drugs were used in only 6 cases; however, relatively lower doses and shorter durations were used (data not shown). Taken together, inappropriate initial treatment with beta-lactams or other drugs with no anti-mycoplasmal activity, and delayed administration of anti-mycoplasmal drugs may be an important factor in the etiology of fulminant MPP.

Administration of anti-mycoplasmal drugs with steroids was selected in this study as a

major treatment option after onset of respiratory failure. The administration of steroids without anti-mycoplasmal drugs also led to the improvement of respiratory failure. These findings support that steroids suppress cellular immunity, and they should thus be considered reasonable for management of fulminant MPP involving hyperactivated cellular immunity. However, the effect of steroids may reduce the native immune response to MP and increase the duration for MP eradication from the body. Therefore, longer periods of steroid administration should be avoided. Although it is difficult to illustrate the optimal duration and dose of steroids from the result of this study or other studies, methylprednisolone 500-1000 mg/day for 3 to5 day administration may be essential for patients with fulminant MPP especially for those who require mechanical ventilation. Furthermore, methylprednisolone 125-250 mg/day for 3 to5 day administration or more than 20mg/day of prednisolone for 5 to 7 days administration may be considered for the MPP patients without respiratory failure but with persistent fever or cough, dyspnea, wheezes, or diffuse pneumonia. Needless to say, the administration of appropriate anti-mycoplasmal drugs is strongly required for both conditions. Prospective studies may be warranted to determine the appropriate duration and dose of steroid administration in fulminant MPP.

To enable the early and appropriate usage of anti-mycoplasmal drugs, early and precise

detection of MP infection is essential to prevent deterioration. As presented in this study, definite diagnosis remains dependent on serological tests, which may require several weeks, and the culture of mycoplasma is not practical. Although current rapid diagnostic tools using PCR, which has high specificity and sensitivity, are available [14,15], they may not be applicable in every medical institute. Thus, the development of newer diagnostic tools is warranted.

Fulminant MPP case was defined as the presence of MP pneumonia with hypoxia in this study, and an apparent definition has not been established yet due to scarcity. Since our study is a descriptive and retrospective literature review of data from multiple institutes using our own case definition, there is a potential ascertainment bias in the patient selection as the limitation of the study.

In conclusion, our analysis of the literature on fulminant MPP cases indicates that initial inappropriate use of antibiotics may be a risk factor for fulminant MPP and that early administration of appropriate anti-mycoplasmal drugs with steroids as cellular immune suppressors is required.

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Table 1. Underlying diseases of fulminant *Mycoplasma pneumoniae* pneumonia cases

underlying diseases	number of case (%)
diabetes mellitus	1 (2.0)
bronchial asthma	5 (9.8)
chronic bronchitis	3 (5.9)
collagen diseases	1 (2.0)
hyperthyroidism	1 (2.0)
spincerebellar degeneration	1 (2.0)
pregnancy	1 (2.0)
hypertension	2 (3.9)
hypertrophic cardiomyopathy	1 (2.0)
none	37 (72.5)

Table 2. Symptoms and signs of fulminant *Mycoplasma pneumoniae* pneumonia cases

symptoms and signs	number of case (%)
fever (°C)	52 (100.0)
< 37.0	1 (3.8)
37.0 ~ 37.9	6 (11.5)
38.0 ~ 38.9	24 (46.2)
39.0 ~ 39.9	16 (30.8)
> 39.9	5 (9.6)
dyspnea	43 (82.7)
cough	51 (98.1)

Table 3. Pathological findings of fulminant *Mycoplasma pneumoniae* pneumonia cases (24 cases)

pathological findings	number of case	average days from onset to pathological examination
acute bronchiolitis	6	9.8
organizing pneumonia	12	17.9
alveolitis	9	34.2
alveolitis with granuloma formation	4	27.5
diffuse alveolar damage	1	15.0
normal lung tissue	1	18.0

Table 4. Summary of treatment prior to the presence of respiratory failure in fulminant *Mycoplasma pneumoniae* pneumonia cases (52 cases)

treatment	number of case (%)
tetracyclines	0 (0.0)
macrolides	4 (7.7)
clindamycin	2 (3.8)
penicillins	
cephems	32 (61.5)
aminoglycosides	
no antibiotics	9 (17.3)
unknown	5 (9.6)

Table 5. Summary of treatment after the presence of respiratory failure in fulminant *Mycoplasma pneumoniae* pneumonia cases (51 cases)

treatment	number of case (%)
antibiotics (only)	18 (35.2)
minocycline	9 (16.0)
doxycycline	2 (4.0)
erythromycin	5 (10.0)
clarithromycin	2 (4.0)
antibiotics + steroids	23 (45.1)
minocycline + steroid	10 (19.6)
erythromycin + steroid	5 (9.8)
clarithromycin + steroid	5 (9.8)
azithromycin + steroid	2 (3.8)
minocycline + erythromycin + steroid	1 (1.8)
steroid only	9 (17.6)
methylprednisolone	6 (11.8)
prednisolone	3 (5.9)
none	1 (2.0)

Table 6. Summary of efficacy of steroid in fulminant *Mycoplasma pneumoniae* pneumonia cases (18 cases)

case	age	sex	radiological pattern	steroid hormone used and dose (days used)		days for improvement of respiratory failure
1	40	F	alveolar	mPSL	1000mg (5)	5
2	26	F	alveolar	mPSL	1000mg (5)	5
3	35	F	mixed	mPSL	125mg (7)→250 (3)	8
4	49	M	interstitial	PSL	40mg (7)	5
5	21	F	alveolar	mPSL	1000mg (3)→PSL tapered	3
6	52	F	interstitial	mPSL	1000mg (3)→PSL tapered	3
7	26	F	mixed	mPSL	1000mg (5)	4
8	35	M	mixed	PSL	60mg (5)	5
9	16	F	alveolar	PSL	20mg (7)	5
10	37	M	interstitial	Hydrocortisone	1000mg (3)	8
11	36	M	interstitial	mPSL	500mg (5)→PSL tapered	3
12	24	M	mixed	mPSL	300mg (5)	3
13	60	F	interstitial	PSL	60mg (4) 40mg (2)	8

14	60	F	interstitial	PSL	40mg (7)	14
15	37	M	interstitial	PSL	40mg (7)	7
16	64	F	alveolar	mPSL	500mg	unknown
17	37	M	alveolar	mPSL	1000mg (3)→PSL tapered	5
18	38	F	interstitial	PSL	30mg→20mg	6

M, male; F, female; mPSL, methylprednisolone; PSL, prednisolone

Conflicts of interest:

Koichi Izumikawa received honorarium from Pfizer Japan Inc., Dainippon Sumitomo Pharma Co., Ltd., MSD K. K., Astellas Pharma Inc., Taisho Toyama Pharmaceutical Co., Ltd., and Daiichi Sankyo Co., Ltd. Yoshifumi Imamura received honorarium from Pfizer Japan Inc., Dainippon Sumitomo Pharma Co., Ltd., MSD K. K., Taisho Toyama Pharmaceutical Co., Ltd., and Daiichi Sankyo Co., Ltd. Shigeru Kohno and Katsunori Yanagihara received honorarium and research grant from Pfizer Japan Inc., Dainippon Sumitomo Pharma Co., Ltd., MSD K. K., Astellas Pharma Inc., Taisho Toyama Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Shionogi & Co., Ltd., and Meiji Seika Pharma Co., Ltd.

REFERENCES

1. Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med. 1995; 333: 1618-24.

2. Hammerschlag MR. *Mycoplasma pneumoniae* infections. Curr Opin Infect Dis. 2001; 14: 181-6.

3. Ishida T, Hashimoto T, Arita M, Tojo Y, Tachibana H, Jinnai M. A 3-year prospective study of a urinary antigen-detection test for *Streptococcus pneumoniae* in community-acquired pneumonia: utility and clinical impact on the reported etiology. J Infect Chemother. 2004; 10: 359-63.

4. Saito A, Kohno S, Matsushima T, et al. Prospective multicenter study of the causative organisms of community-acquired pneumonia in adults in Japan. J Infect Chemother. 2006; 12: 63-9.

5. Miyashita N, Fukano H, Mouri K, et al. Community-acquired pneumonia in Japan: a prospective ambulatory and hospitalized patient study. J Med Microbiol. 2005; 54: 395-400.

6. Chan ED, Welsh CH. Fulminant *Mycoplasma pneumoniae* pneumonia. West J Med. 1995; 162: 133-42.

7. Miyashita N, Obase Y, Ouchi K, et al. Clinical features of severe *Mycoplasma pneumoniae* pneumonia in adults admitted to an intensive care unit. J Med Microbiol. 2007; 56: 1625-9.

8. Takiguchi Y, Shikama N, Aotsuka N, Koseki H, Terano T, Hirai A. Fulminant *Mycoplasma pneumoniae* pneumonia. Intern Med. 2001; 40: 345-8.

9. Fernald GW, Clyde JWA, Denny FW. Immunology of Mycoplasma infection. New York: Plenum Medical Book Co; 1981.

10. Tanaka H, Narita M, Teramoto S, et al. Role of interleukin-18 and T-helper type 1 cytokines in the development of *Mycoplasma pneumoniae* pneumonia in adults. Chest. 2002; 121: 1493-7.

11. Takeuchi O, Kawai T, Mühlradt PF, Morr M, Radolf JD, Zychlinsky A, Takeda K, Akira S. Discrimination of bacterial lipoproteins by Toll-like receptor 6. Int Immunol. 2001;13: 933-40.

12. Park SJ, Pai KS, Kim AR, Lee JH, Shin JI, Lee SY. Fulminant and Fatal Multiple Organ Failure in a 12-Year-Old Boy With *Mycoplasma pneumoniae* Infection. Allergy Asthma Immunol Res. 2012; 4: 55-7.

13. Kannan TR, Hardy RD, Coalson JJ, et al. Fatal outcomes in family transmission of *Mycoplasma pneumoniae*. Clin Infect Dis. 2012; 54: 225-31.

14. Blackmore TK, Reznikov M, Gordon DL. Clinical utility of the polymerase chain reaction to diagnose *Mycoplasma pneumoniae* infection. Pathology. 1995; 27: 177-81.

15. Dorigo-Zetsma JW, Verkooyen RP, van Helden HP, van der Nat H, van den Bosch JM. Molecular detection of *Mycoplasma pneumoniae* in adults with community-acquired pneumonia requiring hospitalization. J Clin Microbiol. 2001; 39: 1184-6.