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ORIGINAL ARTICLE

마이코플라스마 폐렴에서 나타나는 폐외 증상의 발생률과 위험 인자

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The incidence and risk factors of extrapulmonary manifestations in *Mycoplasma pneumoniae* pneumonia

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Purpose: *Mycoplasma pneumoniae* pneumonia (MP) is a major cause of community-acquired pneumonia (CAP) in children and is associated with extrapulmonary manifestations (EPM). The incidence and risk factors for EPM in children are unknown.

Methods: This was a retrospective study involving 65,243 pediatric patients with CAP between 2010 and 2015 at 23 nationwide hospitals in South Korea. Medical records were reviewed to collect information regarding the clinical characteristics, radiological results, and laboratory findings. Logistic regression with multivariate analysis was performed to evaluate the risk factors associated with EPM in MP.

Results: The incidence of EPM was 23.9%, including elevation of liver enzymes (18.1%), mucocutaneous manifestations (4.4%), proteinuria (4.1%), cardiovascular and neurological manifestations (0.4%), hematologic manifestations (0.2%), and arthritis (0.2%). Statistical analysis showed that mucocutaneous manifestations significantly increased with elevated alanine aminotransferase (adjusted odds ratio [aOR], 3.623; 95% confidence interval [CI], 1.933-6.790) and atopic sensitization (aOR, 2.973; 95% CI, 1.615–5.475) and decreased with respiratory virus coinfection (aOR, 0.273; 95% CI, 0.084–0.887). Elevated liver enzymes were significantly associated with elevated lactate dehydrogenase (aOR, 3.055; 95% CI, 2.257–4.137), presence of pleural effusion (aOR, 2.635; 95% CI, 1.767–3.930), and proteinuria with respiratory virus coinfection (aOR, 2.245; 95% CI, 1.113–4.527).

Conclusion: Approximately 24% of pediatric patients with MP had various EPM. As the risk factors associated with each EPM were different, it is necessary to evaluate the various clinical aspects and findings of MP to predict and prepare for the occurrence of EPM. (*Allergy Asthma Respir Dis 2022;10:207-214*)

Keywords: *Mycoplasma pneumonia*, Risk factors, Incidence, Extrapulmonary manifestation

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INTRODUCTION

Mycoplasma pneumoniae is one of the most common pathogens responsible for community-acquired pneumonia (CAP) in children, which is characterized by fever, cough, and sputum and a considerable portion of children need hospitalization.[1,2] *Mycoplasma pneumoniae* pneumonia (MP) epidemic occurs in Korea about every 3 to 4 years[3] and could lead to an increased burden in the pediatric community. The characteristics of MP are various from self-limiting to having long-term sequelae such as bronchiolitis obliterans and bronchiectasis.[4] In addition, macrolide-resistant MP (MRMP) is an emerging issue these days.[5-7]

Besides respiratory symptoms, MP pathogenesis can also involve extrapulmonary manifestations (EPM) that affect almost all the body organs and are associated with mucositis, Stevens-Johnson syndrome (SJS), rash, tendinitis, and central nervous system infection.[8-10] Mycoplasma infection can lead to several EPM such as proteinuria, acute hepatitis, myocarditis, Kawasaki disease, peripheral neuropathy, Guillain-Barré syndrome, and hemophagocytic syndrome. The incidence of EPM and the associated risk factors have not been extensively studied. Furthermore, although MP is a common cause for CAP, the mechanism of MP-driven periodic epidemics and etiology of various clinical characteristics, including EPM, are not yet understood leading to difficulty in treatment.

Macrolide is the first-choice antibiotic agent for the treatment of MP in children. But, MRMP could be treated with tetracycline and quinolones, although their use in pediatric patients is limited due to safety concerns, such as permanent tooth discoloration by tetracycline and side effects involving muscles, tendons, or joints by quinolones. MRMP is increasing abruptly[5-7] resulting in clinical deterioration despite treatment.[11-14] It has also been reported that MRMP could be a risk factor for the severity and development of EPM,[11] but some reported that there are no significant differences in clinical symptoms and disease severity between MRMP and macrolide-sensitive MP (MSMP).[15]

In this study, we aimed to study clinical aspects of pediatric MP patients and to evaluate the incidence of EPM and associated risk factors.

MATERIALS AND METHODS

1. Study population

This study was conducted based on the data collected from 23 medical centers on pediatric CAP patients hospitalized between January 1, 2010 and December 31, 2015. The data were collected in cooperation with secondary and tertiary medical centers under the 'Pneumonia and Respiratory Diseases study group' of the Korean Academy of Pediatric Allergy and Respiratory Disease.[3] Data from a total of 65,243 pediatric CAP patients under the age of 18 years were collected by a retrospective chart review. Of these, patients of 9,190, diagnosed with MP, were included in this analysis.

To identify differences in the incidence of EPM according to age, two age groups were considered; (1) preschool children (< 60 months old) and (2) school children (≥ 60 months old).

Clinical characteristics, including respiratory symptoms with or without intensive treatment, underlying diseases, such as doctor-diagnosed asthma and atopic sensitization to common aeroallergens, - and laboratory and radiological findings were collected from a retrospective chart review of medical records.

The study protocol was approved by the Institutional Review Board at each institution and written informed consent was waived for this retrospective study with medical record review.

2. Definition of MP

Pneumonia was diagnosed by pediatricians based on both physical examinations and radiological assessments.[1] MP was considered when: (1) a 4-fold or greater increase in serum IgM and/or IgG antibody titers between acute and convalescent stages was observed and/or (2) polymerase chain reaction (PCR) or real-time PCR showed positive results for mycoplasma in nasopharyngeal aspiration or sputum samples.[5,16]

The response of patients with MP to macrolide treatment was divided into three categories based on the fever duration in each pneumonia episode after the initiation of macrolide treatment. We defined clinical MSMP, MRMP, and macrolide-less effective MP (MLMP) as fever for ≤ 3 days after the macrolide treatment, > 7 days, and > 3 days but ≤ 7 days, respectively.[3]

3. EPM of MP

EPM were classified into seven categories as elevation of liver enzyme (if either aspartate aminotransferase [AST] or alanine aminotransferase [ALT] is 40 U/L or higher), mucocutaneous manifestations (rash, urticaria, SJS, erythema multiforme, and mucositis), proteinuria (protein ≥ 1+ in urinalysis dipstick test), cardiovascular (myocarditis and Kawasaki disease), neurologic (encephalitis, meningitis, peripheral neuropathy, transverse myelitis and

Guillain-Barré syndrome) and hematologic manifestations (hemolytic anemia, thrombocytopenia, hemophagocytic syndrome and disseminated intravascular coagulation) and arthritis, which were occurred in the acute phase.

4. Laboratory and radiologic studies

Real-time PCR analyses were performed to identify the causative respiratory viruses; adenovirus, human rhinovirus, influenza virus, parainfluenza virus, human metapneumovirus, respiratory syncytial virus, bocavirus, and human coronavirus were identified.

The laboratory results were including complete blood count with differential counts, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), AST, ALT, and lactate dehydrogenase (LDH).

Chest x-ray findings were classified as bronchopneumonia and lobar pneumonia with or without pleural effusion and atelectasis in the worst condition.

5. Statistical analysis

Continuous variables were presented as mean ± standard deviation and frequency (percentage) for categorical variables. Differences in baseline characteristics between groups were explored using an independent 2-sample *t*-test and chi-square test (or Fisher exact test) where appropriate.

To identify the independent risk factors for EPM, a multivariable logistic regression model was performed using an enter method that included variables with a probability value <0.05 in the univariable analysis. Odds ratios (ORs) and their 95% confidence intervals (CIs) were also calculated.

A 2-tailed *P*-value of less than 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Characteristics of the study participants

The clinical characteristics of the pediatric patients of this study are presented in Table 1. The incidence of EPM in children with MP was 23.9% (2,192 of 9,190) and 14.6% (319 of 2,192) showed more than two kinds of EPM. The mean age of the 9,190 enrolled children with MP was 64.3 months. Mean age was older in children with EPM compare to without EPM (70.9 ± 41.8 months vs. 64.0 ± 39.7 months, $P<0.001$), however, there was no difference in EPM occurrence between school children and preschool children ($P=0.141$). The portion of male and female patients was sim-

Table 1. Clinical characteristics of the study participants

Variable	Total (n=9,190)	Without EPM (n=6,998)	With EPM (n=2,192)	*P*-value
Age (mo)	64.3±39.8	64.0±39.7	70.9±41.8	<0.001
<60	4,802 (52.3)	3,627 (51.8)	1,175 (53.6)	0.141
≥60	4,387 (47.7)	3,371 (48.2)	1,016 (46.4)	
Sex				
Female	4,643 (50.5)	3,588 (51.3)	1,055 (48.1)	0.010
Male	4,547 (49.5)	3,410 (48.7)	1,137 (51.9)	
Groups depending on the response to macrolide treatment				
MSMP	7,107 (77.3)	5,649 (80.7)	1,458 (66.5)	<0.001
MLMP	1,613 (17.6)	1,093 (15.6)	520 (23.7)	
MRMP	470 (5.1)	256 (3.7)	214 (9.8)	
Cyanosis	201 (2.3)	95 (1.5)	106 (5.0)	<0.001
Dyspnea	1,241 (14.2)	855 (13.0)	386 (18.1)	<0.001
Oxygen treatment	409 (4.5)	248 (3.5)	161 (7.3)	<0.001
Ventilator treatment	16 (0.2)	4 (0.1)	12 (0.5)	<0.001
Any respiratory virus coinfection	1,728 (18.8)	1,245 (17.8)	483 (22.0)	<0.001
Past history/underlying diseases				
Asthma	627 (7.2)	516 (7.9)	111 (5.2)	<0.001
Atopic sensitization	552 (7.4)	438 (7.6)	114 (6.9)	0.326

Values are presented as a mean ± standard deviation or number (%).
EPM, extrapulmonary manifestations; MSMP, macrolide-sensitive mycoplasma pneumonia; MLMP, macrolide-less effective mycoplasma pneumonia; MRMP, macrolide-resistant mycoplasma pneumonia.

Table 2. Difference in laboratory and radiological findings depending on the presence of extrapulmonary manifestations

Variable	Without EPM (n=6,998)	With EPM (n=2,192)	*P*-value
Laboratory findings			
WBC (/mm^3)	9,574±4,755	9,194±4,747	0.119
AST (U/L)	42±117	67±141	<0.001
ALT (U/L)	26±114	53±111	<0.001
LDH (U/L)	517±350	779±614	<0.001
CRP (mg/dL)	7.7±19.0	6.5±14.2	0.111
ESR (mm/hr)	34±23	34±23	0.958
Radiological findings			
Lobar pneumonia	2,558 (39.3)	972 (46.8)	<0.001
Pleural effusion	367 (5.6)	317 (15.6)	<0.001
Chest tube insertion	20 (0.3)	69 (3.1)	<0.001

Values are presented as a mean±standard deviation or number (%).
EPM, extrapulmonary manifestations; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

ilar in total (49.5% vs. 50.5%), although EPM occurred more frequently in male patients (51.9% vs. 48.1%, $P=0.010$).

The proportion of MP depending on the patient responses to macrolide treatment was MSMP 7,107 (77.3%), MLMP 1,613 (17.6%), and MRMP 470 (5.1%). EPM was more common in children with MRMP than that with MSMP ($P<0.001$). Children with respiratory difficulty, such as cyanosis and dyspnea, were more prone to develop EPM ($P<0.001$), and therefore oxygen therapy and ventilator care were more accompanied in children with EPM ($P<0.001$). Children with asthma history showed less EPM ($P<0.001$), however, atopic sensitization was not associated with EPM ($P=0.326$).

In addition to the clinical characteristics, laboratory and radiological findings were significantly different between children with and without EPM (Table 2). Liver enzymes and LDH were higher in children with EPM ($P<0.001$, respectively), but CRP levels and ESR were not statistically different ($P=0.111$ and $P=0.958$, respectively). EPM was developed more in children with lobar pneumonia and pleural effusion ($P<0.001$, respectively).

2. Incidence of EPM

The incidence of EPM in children with MP was 23.9% (2,192 of 9,190) (Fig. 1). Elevation of liver enzyme was the most common EPM (n=1,665, 18.1%). Mucocutaneous manifestation occurred in 4.4% (n=402) of patients, and proteinuria (n=376, 4.1%), cardiovascular manifestation (n=41, 0.4%), neurologic manifestation (n=38, 0.4%), hematologic manifestation (n=19, 0.2%) and arthritis (n=22, 0.2%) were the other EPM observed.

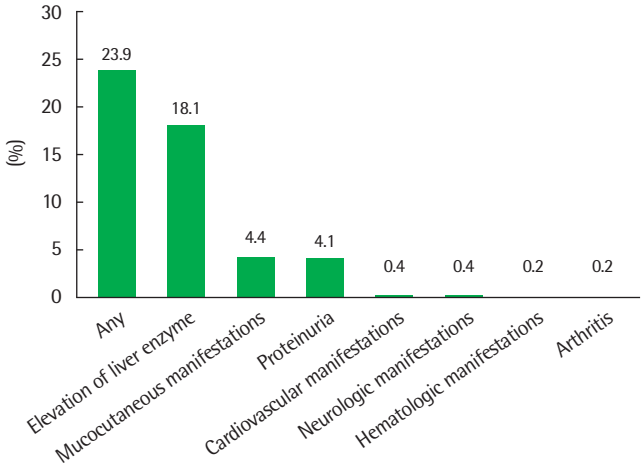

Fig. 1. Incidence of extrapulmonary manifestations (EPM). The incidence of any EPM (n=2,192, 23.9%) and that of each kind of EPM, such as elevation of liver enzyme (n=1,665, 18.1%), mucocutaneous manifestation (n=402, 4.4%), proteinuria (n=376, 4.1%), cardiovascular (n=41, 0.4%), neurologic (n=38, 0.4%), and hematologic manifestation (n=19, 0.2%) and arthritis (n=22, 0.2%), are shown.

3. Risk factors associated with mucocutaneous manifestations

The univariable logistic regression model showed that the main parameters associated with mucocutaneous manifestation include schoolchildren, male patients, MRMP and MLMP, elevated ALT and LDH levels, respiratory virus coinfection, pleural effusion, and atopic sensitization (Table 3). Schoolchildren compared to preschool children (OR, 1.474; 95% CI, 1.204–1.803) and male patients in comparison to female patients (OR, 1.314; 95% CI, 1.074–1.606) were more likely to develop mucocutaneous manifestations. According to the response to macrolide treatment, mucocutaneous manifestation was significantly higher in the MLMP and MRMP group than in the MSMP group (OR, 1.867; 95% CI, 1.473–2.367; OR, 3.440; 95% CI, 2.511–4.714, respectively). Laboratory findings showed that the elevated ALT and LDH levels were associated with increased incidence of mucocutaneous manifestation (ALT: OR, 3.959; 95% CI, 3.100–5.054; LDH: OR, 2.251; 95% CI, 1.641–3.088, respectively). Respiratory virus coinfection was negatively associated with mucocutaneous manifestation (OR, 0.719; 95% CI, 0.541–0.954), whereas pleural effusion was positively associated with mucocutaneous manifestation (OR, 2.904; 95% CI, 2.180–3.868). Furthermore, children with atopic sensitization were significantly associated with the occurrence of mucocutaneous manifestation (OR, 1.954; 95% CI, 1.361–2.806).

To assess the relationships between more than one predictor and

Table 3. Risk factors associated with mucocutaneous manifestations

Variable	Without EPM (n=8,788)	With EPM (n=402)	Univariable analysis, OR (95% CI)	Multivariable analysis, aOR (95% CI)
Age (mo)				
<60	4,629 (52.7)	173 (43.0)	1.000	1.000
≥60	4,158 (47.3)	229 (57.0)	1.474 (1.204–1.803)	0.625 (0.370–1.056)
Male sex	4,322 (49.2)	225 (56.0)	1.314 (1.074–1.606)	1.154 (0.693–1.921)
Response to macrolide treatment				
MSMP	6,859 (78.0)	248 (61.7)	1.000	1.000
MLMP	1,511 (17.2)	105 (25.4)	1.867 (1.473–2.367)	0.438 (0.188–1.020)
MRMP	418 (4.8)	52 (12.9)	3.440 (2.511–4.714)	0.574 (0.244–1.352)
ALT (>40 U/L)	626 (7.6)	96 (24.6)	3.959 (3.100–5.054)	3.623 (1.933–6.790)
LDH (>479 U/L)*	1,635 (48.9)	127 (68.3)	2.251 (1.641–3.088)	1.265 (0.727–2.202)
ESR (>10 mm/hr)	4,945 (86.0)	245 (87.8)	1.170 (0.811–1.688)	0.900 (0.463–1.750)
Respiratory virus coinfection	1,670 (19.0)	58 (14.4)	0.719 (0.541–0.954)	0.273 (0.084–0.887)
Dyspnea	175 (2.1)	26 (7.3)	1.208 (0.909–1.604)	0.754 (0.328–1.732)
Pleural effusion	621 (7.6)	63 (19.2)	2.904 (2.180–3.868)	1.505 (0.709–3.193)
Atopic sensitization	516 (7.2)	36 (13.2)	1.954 (1.361–2.806)	2.973 (1.615–5.475)

Values are presented as number (%).
EPM, extrapulmonary manifestations; OR, odds ratio; CI, confidence interval; MSMP, macrolide-sensitive mycoplasma pneumonia; MLMP, macrolide-less effective mycoplasma pneumonia; MRMP, macrolide-resistant mycoplasma pneumonia; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate.
*Median value of LDH level was used as cutoff value.

Table 4. Risk factors associated with elevated liver enzymes

Variable	Without EPM (n=7,525)	With EPM (n=1,665)	Univariable analysis OR (95% CI)	Multivariable analysis aOR (95% CI)
Age (mo)				
<60	925 (12.3)	352 (21.1)	1.000	1.000
≥60	2,927 (38.9)	599 (36.0)	0.538 (0.462–0.625)	0.869 (0.660–1.143)
Male sex	3,683 (48.9)	864 (51.9)	1.125 (1.012–1.251)	1.233 (0.994–1.609)
Response to macrolide treatment				
MSMP	6,038 (80.2)	1,069 (64.2)	1.000	1.000
MLMP	1,188 (15.8)	425 (25.5)	2.021 (1.777–2.298)	0.862 (0.504–1.473)
MRMP	299 (4.0)	171 (10.3)	3.230 (2.648–3.941)	1.511 (0.879–2.600)
LDH (>479 U/L)*	1,261 (43.8)	501 (77.1)	4.320 (3.547–5.261)	3.055 (2.257–4.137)
ESR (>10 mm/hr)	4,137 (86.2)	1,053 (85.6)	0.949 (0.793–1.135)	0.699 (0.488–1.000)
Respiratory virus coinfection	1,346 (17.9)	382 (22.9)	1.367 (1.202–1.554)	1.176 (0.801–1.725)
Dyspnea	931 (13.2)	310 (18.8)	1.523 (1.323–1.755)	1.054 (0.709–1.566)
Pleural effusion	413 (5.9)	271 (17.3)	3.312 (2.810–3.904)	2.635 (1.767–3.930)
Atopic sensitization	472 (7.6)	80 (6.4)	0.827 (0.647–1.057)	1.317 (0.881–1.969)

Values are presented as number (%).
EPM, extrapulmonary manifestations; OR, odds ratio; CI, confidence interval; aOR, adjusted OR; MSMP, macrolide-sensitive mycoplasma pneumonia; MLMP, macrolide-less effective mycoplasma pneumonia; MRMP, macrolide-resistant mycoplasma pneumonia; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate.
*Median value of LDH level was used as cutoff value.

the outcome, the multivariable logistic regression was also evaluated. The elevated ALT levels and atopic sensitization were found to be positively associated with mucocutaneous manifestation (ALT: aOR, 3.623; 95% CI, 1.933–6.790; atopic sensitization: aOR, 2.973; 95% CI, 1.615–5.475, respectively), whereas respiratory virus coinfection was negatively associated (aOR, 0.273; 95% CI, 0.084–0.887).

4. Risk factors associated with the elevation of liver enzymes

Table 4 shows the result of the univariable and multivariable analysis between elevated liver enzymes and various risk factors. The univariable logistic regression model showed that the school-children were less likely to develop elevated liver enzymes (OR, 0.538; 95% CI, 0.462–0.625), while male patients were found to be

Table 5. Risk factors associated with proteinuria

Variable	Without EPM (n=8,814)	With EPM (n=376)	Univariable analysis OR (95% CI)	Multivariable analysis aOR (95% CI)
Age (mo)				
<60	4,657 (52.8)	145 (38.6)	1.000	1.000
≥60	4,156 (47.2)	231 (61.4)	1.785 (1.444–2.206)	1.488 (0.818–2.715)
Male sex	4,342 (49.3)	205 (54.5)	1.235 (1.004–1.519)	1.389 (0.772–2.499)
Response to macrolide treatment				
MSMP	6,879 (78.0)	228 (60.6)	1.000	1.000
MLMP	1,515 (17.2)	98 (26.1)	1.952 (1.530–2.489)	0.689 (0.257–1.850)
MRMP	420 (4.8)	50 (13.3)	3.592 (2.604–4.954)	0.713 (0.259–1.966)
ALT (>40 U/L)	668 (8.1)	54 (15.0)	1.995 (1.478–2.692)	1.981 (0.896–4.379)
LDH (>479 U/L)*	1,655 (49.0)	107 (68.6)	2.269 (1.608–3.204)	1.715 (0.896–3.281)
ESR (>10 mm/hr)	4,942 (85.9)	248 (89.9)	1.450 (0.974–2.158)	0.932 (0.420–2.067)
Respiratory virus coinfection	1,628 (18.5)	100 (26.6)	1.306 (1.160–1.470)	2.245 (1.113–4.527)
Dyspnea	1,161 (13.9)	80 (21.3)	1.679 (1.301–2.166)	1.374 (0.615–3.068)
Pleural effusion	622 (7.6)	62 (18.4)	2.746 (2.060–3.660)	1.868 (0.825–4.231)
Atopic sensitization	537 (7.5)	15 (5.3)	0.686 (0.405–1.162)	0.749 (0.288–1.947)

Values are presented as number (%).
EPM, extrapulmonary manifestations; OR, odds ratio; CI, confidence interval; aOR, adjusted OR; MSMP, macrolide-sensitive mycoplasma pneumonia; MLMP, macrolide-less effective mycoplasma pneumonia; MRMP, macrolide-resistant mycoplasma pneumonia; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate.
*Median value of LDH level was used as cutoff value.

associated (OR, 1.125; 95% CI, 1.012–1.251). Elevation of liver enzymes was significantly higher in the MLMP and MRMP group compared to the MSMP group (OR, 2.021; 95% CI, 1.777–2.298; OR, 3.230; 95% CI, 2.648–3.941, respectively). Elevated LDH levels (OR, 4.320; 95% CI, 3.547–5.261), respiratory virus coinfection (OR, 1.367; 95% CI, 1.202–1.554), and dyspnea (OR, 1.523; 95% CI, 1.323–1.755) increased the risk of elevation of liver enzymes. Similarly, pleural effusion increased the risk of elevation of liver enzymes (OR, 3.312; 95% CI, 2.810–3.904), however, atopic sensitization was not significantly associated (OR, 0.827; 95% CI, 0.647–1.057).

In multivariable analysis, elevated LDH levels and pleural effusion were significantly associated with elevation of liver enzymes (LDH: aOR, 3.055; 95% CI, 2.257–4.137; pleural effusion: aOR, 2.635; 95% CI, 1.767–3.930, respectively).

5. Risk factors associated with proteinuria and other manifestations

The results of the univariable and multivariable analysis between proteinuria and various risk factors are shown in Table 5. The univariable logistic regression model showed more tendency of school children and male patients to develop proteinuria (OR, 1.785; 95% CI, 1.444–2.206; OR, 1.235; 95% CI, 1.004–1.519, respectively). Proteinuria was significantly higher with MLMP and MRMP groups compared to the MSMP group (OR, 1.952; 95% CI, 1.530–2.489; OR, 3.592; 95% CI, 2.604–4.954, respectively). Elevated ALT and LDH levels were also positively associated with proteinuria (OR, 1.995; 95% CI, 1.478–2.692; OR, 2.269; 95% CI, 1.608–3.204, respectively). Respiratory virus coinfection, dyspnea, and pleural effusion increased the risk of proteinuria (OR, 1.306; 95% CI, 1.160–1.470; OR, 1.679; 95% CI, 1.301–2.166; OR, 2.746; 95% CI, 2.060–3.660, respectively), whereas atopic sensitization was not significantly associated with proteinuria.

Respiratory virus coinfection was the only factor that was significantly associated with proteinuria in multivariable logistic regression analysis (aOR, 2.245; 95% CI, 1.113–4.527).

Rare complications, such as cardiovascular, neurologic, and hematologic manifestations, and arthritis, did not show any association with the clinical, laboratory, and radiological factors in the multivariable logistic regression analysis (data not shown).

DISCUSSION

MP is the common cause of CAP in children globally and is frequently associated with a wide range of EPM with or without respiratory symptoms.[8] In this study, EPM was developed in 23.9% of children with MP, and elevation of liver enzymes was the most common EPM, followed by mucocutaneous manifestations and proteinuria. The risk factors associated with each EPM were dif-

ferent. Mucocutaneous manifestation was associated with elevated ALT and atopic sensitization, elevation of liver enzymes occurred more frequently with higher LDH levels and pleural effusion, and proteinuria was developed more with respiratory virus coinfection.

Mycoplasma pneumoniae is known to cause various EPMs that affect several organs of the human body,[8] although the exact mechanisms are not yet known. Possibly, it includes either the direct effect of mycoplasma pathogen itself or the indirect effect of the bacterium, such as autoimmunity or formation of immune complexes and the last, vascular occlusion either directly or indirectly by mycoplasma.[8,17,18] Since EPM are distinguishable from other bacterial or viral pneumonia, they are always associated with mycoplasma. However, the incidence of EPM during mycoplasma infection is mostly reported in case reports.[9,10] Therefore, it is important to investigate the incidence of EPM during mycoplasma infection through more studies. This study was aimed to evaluate the incidence of EPM associated with mycoplasma infection to determine the importance of EPM to consider and prevent in treating. Previously, a report from China on 150 pediatric MP patients showed 20% incidence of EPM. Skin manifestation was the most frequent one (36.7%) followed by the digestive system (23.3%) and atopy may be a risk factor for the EPM.[17] In our study, the incidence of EPM was 23.9% which is similar to the previous study, but elevated LFT was the most frequent EPM. Atopy is a tendency to produce IgE antibodies in response to allergens, which is associated with asthma. In previous studies, MP was reported to have a strong clinical association with asthma exacerbation[19] and higher serum total IgE levels, especially in children with EPM.[20] Although the mechanism of the influence of atopy on EPM is not yet well known, the immune-mediated mechanism has been suggested and the breakdown of the immune balance between Th17 cell response and both Treg and IL-10 may be part of the process to lead to the subsequent development of EPM.[21] We, herein, have found a similar feature that atopic sensitization was significantly associated with mucocutaneous manifestation.

In this study, age and gender of the patients were the factors that may be associated with the development of EPM in MP. Many reports have confirmed that EPM owing to MP frequently occurs in children.[18] A report showed that the incidence of EPM in adults was only 2.2%.[22] Even among children, the incidence of EPM may be different and school children are more prone to occur EPM than preschool children are. In addition, increasing MRMP is an emerging issue and a previous study in China has shown that EPM is a risk factor for refractory Mycoplasma pneumonia and macrolide resistance.[11,23] EPM rates were significantly related to the extent of macrolide resistance, with the MRMP population being prone to have a higher risk of all complications. In our study, MRMP was also associated with the increased development of each EPM in univariable logistic regression analysis, but not in multivariable analysis. Higher levels of LDH have been reported to be related to MRMP[24] and could be another risk factor for EPM and it was associated with not all EPM but elevated liver enzymes in this study. Clinically and radiologically severe patients, such as those with pleural effusion, the requirement of oxygen supply or ventilator use, moderate to severe dyspnea, and the need for intensive care unit care, were at risk of developing EPM. Therefore, further studies are needed to consider whether severe and macrolide non-responsive patients concomitant EPM in MP.

According to the findings of this study, each EPM is associated with different factors and requires further investigation to understand the mechanism that causes a particular EPM in MP. Mucocutaneous manifestations are more prominent in children with higher ALT levels and atopic sensitization, but less frequently when respiratory viruses are coinfected. Abnormal liver function was associated with higher levels of LDH and pleural effusion, whereas proteinuria developed more in children with respiratory virus coinfection. It is thought the difference of the risk factors between EPM may tell that the mechanism of the development of each EPM may be various and different. Especially proteinuria was associated with respiratory virus coinfection, which was different from other EPMs. Although the mechanism of the development of proteinuria with MP infection is not known well yet, in a previous report, kidney biopsy confirmed disrupted Bowman's capsules and necrotizing lesions and Immunofluorescence showed coarse granular mesangial C3 deposits with negative IgM, IgG, IgA, and more.[25] MP is common CAP, but we do not understand the aspects of it much, so further research is needed.

The strength of this study is that it was a multicenter study (n = 23) with a large number of study participants (n = 9,190). Previous studies were limited due to the involvement of less number of hospitals (1 or 2) and, hence could provide fewer patient data. Additionally, pediatric pulmonary specialists, participating in the Pneumonia and Respiratory Disease Study Group of the Korean Academy of Pediatric Allergy and Respiratory Disease, have joined this study to evaluate and treat MP. However, there are limitations.

First, this study was a retrospective study with chart review and some missing data that may cause bias, suggesting the need for further prospective studies. In addition, the definition of underlying diseases, such as asthma and atopic sensitization, were entrusted to specialists in each hospital, which could cause a bias. Second, since the data collected in this study were from hospitalized in tertiary hospitals, more severe patients could have been analyzed.

In conclusion, we found that 23.9% of children with MP showed EPM in Korean children, and elevation of liver enzymes, mucocutaneous manifestation, and proteinuria were the frequent EPM. Various EPMs were associated with different risk factors. Further studies are needed to reveal the risk factors and pathophysiology of EPM in mycoplasma infection.

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