Clinical characteristics of Kawasaki disease complicated with Mycoplasma pneumoniae pneumonia
A retrospective study
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Abstract
This study aimed to investigate the inner linkage and mechanism of Mycoplasma pneumoniae (MP) infection and Kawasaki disease (KD), as well as the risk factors of outcome in this cohort of patients.

A retrospective study was performed in 210 patients diagnosed with KD complicated with community acquired pneumonia (CAP) in Children’s Hospital, Zhejiang University School of Medicine from January 2014 to December 2017. They were divided into two groups based on MP infection: MP infection group (n=97) and non-MP infection group (n=113). We compared the variables of these two groups based on medical records.

The MP infection group had higher ESR than the non-MP infection group. During hospitalization, the non-MP infection group had higher levels of WBC during hospital, LDH, PCT, and lower HB when compared to the MP infection group. No differences were found in the hs-CRP level, N%, PLT, ALT, CKMB, and cytokine levels (IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ) between MP and non-MP infection group. Likewise, no difference was found in fever duration or hospital stays between them. Totally 19 patients in the infection group had CAA with a rate of 19.59%; and 27 (23.89%) patients had CAA in the non-MP infection group. Unfortunately, no difference was found in CAA rate between the two groups.

MP infection may occur simultaneously in children with Kawasaki disease. KD patients with MP infection tended to occur in older population. MP infection may not increase the risk of CAA, which still needs further large-scaled studies to confirm. Clinicians should be alert to KD patients with high level of ESR. MP should be screened and early treatment with macrolides should be given timely.

Abbreviations: AHA = American heart association, ALB = albumin, ALT = alanine transaminase, CAA = coronary artery abnormalities, CAP = community acquired pneumonia, CKMB = creatine kinase MB activity, ELISA = enzyme-linked immunosorbent assay, ESR = erythrocyte sedimentation rate, HB = hemoglobin, hs-CRP = high sensitivity-C-reactive protein, IFN-γ = interferon-γ, IL = interleukin, IG = intravenous immunoglobulin, KD = Kawasaki disease, LDH = lactic dehydrogenase, MP = Mycoplasma pneumoniae, MPEPDs = MP-related extra-pulmonary diseases, MPP = Mycoplasma pneumoniae pneumonia, N% = neutrophils percentage, NPA = nasopharyngeal aspirate, PCR = polymerase chain reaction, PCT = procalcitonin, PLT = platelet, RMPP = refractory Mycoplasma pneumoniae pneumonia, SMPP = severe Mycoplasma pneumoniae pneumonia, TNF-α = tumor necrosis factor-α, WBC = white blood cell.

Keywords: coronary artery abnormalities, Kawasaki disease, mycoplasma pneumoniae, mycoplasma pneumoniae pneumonia.

1. Introduction

Kawasaki disease (KD), firstly reported by Tomisaku Kawasaki in 1967, is an acute febrile systemic vasculitis with unknown etiology and often occurs in children aged 6 months to 5 years.[1] It is normally a self-limited heterogeneous disease with favorable outcomes. Generally speaking, KD is a multisystem vasculitis that primarily affects the coronary arteries of young children.
However, coronary artery abnormalities (CAA) may develop in severe cases; and aneurysms may develop and lead to severe sequelae, including myocardial ischemia, myocardia infarctions, and even sudden death.[2] As a result, KD is recognized as the leading cause of pediatric acquired heart diseases in many countries[3] and is a risk factor of adult ischemic heart disease.[4]

*Mycoplasma pneumoniae* (MP) is a common pathogen causing pediatric respiratory tract infections. About 10% to 40% community acquired pneumonia (CAP) are caused by MP.[5] MP is regarded as the primary causative agent of pneumonia in school children. Recently, a growing number of MP pneumonia (MPP) cases in children under 5 years of age have been reported. And KD also predominately affects children under 5 years old. Epidemiologic studies revealed that children with MPP tend to have longer fever period and more complications than before, which is considered to be related with immune overreaction induced by macrolide-resistant strain MP.[6,7] Use of steroids for the patients infected with macrolide-resistant MP achieved remarkable efficacy.[8] These together indicate the involvement of excessive immune response in MP infection. Since KD is an acute self-limiting systemic inflammation that involves multiple organs, it has been proposed that there are etiologic substances that induce systemic inflammation.[9] Moreover, a few cases reported that MP infection is considered to be one of the predisposing factors of KD.[10-12] In detail, Lee et al reported that among 54 KD patients with concurrent pneumonia, 22.2% patients had MP infection.[12] Similarly, Tang et al showed that of the 450 KD patients, MP infection was found in 62 cases.[13] Therefore, the linkage of MP infection and development of KD and long-term risk of CAA is of particular interest and still need to be further studied through large-sample analysis.

This study retrospectively analyzed 210 pediatric patients with KD complicated with pneumonia. We compared the difference of clinical characteristics and outcome in patients with MP infection and non-MP infection. We aimed to investigate the inner linkage and mechanism of MP infection and KD, as well as the risk factors of outcome in this cohort of patients.

### 2. Methods

This study was approved by Ethical Committee of Children’s Hospital, Zhejiang University School of Medicine. This study was a retrospective study, informed consents were obtained.

#### 2.1. Inclusion and exclusion criteria

Inclusion of complete KD was based on criteria defined by American heart association (AHA)[14], fever lasting at least 5 days plus four of the following five principal clinical criteria:

1. rash,
2. bilateral conjunctivitis without exudate,
3. inflammation of oral mucosa,
4. cervical lymphadenopathy and
5. extremity changes.

Incomplete KD was diagnosed based on the criteria defined by AHA.[14] Diagnosis of CAP was based on criteria defined by Chinese Pediatric Association.[15] In brief, CAP was diagnosed on the presence of the following criteria:

1. any respiratory signs and symptoms such as cough, tachypnea, wheezing, chest retractions, and abnormal auscultatory findings;
2. any radiologic evidence of pneumonia consisting of the presence of abnormal inflammatory densities in lung parenchyma.

MP infection was diagnosed based on the criteria defined as follows: MP IgM antibodies detected by enzyme-linked immunosorbent assay (ELISA) ≥1.0 or respiratory samples (sputum, throat swab, bronchoalveolar lavage fluid) detected by polymerase chain reaction (PCR) with positive results for MP. The MP genome was detected in nasopharyngeal aspirate (NPA) by real-time RT-PCR as described previously.[16] In brief, MP DNA was extracted, and then MP sequence was specifically analyzed using quantitative diagnostic kit for MP DNA (PCR fluorescence probing) (Da An Gene Co., Ltd. of Sun Yat-sen University, China). Amplification, detection, and data analysis were performed with 7500 real-time PCR system (Applied Biosystems, Foster, CA). Additionally, the levels of anti-IgM was measured using MP IgM enzyme-linked immunosorbent assay (ELISA) kit (Shanghai B&C Biological Technology, Co. Ltd., China) according to the manufacturer’s instructions. The assay was regarded as positive if the ratio of optical density value of specimen to that of negative control over 1.1.[16]

Coronary artery abnormalities (in echocardiography) was defined as an internal lumen diameter ≥3 mm in children ≤5 years of age or ≥4 mm in children >5 years of age. Coronary artery aneurysm was defined as a segmental internal diameter of any segment ≥1.5 times greater than that of an adjacent segment. Giant coronary aneurysm was referred to a segmental internal diameter ≥8 mm.[11,4] The concept of z-score was introduced several years ago to compare the coronary artery diameter to the body surface area and measure the standard deviation from the average in Z units (SD, z-score). The z-score <2 indicates the absence of coronary artery involvement, the z-score between 2 and 2.5 indicates the presence of coronary artery dilation, and the z-score ≥2.5 indicates the presence of coronary artery aneurysm.[17]

Exclusion criteria were

1. with connective tissue diseases including Scarlet fever, rheumatic fever, and fever with unknown origin;
2. without intravenous immunoglobulin (IVIG) treatment or those treated not according to the clinical guideline by Marchesi et al[18];
3. with incomplete or incorrect medical records.

A total of 210 patients diagnosed with KD complicated with CAP at Children’s Hospital, Zhejiang University School of Medicine from January 2014 to December 2017 were included in this study. All patients received IVIG at a dosage of 1 g/kg/day for 2 days and oral aspirin at 30 to 50 mg/kg/day. The dosage of aspirin was reduced at day 3 post normal temperature to 3 to 5 mg/kg/day for 6 to 8 weeks; if with CAA, aspirin was given until 6 to 8 weeks after coronary artery recovering to be normal. If with CAA and remarkable increased platelet level, oral dipyridamole was given at a dosage of 3 to 5 mg/kg/day; if with MP infection, intravenous azithromycin was given at a dosage of 10 mg/kg/day for 3 days for mild patients and 5 to 7 days for severe patients. Laboratory findings were obtained upon hospital admission and before IVIG administration, which included white blood cell count (WBC), neutrophils percentage (%), hemoglobin (HB), high sensitivity-C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), albumin (ALB), alanine transaminase (ALT), lactic dehydrogenase (LDH), creatine kinase MB activity (CKMB), procalcitonin (PCT), PCR results of respiratory samples (sputum, throat swab or bronchoalveolar
lavage fluid) for MP-PCR, ELISA MP-IgM antibody level. Echocardiography was performed in all patients on the fifth to tenth day of fever. The internal lumen diameter of coronary artery was recorded through echocardiography.

All patients were followed up at outpatient department regularly at 1, 3, 6, 12, 24 months after discharged. Routine blood, hs-CRP, ESR, and biochemistry (if abnormal when discharged) were tested and echocardiography was performed during the follow-up.

2.2. Statistical analysis

SPSS (version 20.0) software package was used for data analysis. The continuous variables with normal distribution (e.g., hemoglobin) were expressed as calculated mean±SD and Student’s t test was used for comparison. For continuous variables with non-normal distribution (e.g., age), data were expressed in terms of the median (25th percentile, 75th percentile) and Mann–Whitney U test was used for comparison. We used n (%) for categorical variables (e.g., gender) and assessed differences with the χ² test. A two-tailed P value <.05 was considered statistically significant.

2.3. Data availability

The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

3. Results

A total of 3026 patients were diagnosed with KD from January 2014 to December 2017. Of the 3026 KD patients, MP was positive in 325 (10.7%) patients. Two hundred ten KD patients with CAP were recruited into this study, 97 of whom had MP infection (MP infection group), the remaining 113 patients without MP infection (non-MP infection group), the remaining 113 patients without MP infection (non-MP infection group). In detail, 96 of the 97 patients in the MP group had serum MP IgM test, 92 (95.8%) was positive for MP specific IgM. Meanwhile, 32 patients in the MP group took NPA PCR test, 16 (50.0%) were positive for MP DNA. Collectively, 11 patients in MP group took NPA PCR test, 16 (50.0%) were positive for MP specific IgM.

The median age of all these patients was 20.00 (11.00–41.25) months. There were 55 boys and 42 girls in the MP infection group with a median age of 28.00 (14.00–49.00) months, while the non-MP infection group consisted of 78 boys and 35 girls with a median age of 17.00 (7.97–30.50) months. There was no difference of gender between the two groups (P = .658). However, the mean ages of the two groups were significantly different (P < .001).

These patients’ relevant clinical and laboratory data are shown in Table 1. In brief, there was no significant difference between the two groups with respect to routine blood tests on admission, fever duration, hospital stays, cytokine levels, ALT, ALB, and CK-MB levels. However, the ESR was significantly higher in MP infection group than in non-MP infection group. Inversely, significantly higher levels of PCT, WBC during hospital, LDH were found in the non-MP infection group than in MP infection group.

Nineteen (19.59%) patients in the MP infection group had CAA, while 27 (23.89%) patients had CAA in the non-MP infection group. No difference was found in CAA rate between the two groups (P = .452). Similarly, there was no significant difference in the rate of z-score ≥2.0 cases between the two groups (MP infection group: 11 (11.3%) vs non-MP infection group: 17 (15.0%), P = .150). During the follow-up, the inner lumen of the 19 patients in the MP infection group reduced to be normal in 6 months after discharge. In the non-MP infection group, 3 patients had increased inner lumen diameter, and all reduced to be normal in 12 months after discharge. The abnormal test results (e.g., WBC, CRP, and ESR) gradually converged to the normal range during the follow-up, and all the laboratory data were within the normal range at the last follow-up in both groups. None of the children enrolled had serious complications, surgical treatment or death.

4. Discussion

KD has been reported globally, and the incidence rate is the highest in East Asia.[19] Since Dr Tomisaku Kawasaki first reported this disease in 1967, the pathogenesis of KD still remains unclear to date. Many studies have suggested that infectious agents (bacteria, virus, and mycoplasma)[20,21] may trigger KD in genetically predisposed individuals.[12] Park et al suggested that symptoms of MP infection may be similar to those of KD, and concomitant infection with MP in KD patients is possible.[12] Similarly, we found 46.19% of the KD patients with pneumonia had concurrent infection with MP, suggesting MP infection may occur simultaneously in children with Kawasaki disease.

The etiology of MP infection is still elusive. The main mechanism of MP may be related to direct immunotoxicity and immunologic injury. So immunologic mechanism is one of the most important mechanisms for MP infection, which is very similar to KD.[23–25] In detail, it is reported that the process of superantigens activating T cell might be crucial in the pathophysiology of KD.[123] Similarly, Mycoplasma arthritidis has been shown to produce superantigens, and it is therefore possible that Mycoplasma species, like MP, may do likewise.[124] Moreover, MP infection can induce very complicated immune reaction.[26,27] Many researchers found MP infection may cause disturbance of Th1/Th2 immune response balance, with a domination of Th2 cytokines.[28–31] Similar to KD, children with MP pneumonia were also reported to be complicated with pericarditis and endocarditis.[31] Therefore, it is important to closely look for concurrent infection of MP in KD patients.

Different from previous study that mainly focus on the patient with KD,[40] we pay our attention on the KD children with CAP in the present study. This KD with CAP population should be highlighted in clinical practice. Similar to those previous report,[6,12] we found that MP infection was quite common in KD patients with CAP, but the respiratory symptoms were not serious, and the early lung signs (moist rales) were not obvious in most cases. Clinicians may neglect the possibility of MP infection in KD patients. The mean age of KD patients is generally considered to be 3 years old; the onset age of KD may be
Generally, MP infection, contributing to the high incidence of pneumonia or bronchitis, is mainly found in school-aged children. However, MP infection is commonly found in younger children in China due to earlier exposure with daycare attendance. Our study also found such tendency with significantly higher age in the MP infection group than that in the non-MP infection group.

In our study, we showed MP infection group were much older than non-MP infection group which was in accordance with previous studies. In detail, Lee et al found that the MP group (5.5 ± 3.5 years) was significantly older than the non-MP group (2.8 ± 2.2 years) in KD patients. Likewise, Tang et al reported the median age of the MP+KD+ group (25 months) was significantly older than the MP-KD+ group (14.5 months). These data together indicate that KD concurrent with MP infection is more likely to occur in older children.

Generally, fever is one of the most common manifestations of MP infection. However, in our study, MP infection group did not show prolonged fever durations when compared to non-MP group. Similarly, Lee et al reported that there was no statistical difference in duration of fever between the MP positive group and MP negative group. In contrast, in another study it was shown that mycoplasma infection is considered as a possible cause for the prolonged fever after intravenous immunoglobulin treatment of patients with KD. The different result from these studies may be caused by the different selection criteria for patients and the racial composition of the populations of various countries.

Our previous study showed that the MP positive rates in summer, autumn, spring, and winter were 27.8%, 23.9%, 18.0%, and 11.6%, respectively in a descending order. However, the highest rate of MP positive rate in KD patients was in spring (32.0%), followed by summer (26.8%). Of note, no difference was observed in season distribution of KD between MP and non-MP group in present study. These findings imply that MP infection in lower respiratory tract may not increase the incidence of MP associated KD.

### Table 1
Clinical characteristics of Kawasaki disease patients with or without Mycoplasma pneumoniae (MP) infection.

| Variables                                | MP (n=97)          | non-MP (n=113)         | P    |
|------------------------------------------|--------------------|------------------------|------|
| Laboratory examination on admission     |                    |                        |      |
| White blood cell (WBC) (×10^9/L)         | 10.85 (7.49–14.55) | 10.61 (6.97–16.36)     | .773 |
| Abnormal WBC (n)                         | 41                 | 55                     | .353 |
| Neutrophils (N%) (%)                     | 58.10 (45.40–70.05) | 59.00 (42.80–75.55)    | .524 |
| Abnormal N% (n)                          | 51                 | 72                     | .152 |
| Hemoglobin (Hb) (g/L)                    | 110.52±12.41       | 104.74±14.25           | .002 |
| Abnormal Hb (n)                          | 41                 | 66                     | .020 |
| Platelet (PLT) (×10^9/L)                 | 377.00 (299.00–497.00) | 352.00 (284.75–504.75) | .477 |
| Abnormal PLT (n)                         | 39                 | 53                     | .330 |
| C-reactive protein (CRP) (mg/L)          | 38.00 (11.00–84.00) | 55.00 (15.00–105.00)   | .229 |
| Abnormal CRP (n)                         | 76                 | 92                     | .580 |
| Erythrocyte sedimentation rate (ESR) (mm/h) | 75.00 (52.00–93.50) | 60.00 (27.50–91.00)    | .031 |
| Abnormal ESR (n)                         | 91                 | 90                     | .003 |
| Fever duration (days)                    | 8.00 (7.00–11.00)  | 8.00 (7.00–10.00)      | .052 |
| Hospital stays (days)                    | 6.00 (5.00–9.00)   | 7.00 (6.00–9.00)       | .464 |

During hospitalization

| WBC (×10^9/L)                             | 13.53 (9.29–16.76) | 14.98 (10.33–20.49) | .040 |
| Abnormal WBC (n)                          | 56                 | 81                     | .034 |
| Neutrophils (N%) (%)                      | 65.50 (54.50–76.60) | 69.60 (46.75–78.35)   | .777 |
| Abnormal N% (n)                           | 57                 | 74                     | .316 |
| Hemoglobin (Hg/L)                         | 109.00 (100.50–117.00) | 102.00 (92.00–112.00) | .001 |
| Abnormal Hb (n)                           | 50                 | 78                     | .010 |
| Platelet (PLT) (×10^9/L)                  | 506.00 (425.50–635.00) | 524.00 (411.50–745.50) | .250 |
| Abnormal PLT (n)                          | 90                 | 90                     | .818 |
| CRP (mg/L)                                | 57.00 (20.00–106.50) | 70.00 (22.00–115.00)   | .467 |
| Abnormal CRP (n)                          | 83                 | 98                     | .808 |
| Procalcitonin (PCT) (ng/mL)               | 0.33 (0.10–2.78)   | 0.91 (0.19–3.00)       | .020 |
| Abnormal PCT (n)                          | 46                 | 70                     | .035 |

Elevated cytokine

| IL-6 (n)                                  | 56                 | 74                     | .249 |
| IL-10 (n)                                 | 57                 | 72                     | .462 |
| IL-4 (n)                                  | 29                 | 44                     | .770 |
| IL-2 (n)                                  | 3                  | 1                      | .243 |
| TNF-α (n)                                 | 5                  | 10                     | .300 |
| IFN-γ (n)                                 | 11                 | 20                     | .195 |

Elevated biochemical test

| Alanine transaminase (n)                  | 24                 | 25                     | .655 |
| Lactic dehydrogenase (n)                 | 25                 | 52                     | .002 |
| Creatine kinase MB activity (n)           | 41                 | 43                     | .534 |

Decrease biochemical test

| Albumin (n)                               | 13                 | 16                     | .874 |

n=number.
MP-related extra-pulmonary diseases (MPEPDs) including cardiovascular system (e.g., Kawasaki disease) were widely described in children, and immune-mediated mechanisms were proposed to be implicated in MPEPDs.\textsuperscript{13,14} Similarly, exaggerated inflammatory response triggered by bacterial superantigens is involved in the mechanism of KD. MP N602 protein, a lipid-associated membrane protein of MP, has inflammatory capacity and can act as a potential superantigens leading to vascular changes.\textsuperscript{13} It was reported that coinfection by MP may be an important cofactor for coronary artery disease, suggesting a closed relationship between MP and vascular changes.\textsuperscript{16}

Unfortunately, there was no difference in CAA rate between the MP and non-MP group in present study. In accordance with our results, another two study conducted by Lee et al and Tang et al, respectively, also found no difference of coronary arterial lesions between MP+ KD patients and MP-KD cases.\textsuperscript{12,13} Therefore, large study samples is needed to verify the relationship between MP and CAA.

Additionally, the hospital stays and rate of CAA were similar between the two groups; therefore, there is no evidence that MP infection may exacerbate the condition or increase the rate of CAA in KD patients. Another finding is that the MP infection group had much higher ESR than the non-MP infection group; so early detecting MP infection is essential in KD patients with higher ESR though there might be mild respiratory symptoms at early stage. The non-MP infection group had low HB than the MP infection group, which indicated the pathological changes in the blood system. PCT, WBC during hospital, LDH were found significantly higher in the non-MP infection group than in the MP infection group. It gives us a clue of possible co-mixed infection of other pathogens in KD patients. But, we found no positive results of any pathogens in non-MP infection group. No differences were found in other laboratory variables including N%, PLT, and hs-CRP between the two groups, suggesting these indices may not be so valuable in the differentiation of MP infection. What's more, in the present study, no severe complications (e.g., respiratory failure, death) occurred in the MP group treated with macrolides as well as the non-MP group treated with penicillins or cephalosporins. This indicates concurrent infection may not exacerbate conditions of KD patients with timely anti-infection therapy, and we need not to be so worried when meeting KD patients with MPP. Actually, extrapulmonary complications are common in MP infection particularly in MPP. In recent years, cases with refractory \textit{Mycoplasma pneumoniae} pneumonia (RMPP) and severe \textit{Mycoplasma pneumoniae} pneumonia (SMPP) increased remarkably which may be related to the increasingly emerged drug resistant strain of MP. Generally the outcome of MPP is favorable even with RMPP or SMPP in clinical practice. We think that MP may not lead to poor outcome in KD patients; however, some KD patients with CAA may have poor outcome even sudden death due to rupture of aneurysm.\textsuperscript{15} The rate of CAA in the MP infection group is similar with non-MP infection group. And the inner lumen diameter of 17 patients with CAA in the MP infection group recovered to be normal up to 6 months after discharge. For the 27 patients with CAA in the non-MP infection group, the inner lumen diameter recovered to be normal in 1 year. Recent studies showed that macrolides have immunomodulatory effects besides its antimicrobial effects.\textsuperscript{17,18} Further studies should be carried out to investigate the immunomodulatory effects of azithromycin (a classic drug for anti-mycoplasma infection) on KD with a pathogenesis of immunologic injury.

There are several limitations of this retrospective study. First, the sample size of this study is still relatively small. Following possibilities:

1. children of different ages are susceptible to different pathogens, young children have less chance on exposure to pathogens and
2. older children with mature immunity have tolerability or immunity to pathogens, may more or less cause changes in the laboratory examinations.

Thus, larger study with patients within the similar age range is needed. Secondly, we have not classified the severity of MPP in this study, and the relationship of severity of MP infection and KD was not investigated in the present study. Further studies will be focused on the correlation of MP infection of various severities with the development of KD. Thirdly, overdiagnosis or underdiagnosis may exist for the lack of golden diagnostic criteria for MP infection. Stricter criteria for the selection of MP infection will be performed in our further study to reduce selection bias. Fourthly, because no positive results of pathogen were found in non-MP infection group, the choice of antibiotic treatment was empirical, which may have led to the prolonged use of antibiotics and unsatisfactory therapeutic efficacy. What's more, the type of antibiotics, time point and length of antibiotic usage in the present study may also influence our results.

5. Conclusion

MP infection may occur simultaneously in children with KD. MP infection may not exacerbate the condition of KD or increase the risk of CAA. Clinicians should be alert of KD patients with high ESR; though these patients may have mild respiratory symptoms, MP should be screened and early treatment with macrolides given for MP infection. The laboratory indices including PLT, hs-CRP, and N% are of minor value for differentiating MP infection. Although we suspect there may exist certain correlation between MP and KD development, there is still no direct evidence of MP as a trigger of KD. Further prospective studies should be carried out for finding possible inner mechanism.

Acknowledgments

We thank the participants and their families. We gratefully thank Dr Yanfeng Meng, MD, PhD, who was the faculty of Washington University School of Medicine, for English language polishing in the revised manuscript.

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