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Clinical features according to chest radiologic patterns of *Mycoplasma* pneumonia in children

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Background: Clinical differences in *Mycoplasma* pneumonia (MP) in children and adolescent patients according to abnormal infiltrate patterns on the chest X-ray were compared.
Methods: From 2012 to 2015, patients (n=336) diagnosed with MP at Yeungnam University Medical Center have been classified as eiher lobar pneumonia or bronchopneumonia based on the infilterate patterns observed on chest X-ray. Cases were analyzed retrospectively for gender, age, seasonal incidence rate, main symptoms (fever duration, extrapulmonary symptoms), and laboratory results, including white blood cell count, hemoglobin, platelets, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), as well as concurrent respiratory virus infection.
Results: The following results were observed. First, lobar pneumonia affected 22.0% of all MP patients and was the most common in preschool children, with a high incidence rate in November and December. Second, lobar pneumonia had a longer fever duration than bronchopneumonia (p<0.001), and also showed significantly higher platelets (336.8 vs. 299.1 k/μL, p=0.026), ESR (46.3 vs. 26.0 mm/hr, p<0.001) and CRP (4.86 vs. 2.18 mg/dL, p=0.001). Third, viral co-infection was more common in bronchopneumonia (p=0.017), affecting 66.7% of infants and toddlers (p=0.034). Finaly, lobar consolidation was most common in both lower lobes.
Conclusion: MP in children has increased in younger age groups, and the rate of lobar pneumonia with severe clinical symptoms is higher in older children.

Keywords: Clinical features; Lobar consolidation; *Mycoplasma* pneumonia; Children

INTRODUCTION

Mycoplasma pneumoniae was identified as the Eaton's agent in 1944, subsequent to Reimann's description of an acute respiratory infection with an atypical pneumonia pattern in 1938. In 1962, The Eaton's agent was cultured in an agar for the first time and was named *M. pneumoniae* [1]. It has been consistently reported as the primary agent for community-acquired atypical pneumonia. *M. pneumoniae* infection can cause symptoms of various degrees, ranging from slight upper airway infection to severe pneumonia; in addition, a variety of extrapulmonary manifestations can also appear [2]. It accounts for up to 10-40% of community-acquired pneumonia in children, with a higher incidence rate during epidemics [3]. *Mycoplasma pneumonia* (MP) occurs in all seasons, but previous Korean studies have shown an epidemic incidence with periodicity of every 3-4 years [3,4], and it has been seen more commonly in older children or adolescents [2,5]. However, a high incidence rate has also recently been reported in 1-4-year-old children [3,6-9].

The typical radiologic finding of MP is the presence of

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diffuse, reticular infiltrates with a bronchopneumonia pattern in the perihilar region and the lower lobes [2]. However, recent studies have reported that a lobar consolidation pattern is seen in 28-50% of MP cases in children [8,10-14].

This study attempt to determine whether MP patterns in children show similar trends of increasing MP incidence rate in younger children and increasing lobar consolidation pattern pneumonia, by conducting a retrospective survey of clinical and laboratory findings in accordance with the chest X-ray consolidation pattern in patients with MP.

MATERIALS AND METHODS

Between January 2012 and December 2015, a total of 336 patients younger than 18 years of age, who were diagnosed with MP and treated at Yeungnam University Medical Center, were included for analysis. Clinical features, including age, gender, seasonal incidence, fever duration, and extrapulmonary symptoms, as well as white blood cell (WBC) count, hemoglobin (Hb) level, platelet level, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), respiratory virus co-infection, and chest X-ray results were compared.

Subjects were limited to cases with prominent respiratory symptoms (e.g. productive cough, sore throat) and fever, and *M. pneumoniae* was confirmed positive in these subjects by an immunoglobulin M (IgM) testing. When clinical symptoms were suspicious, but *M. pneumoniae* IgM was negative or unclear, a follow-up testing was performed within 15 days. This was the case in 44 patients, of which, 16 patients were converted to positive. When *M. pneumoniae* IgM was positive, patients without imaging data, with impaired immune function (e.g., chemotherapy or bone marrow transplantation patients), or with chronic lung disease or tuberculosis were excluded from the survey.

Two pediatricians read the chest X-rays for concurrence; based on the findings, they categorized the cases into two groups: Clear, patchy consolidation in a lobar or segmental distribution were categorized into the lobar pneumonia group, and those with diffuse, bilateral reticulonodular infiltration into the bronchopneumonia group. The lobar pneumonia group was again divided into three age groups: Infants and toddlers (less than 3 years), preschool children (3-7 years), and school-aged children (8 years or higher). Viral co-infection was confirmed by examining the nasal swab samples with a polymerase chain reaction test for nine different viruses: influenza virus (A, B), respiratory syncytial virus (RSV), metapneumovirus, adenovirus, coronavirus, human rhinovirus, human enterovirus, human bocavirus, and parainfluenza virus. Fever duration was defined as the duration of body temperature 38℃ or higher during the disease period.

Data were analyzed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). The differences among the positive rates in different groups were analyzed using chi-square test, T-test, Kruskal-Wallis test, and Mann-Whitney test, with $p<0.05$ defined as statistical significance.

This study was approved by the institutional review board of the Yeungnam University Medical Center (YUMC 2016-08-031).

RESULTS

1. Demographic data

A total of 336 patients who met the criteria were diagnosed with MP in Yeungnam University Medical Center between January 2012 and December 2015, with a similar gender ratio of 1.14:1 (179 boys, 157 girls). The median age of patients was 5 years (4 months-18 years); there were 99 cases (29.5%) of infants and toddlers, 120 cases (35.7%) of preschool children, and 117 cases (34.8%) of school-aged children. When divided by chest X-ray findings, there were 74 cases (22.0%) with lobar pneumonia and 262 cases (78.0%) with bronchopneumonia (Table 1). The annual incidence rate of MP in children had peaks in April and October (Fig. 1), and the lobar pneumonia group showed a sharp increase in the rate since 2013 (Fig. 2); the proportion of lobar pneumonia in MP increased during the winter (Fig. 3).

2. Clinical findings

The mean fever duration was 4.7±3.8 days, with 6.8±4.4 days for lobar pneumonia, which was significantly longer than the 4.1±3.4 days for bronchopneumonia ($p<0.001$). Extrapulmonary symptoms were present in 93 cases (27.7%), with gastroenterologic symptoms in 41 cases (diarrhea in 36 cases (only selected if diarrhea developed before receiving antibiotics), liver enzyme elevation in four cases, hepatomegaly in one case), followed by dermatologic symptoms in 17 cases

(skin rash in 16 cases, Henoch-Schönlein purpura in one case), acute otitis media in 16 cases, hematologic symptoms in 13 cases (leukopenia in seven patients, bicytopenia in three cases, thrombocytopenia in two cases, autoimmune hemolytic anemia in one case), neurologic symptoms in eight cases (meningitis in four cases, Guillain-Barre syndrome in three cases, encephalitis in one case), arthralgia in five cases, and hematuria in two cases.

Extrapulmonary symptoms were present in 23 cases (31.1%) with lobar pneumonia and 70 cases (26.7%) with bronchopneumonia, with no significant difference between the two groups (p=0.459). However, pleural effusion was present in five cases with lobar pneumonia, one of whom needed chest tube insertion. Four of the five cases with pleural effusion were school-aged children, and the remaining one case was a toddler.

3. Laboratory findings

There was no difference between the two groups regarding WBC count and Hb, with 11.2 vs. 10.7 k/μL and 12.45 vs. 12.62 g/dL in the lobar pneumonia and bronchopneumonia groups (p=0.578, p=0.281, respectively). However, the lobar pneumonia group showed significantly higher platelets, ESR, and CRP (336.8 vs. 299.1 k/μL, p=0.026; 46.3 vs. 26.0 mm/hr, p<0.001; and 4.86 vs. 2.18 mg/dL, p=0.001, respectively) (Table 2).

Table 1. Characteristics of children with *Mycoplasma* pneumonia

Characteristic	Value
Age (yr)[a]	5 (0.4-18)
Gender	
Male (n, %)	179 (53.27)
Female (n, %)	157 (46.73)
Chest X-ray pattern	
Lobar pneumonia (n, %)	74 (22.02)
Bronchopneumonia (n, %)	262 (77.98)
Clinical findings	
Fever duration (days)[b]	4.7±3.8
Extrapulmonary symptoms	
Yes (n)	93
No (n)	243
Pleural effusion (n)	5
Laboratory findings	
White blood cell count (k/μL)[b]	10.80±6.20
Hemoglobin (g/dL)[b]	12.59±1.20
Platelet count (k/μL)[b]	307.40±128.50
C-reactive protein (mg/dL)[b]	2.77±4.43
Erythrocyte sedimentation rate (mm/hr)[b]	30.60±24.50
Viral co-infection	
Yes (n)	147
No (n)	160

[a]Median (range), [b]mean±standard deviation.

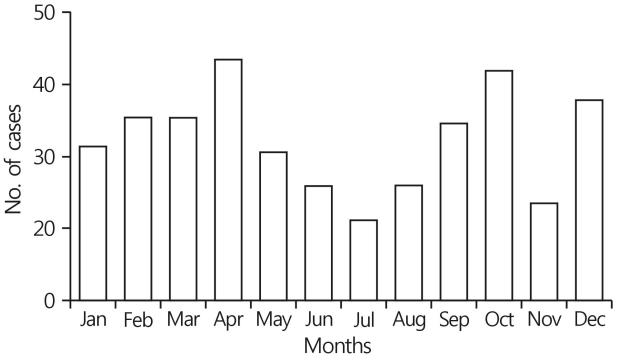

Fig. 1. Monthly incidence of *Mycoplasma* pneumonia patients.

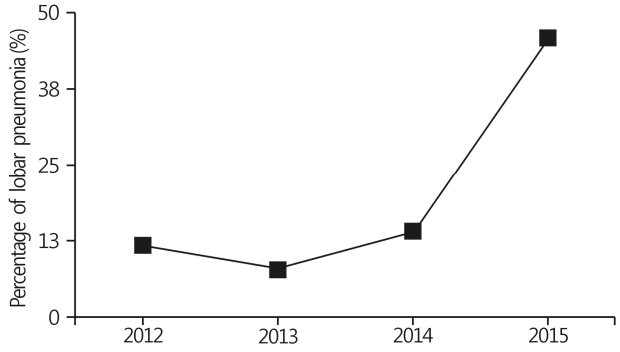

Fig. 2. Annual incidence of lobar pneumonia in children with *Mycoplasma* pneumonia.

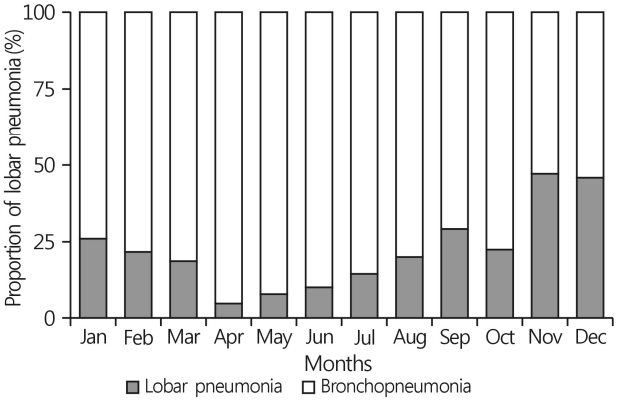

Fig. 3. Monthly proportion of lobar pneumonia in children with *Mycoplasma* pneumonia.

Table 2. Comparison of lobar pneumonia and bronchopneumonia in *Mycoplasma* pneumonia in children

Variable	Lobar pneumonia (n=74)	Bronchopneumonia (n=262)	*p*-value
Gender			0.366
Male (n)	36	143	
Female (n)	38	119	
Age (y)			0.001
<3 (n)	9	90	
3-7 (n)	36	84	
≥8 (n)	29	88	
Clinical findings			
Fever duration (days)[a]	6.8±4.4	4.1±3.4	<0.001
Extrapulmonary symptoms			0.459
Yes (n)	23	70	
No (n)	51	192	
Pleural effusion	5	0	
Laboratory findings			
White blood cell count (k/μL)[a]	11.20±6.30	10.70±6.20	0.578
Hemoglobin (g/dL)[a]	12.45±1.17	12.62±1.21	0.281
Platelet count (k/μL)[a]	336.80±120.0	299.10±129.80	0.026
C-reactive protein (mg/dL)[a]	4.86±6.48	2.18±3.44	0.001
Erythrocyte sedimentation rate (mm/hr)[a]	46.30±26.90	26.00±21.70	<0.001
Viral co-infection			0.017
Yes (n)	23	124	
No (n)	43	117	

[a]Mean±standard deviation.

Table 3. Comparison of *Mycoplasma* pneumonia with lobar consolidation according to age group

Variable	<3 years (n=9)	3-7 years (n=36)	≥8 years (n=29)	*p*-value
Gender				0.579
Male (n)	3	19	14	
Female (n)	6	17	15	
Clinical findings				
Fever duration (days)[a]	8.3±4.7	6.4±3.6	6.8±5.1	0.681
Extrapulmonary symptoms				0.528
Yes (n)	3	9	11	
No (n)	6	27	18	
Pleural effusion (n)	1	0	4	
Laboratory findings				
White blood cell count (k/μL)[a]	11.20±3.90	11.90±7.50	10.20±5.10	0.442
Hemoglobin (g/dL)[a]	12.06±1.24	12.27±1.28	12.81±0.93	0.177
Platelet count (k/μL)[a]	372.30±103.00	343.90±119.00	316.90±126.20	0.309
C-reactive protein (mg/dL)[a]	4.68±8.78	3.27±4.64	6.89±7.28	0.037
Erythrocyte sedimentation rate (mm/hr)[a]	47.00±25.10	40.50±25.3	52.90±28.40	0.186
Viral co-infection				0.034
Yes (n)	6	13	4	
No (n)	3	22	18	

[a]Mean±standard deviation.

Of 307 cases tested, 147 (47.9%) had confirmed viral co-infection. Co-infection was present in 23 (34.9%) lobar pneumonia cases and 124 (51.5%) bronchopneumonia cases, and was significantly higher in the latter group (p=0.017) (Table 2). There were 48 cases of human rhinovirus, 27 of adenovirus, 21 of metapneumovirus, 20 of RSV, and 17 of influenza virus.

4. Comparison of MP with lobar consolidation according to age group

Of those with lobar pneumonia, there were nine infants and toddlers (9.1%), 36 (30.0%) preschool children, and 29 (24.8%) school-aged children, with a significantly lower incidence in infants and toddlers (p=0.001).

There were no significant differences in gender, WBC count, Hb, platelets, and ESR in lobar pneumonia patients divided by age (p=0.579, p=0.442, p=0.177, p=0.309, p= 0.186, respectively), but CRP were significantly higher in school-aged children (4.68 vs. 3.27 vs. 6.89 mg/dL, p=0.037) (Table 3).

Viral co-infection was seen in 66.7% of infants and toddlers, 37.1% of preschool children, and 18.2% of school-aged children, with co-infection most common in infants and toddlers (p=0.034) (Table 3). No differences were found with respect to fever duration and extrapulmonary symptoms between the different age groups (8.33 vs. 6.42 vs. 6.76 days, p=0.681); additionally, no difference was found with respect to extrapulmonary symptoms between the age groups (33.3% vs. 25.0% vs. 37.9%, p=0.528), respectively (Table 3).

5. Location of lobar consolidation on chest X-ray

Lobar pneumonia was present in 45 cases in the right lung and 36 cases in the left. There were 21 cases right lower, 19 cases left lower, 17 cases left upper, 15 cases right middle, and nine cases right upper lobe cases. There were seven cases involving two or more lobes: two cases in the right middle and right lower lobe, two cases in the right middle and left upper lobe, two cases in the right lower and left lower lobe, and one case in the right middle and left lower lobe.

DISCUSSION

This study surveyed the clinical trends in MP patients, by comparing the clinical and laboratory findings based on consolidation patterns on chest X-rays of children diagnosed with MP at a university medical center.

According to a Korean study by Eun et al. [3], 44% of all MP cases occur in children aged less than 5 years, with a decreasing incidence age during epidemics [3,4,9]. In this study, infants and toddlers aged less than 3 years accounted for 29.5% of the entire study cohort, while 65.2% accounted for preschool children aged 7 years or younger. Eun et al. [3] suggested that the increasing number of infants and toddlers attending day care centers might explain the increasing incidence in younger children. Kim et al. [9] suspected that immunity acquired by older children during epidemics every 3-4 years might have led to a lower incidence rate.

The seasonal incidence rate of MP appears to peak around September and October, with a prolonged incidence during the entire winter season [4,9]. This study showed two community peaks, in April and October, i.e., spring and fall. However, MP with a lobar pneumonia pattern on an X-ray increases in the winter (November and December), more commonly in older children.

The chest X-ray in MP shows nonspecific radiologic findings in most cases of interstitial pneumonia or a bronchopneumonia pattern [2,5]. In contrast, some reports showed that lobar pattern pneumonia accounts for about 33-38% [13,14], while other reports showed more localized consolidation, with most radiologic findings appearing as a lobar or segmental consolidation [15,16]. Recently published studies [8,10-14] have shown an increasing lobar pneumonia pattern. This study also confirmed the lobar pneumonia pattern in about a quarter of all MP patients, also reporting on the consolidation [10-13,16] in both lower lobes as the most common location.

The most common cause of lobar consolidation is bacterial pneumonia, with known causative agents including *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, Gram-negative bacilli, etc. [17]. According to Lin et al. [18], community-acquired lobar pneumonia patients have longer fever duration and hospitalization, higher mortality, as well as more elevated WBC and CRP. Youn et al. [8] also reported longer fever duration in patients with a lobar pneumonia pattern, as well as a noticeable increase in CRP. In addition, Gao et al. [10] also reported longer fever duration, elevated levels of WBC and CRP, with associated extrapulmonary symptoms, and longer hospitalization in the lobar pneumonia group. This study

showed a similar trend of longer fever duration and higher platelets, CRP, and ESR in the lobar pneumonia group. Conversely, no significant difference was found in extrapulmonary symptoms between the lobar pneumonia group and the bronchopneumonia group, although all patients with pleural effusion had a lobar pneumonia pattern. This confirmed that lobar pneumonia shows a more severe infectious response as well as a higher incidence rate of complications.

Other studies regarding the clinical progress in child MP patients showed that severe pulmonary lesions have been more noticeable in older children [6-8]. Defilippi et al. [7] reported that the consolidation rate was higher in those aged 5 or older, and Youn [8] reported a severe pneumonia pattern in school-aged children as well. This study also showed that a bronchopneumonia pattern was more common in infants and toddlers, but the rate of lobar pneumonia increased in preschool and school-aged children. Similar to other study results, the median overall age of MP patients decreased, but the lobar pattern MP increased in preshool and school-aged children. In this study, four of five cases with a severe pleural effusion were school-aged children, and the lobar pneumonia pattern group also showed a higher CRP in school-aged children. Meyer et al. suggested that an age-dependent amplification of inflammatory response may be a major factor of the *M. pneumoniae*-associated disease [19]. Narita et al. reported that the severity of MP in children was associated with an increased serum level of interleukin (IL)-8 and IL-18 [20].

Recently, there has been a sharp increase in the incidence of macrolide-resistant *M. pneumoniae* (MRMP) infection in East Asia, and 56.1% of all MP cases in Korea were reported to be MRMP [21,22]. According to Zhou et al. [23], a typical MRMP infection was associated with longer fever duration and hospitalization, with a higher incidence rate of extrapulmonary complications. Moreover, Seo et al. [22] also reported that the likelihood of MRMP is high with CRP of 40 mg/L or higher.

Thus, MP with a lobar pneumonia pattern is most likely to be due to MRMP. However, because this study did not separate *M. pneumoniae* by strain, no correlation between MRMP and lobar pneumonia was confirmed. The reason why this trend is more common in older children needs to be clarified.

According to Korppi et al. [5], mixed infection was confirmed in 51% of MP patients, with the most common invasive pathogen being *S. pneumoniae*, followed by *Chlamydia* species. Only 5% had viral infection. Most studies regarding co-infection were related to bacterial co-infection. In China, Gao et al. [10] confirmed bacterial co-infection in 27.8% of all MP patients, with higher bacterial co-infection rates in younger age groups. Conversely, Phares et al. [6] confirmed mixed infection in 40-50% of all MP patients, with an influenza virus being the most common pathogen. In addition, Defilippi et al. [7] reported four confirmed cases of RSV co-infection in patients aged 2 years or younger, out of 102 MP patients. In Korea, Youn et al. [8] reported that they confirmed only two cases of viral co-infection out of 191 patients. However, although this study did not seek to confirm bacterial co-infection, viral co-infection was confirmed in 47.9% of all MP patients, and was especially more common in the bronchopneumonia group.

This study has a few limitations to consider while interpreting its results. First, it does not describe an MP epidemic across an entire community, as it only includes patients who visited a single tertiary medical center. Second, the diagnostic criterion was the presence of *M. pneumoniae*-specific IgM, which might exclude patients whose antibodies were not yet sufficiently elevated for detection. Third, there was no detailed microbiological testing, and therefore it is possible that bacterial co-infection may not have been ruled out.

The diagnostic tests for *M. pneumoniae* infection offered at the Yeungnam University Hospital include *M. pneumoniae*-specific IgG, IgM, PCR, and cold-agglutinin tests. However, the typical duration of hospital stay is not long enough to monitor any increase in IgG titer. This may limit its use during the treatment period making it difficult to obtain the requisite sputum samples for PCR. Testing for both *M. pneumoniae*-specific IgM and cold-agglutinin is limited due to their cost. Moreover, because blood collection from children may be difficult, consent for a follow-up test may be declined when symptoms improve. For this reason, only 44 of 336 patients included in the present study were retested. The titer was not reported in 10 patients, 16 patients showed seroconversion, and the titer increased in 11 patients. Of those who tested positive in both tests, the titer decreased in eight patients and was unchanged in one patient. Three patients who had positive results in the first test had negative or trace-positive results in the subsequent test. Prior to 2014, Yeungnam University Hospital simply reported the *M. pneumoniae*-specific IgM titer results as either positive or nega-

tive. The results collected since 2014 were expressed guantitatively. For these reasons, it was difficult to use the titers published in existing studies as a reference for diagnosis. Because the present study is retrospective in nature, it was difficult to apply a strict diagnostic criteria. Thus, enhancing the diagnostic criteria based on the study results and conducting a prospective study incorporating a detailed microbiological test would be useful.

MP in children has recently been increasing in younger age groups, despite an increase in the rate of highly-infective lobar pneumonia with severe symptoms in older children. Hence, it is necessary to further investigate the causes and countermeasures. Future studies on the relationship between MRMP and lobar pattern MP are also necessary.

CONFLICT OF INTEREST

The authors have no financial conflicts of interest.

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