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A Study on the Association between Kawasaki Disease and *Mycoplasma pneumoniae* Infection

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ABSTRACT--- ***The etiology of Kawasaki disease (KD) remains unknown, although several infectious agents have been proposed as potential causes. Some studies suggested associations between KD and Mycoplasma pneumoniae (MP) infection. This retrospective study analyzed the association between KD and MP infection. Subjects were 36 patients with KD who admitted to the Bundang Jesaeng General Hospital from January 2013 through August 2014. Patients were assigned to one of two groups, the MP and control group, based on the results of anti-mycoplasmal IgM antibody (AMA) tests. Clinical features, laboratory findings, courses and outcomes of the illness were compared between the two groups. The results of AMA tests were positive or indeterminate in 11 patients (30.6%; MP group) and negative in 25 (69.4%; control group). There were no significant differences between the two groups with respect to age and sex distributions, duration of fever, laboratory results, chest roentgenographic findings, and echocardiographic findings. AMA titers were rechecked in 6 patients in the MP group, of whom titers decreased in 5 patients (83.3%) and increased in 1 (16.7%). Although AMA titers were positive in some patients with KD, it did not appear to influence clinical features, laboratory findings, and courses and outcomes of the illness. AMA titers decreased in the follow-up measurements in most patients in the MP group, suggesting that positive AMA titers were related to previous infections rather than concurrent infections, thus reducing the likelihood of MP infection being a causative factor for KD.***

Keywords: Kawasaki disease, *Mycoplasma pneumonia,* Antibody, Infection

1. INTRODUCTION

Kawasaki disease (KD) is an acute febrile exanthematous illness that usually affects infants and children younger than 5 years. It is characterized by vasculitis involving various tissues and organs, including skin, mucous membrane, lymph nodes, heart, blood vessels, intestines, liver, joints, and meninges. It is also known to cause inflammatory changes in lungs, resulting in parenchymal changes on chest roentgenography, and needs to be differentiated from pneumonia in some cases.

The etiology and pathogenesis of KD have been the subjects of many studies since it was first reported in 1967, but the definitive cause for KD is yet to be identified. However, several studies suggested that certain infections, especially respiratory tract infections, might cause KD. The characteristics of KD that suggests the involvement of infectious etiology in the pathogenesis of KD are as follows: the major symptoms, including fever and skin rash, are also frequently seen in infectious diseases common in infancy and childhood; KD mainly affects infants and young children and is infrequent in older children; the incidence of KD showed seasonal variation[1,2]; there was a temporal correlation between the incidences of viral illnesses and KD[2]; there were more often preceding respiratory illnesses in patients with KD than in control patients[1,3,4]; increased IgA plasma cell infiltration was observed in the proximal respiratory tract of patients with KD[5]; and a KD-associated antigen was found in the proximal bronchial epithelium of patients with KD[6].

*Mycoplasma pneumonia*e (MP) is a common pathogen resulting in respiratory tract infections, such as pneumonia and bronchitis, and is also associated with several extrapulmonary manifestations, including skin rash, as a result of inflammatory responses in other organs[7]. Therefore, there are some cases that require differential diagnosis between KD and MP infection. In addition, it was suggested that KD and MP infection might be present together[8-12], or MP infection might be one of the causes of KD[13-15]. Herein, this retrospective study was conducted to analyze if there is a causal association between KD and MP infection.

2. MATERIALS AND METHODS

A total of 36 patients admitted to the Bundang Jesaeng General Hospital, from January 2013 through August 2014 with a diagnosis of KD, were included in the study. Patients were assigned to one of two groups, the MP and control group, based on the results of anti-mycoplasmal IgM antibody (AMA) tests. Patients were assigned to the MP group if their AMA titers were positive or indeterminant (borderline), and patients were assigned to the control group if their AMA titers were negative. The two groups were compared for their clinical manifestations, laboratory results, chest roentgenographic findings, and echocardiographic findings.

The diagnosis of KD was based on the presence of fever for a minimum of 5 days along with 4 or more of the 5 principal features of KD: (1) bilateral conjunctival injection, (2) changes in lips and oral cavity (red lips, strawberry tongue, and oral mucosal injection), (3) cervical lymphadenopathy more than 1.5 cm in diameter, (4) polymorphous exanthem, and (5) changes in extremities (erythema of palms and soles, edema of hands and feet, periungual desquamation)[16]. Patients having fever for a minimum of 5 days and 3 or fewer of the 5 principal features of KD, with elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), were subjected to echocardiography after excluding other illnesses. Patients with abnormal echocardiographic findings (coronary arterial lesions, decreased left ventricular function, mitral regurgitation, and pericardial effusion) were diagnosed as having KD[16]. Coronary ectasia or aneurysm was defined as the internal diameters of coronary arteries measuring more than 3 mm in children younger than 5 years, or more than 4 mm in children 5 years or older[17]. Coronary ectasia was defined as an abnormally large coronary artery diameter, but within 1.5 times of the normal diameter, in the absence of segmental aneurysmal dilatation[16].

AMA titers were measured by the enzyme immunoassay method (Chorus Trio, DIESSE Diagnostica, Monteriggioni, Italy), and the results were presented as a unit of 'antibody index'. AMA titers were defined as positive if the index was higher than 1.1, indeterminant (or borderline) if the index was 0.9-1.1, and negative if the index was lower than 0.9[18]. Statistical analysis was done by using the Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA). Student t-test was used to compare continuous variables, and χ^2 test was used to compare proportions and rates. *P* values <0.05 were considered statistically significant.

3. RESULTS

AMA titers were positive or indeterminant (borderline) in 11 patients (30.6%; MP group) and negative in 25 (69.4%; control group) (Table 1). The two groups were similar with respect to age and sex distributions, total duration of fever, and the duration of fever after initiation of treatment (Table 2). There were no statistically significant differences in the laboratory results (leukocyte count, ESR, CRP, aspartate aminotransferase, alanine aminotransferase, and total bilirubin) between the two groups (Table 3). Pulmonary parenchymal infiltration was observed on chest roentgenography in 3 patients (27.3%) in the MP group and 3 (12%) in the control group (*P*=0.343) (Table 4).

Echocardiographic abnormalities (coronary ectasia or aneurysm, mitral regurgitation, left ventricular dysfunction, and pericarditis) were observed in 5 patients (45.5%) in the MP group and 8 (32%) in the control group (*P*=0.475) (Table 5). Follow-up echocardiography demonstrated coronary aneurysm in 1 patient in each group (9.1% in the MP group, 4% in the control group; *P*=0.539) (Table6).

At follow-up, AMA titers decreased in 5 patients (83.3%) and increased in 1 (16.7%) among the 6 patients in the MP group, in whom AMA titers were measured later (Table 7). All patients in both groups were successfully treated with intravenous immunoglobulin and oral aspirin. Oral macrolide antibiotics were administered to 4 patients in the MP group before the diagnosis of KD was established, but were stopped subsequently after initiation of treatment for KD.

4. DISCUSSION

KD causes vasculitis in various tissues and organs, including the heart and blood vessels, and is associated with several cardiovascular complications, such as coronary ectasia or aneurysm, myocarditis, pericarditis, ventricular dysfunction, valvular regurgitation, coronary thrombosis, coronary stenosis or occlusion, and ischemic heart disease. Therefore, KD became one of the most common causes of acquired heart disease in infants and children.

Owing to the similarities in the clinical presentation, such as fever and skin rash, of KD and other infectious conditions, it is hypothesized that certain microbial infections may either cause KD or be associated with its pathogenesis. While several studies have found evidences of an association between KD and microorganisms, such as *Staphylococcus aureus*[19,20], *Propionibacterium acnes*[21], *Yersinia pseudotuberculosis*[22], rickettsiae[23], and retrovirus[24], their etiological roles are yet to be confirmed. It is postulated that KD may occur in some susceptible patients following certain microbial infections or following polyclonal activation of T-cells stimulated by superantigens or superantigenic toxins[16,20,25-28].

Rowley et al.[5] identified increased infiltration of immunoglobulin A (IgA) plasma cells in the respiratory mucosa of

patients with KD, in addition to their presence in the vascular tissues. Subsequently, they also demonstrated the KD-associated antigen in the proximal bronchial epithelium of patients with KD using a synthetic antibody[6]. This suggested the possibility that a certain etiologic agent of KD might enter through the upper respiratory tract, trigger an IgA-mediated immune response, and spread systemically, resulting in inflammatory responses in blood vessels and other organs.

MP is a common cause of respiratory illnesses, including pneumonia and bronchitis, in infants, children, and adolescents, and is associated with extrapulmonary manifestations as well. Skin rash is the most common extrapulmonary manifestation of MP infection, present in up to 25% of patients. Other extrapulmonary manifestations include neurologic complications (encephalitis, aseptic meningitis, Guillain-Barre syndrome, and transverse myelitis), renal complications (acute nephritis and IgA nephropathy), hematologic complications (hemolytic anemia, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation), cardiac complications (myocarditis and pericarditis), complications of the gastrointestinal tract (gastroenteritis, hepatitis, and pancreatitis), and ocular complications (conjunctivitis, uveitis, optic neuropathy, and retinitis)[7].

There are similarities in the clinical presentation of KD and MP infection, sometimes making it difficult to clinically differentiate between the two. Studies have suggested that MP infection may either accompany KD[8-12] or be causally related to KD[13-15]. Hence, this study was conducted to examine the association between KD and MP infection. In the present study, there were no significant differences between the MP and the control groups, with respect to age and sex distributions, duration of fever, laboratory results, chest roentgenographic findings, and echocardiographic findings. The decrease in AMA titers during follow-up in some patients in the MP group raised the possibility of the MP infection being a previous infection rather than a concurrent infection.

Recently, Dominguez et al.[29] demonstrated that polymerase chain reaction tests were negative for MP in the nasopharyngeal specimens of all 47 patients with KD who were tested. Moreover, they failed to demonstrate any temporal correlation between the incidence of KD and the rate of MP-positive respiratory samples in their community during the study period.

In conclusion, although AMA titers were positive in some of patients with KD in our study, it did not appear to influence the clinical features, courses, and outcomes of KD. Our results also suggested that positive AMA titers were related to a previous infection, rather than a concurrent infection, thus reducing the likelihood of the MP infection being a causative factor for KD. However, this study was limited by its small sample size and the failure to measure AMA titers in all patients during follow-up. Large prospective studies with strict follow-up protocols are required to confirm our findings regarding the association between KD and MP infection.

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Table 1: Anti-mycoplasmal IgM antibody titers in both groups

MP group (n=11; 30.6%)	7	Positive (>1.1 index)
	4	Indeterminant (0.9~1.1 index)
Control group (n=25; 69.4%)	25	Negative (<0.9 index)

IgM, immunoglobulin M; MP, *Mycoplasma pneumoniae*

Table 2: Characteristics of patients

	MP group (n=11)	Control group (n=25)	*P* value
Age (months)	48.5±25.7	37.1±16.8	0.115
Sex ratio (M:F)	1:1.8	1.1:1	0.481
Total duration of fever (days)	10.5±6.4	7.6±2.1	0.184
Duration of fever after initiation of treatment (days)	4.0±5.6	2.0±2.0	0.267

Values are presented as mean±standard deviation.
MP, *Mycoplasma pneumoniae*

Table 3: Laboratory results

	MP group (n=11)	Control group (n=25)	*P* value
Leukocyte count (cells/㎣)	15,436±5,083	16,064±4,771	0.724
Erythrocyte sedimentation rate (mm/hr)	73.6±30.5	80.9±29.9	0.511
C-reactive protein (mg/dL)	9.27±6.79	10.98±6.69	0.488
Aspartate aminotransferase (IU/L)	280.8±535.8	147.9±157.9	0.258
Alanine aminotransferase (IU/L)	248.7±309.0	109.2±116.5	0.174
Total bilirubin (mg/dL)	0.61±0.28	1.20±1.08	0.023

Values are presented as mean±standard deviation.
MP, *Mycoplasma pneumoniae*

Table 4: Chest roentgenographic findings

	MP group (n=11)	Control group (n=25)	*P* value
Infiltration(+)	3 (27.3%)	3 (12%)	0.343
Normal	8 (72.7%)	22 (88%)	

MP, *Mycoplasma pneumoniae.*

Table 5: Echocardiographic findings

	MP group (n=11)	Control group (n=25)	*P* value
Abnormal	5 (45.5%)	8 (32%)	0.475
Coronary ectasia or aneurysm	1	4	
Mitral regurgitation	3	2	
LV dysfunction	0	2	
Pericardial effusion	1	0	
Normal	6 (54.5%)	17 (68%)	

LV, left ventricle; MP, *Mycoplasma pneumoniae*

Table 6: Follow-up echocardiographic findings

	MP group (n=11)	Control group (n=25)	*P* value
Coronary aneurysm	1 (9.1%)	1 (4%)	0.539
Normal	10 (90.9%)	24 (96%)	

MP, *Mycoplasma pneumoniae*

Table 7: Changes of anti-mycoplasmal IgM antibody titers in MP group

	Initial titer (index)	Follow-up titer (index)
Patient 1	1.3	1.0
Patient 2	0.9	0.1
Patient 3	0.9	0.7
Patient 4	2.1	1.4
Patient 5	5.9	4.7
Patient 6	2.2	2.5

MP, *Mycoplasma pneumoniae*