

인플루엔자 A 및 폐렴미코플라스마 감염과 병발한 가와사키병 1례

문혁수¹ · 허재성¹ · 김미경¹ · 람버트 모리쇼²

전주예수병원 소아청소년과¹, 나미봉구병원, 콩고 민주 공화국²

Kawasaki Disease with Influenza A Virus and *Mycoplasma pneumoniae* Infections: A Case Report and Review of Literature

Hyeok Soo Moon¹, Jae Seong Huh¹, Mi Kyung Kim¹, Mulakwa Morisho Lambert²

¹Department of Pediatrics, Presbyterian Medical Center, Jeonju, Republic of Korea, ²Department of Pediatrics, Nyamibungu Referral Hospital, South Kivu, D.R.Congo

Although an association of Kawasaki disease (KD) with infectious agents has been suggested, none have been proven to cause KD. In this case study, we present a case of KD with concurrent onset of influenza and *Mycoplasma pneumoniae* (MP) infections. A 27-month-old boy presented with prolonged fever, cough, and rhinorrhea. During the initial testing, influenza A infection was identified, and he was treated with oseltamivir. Despite the antiviral therapy, the fever persisted, and he had cervical lymph node enlargement, bilateral conjunctival injection, fissured red lips, strawberry tongue, and erythematous skin lesions on the Bacillus Calmette-Guérin vaccination site. Thus, the patient was diagnosed with KD and was treated with intravenous immunoglobulin (IVIG). The result of the initial antimycoplasma immunoglobulin M (IgM) antibody testing and was positive, and an increased IgM titer from baseline was found in a repeat test. We reviewed the hypotheses on pathogens known to be associated with KD and the etiology of KD. Based on our findings, we suspect that symptoms of KD and coronary artery lesions can occur from various infections besides those caused by *Mycoplasma* species and influenza viruses.

Key Words: Kawasaki disease, *Mycoplasma pneumoniae*, Influenza A

Introduction

Kawasaki disease (KD) is a self-limited systemic

inflammation that occurs predominantly in infants and young children¹⁾. The etiologic agent(s) of KD have yet to be identified. Although various bacterial and viral agents have been suggested to be associated with KD, none has been proven as a causative factor²⁾.

KD has unique epidemiological characteristics. KD appeared as a new disease in East Asian countries, including Japan, South Korea, Taiwan, and China, but there were time-gaps of 5-10 years³⁾. After its appearance, KD became an endemic disease within a decade and occurred in all districts throughout the year with a slowly increasing annual incidence. Thus, it seems

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Correspondence: Mi Kyung Kim

Department of Pediatrics, Presbyterian Medical Center, Jeonju, Korea

Tel: +82-63-230-1390, Fax: +82-63-230-1399

E-mail: kmik7@hanmail.net

that the time of economic growth and westernization in these countries is associated with the appearance of KD³⁾. Additionally, the same age predilection of KD is shown in the emergence of KD in all countries, and there is a marked discrepancy in the incidence across different populations.

Considering the epidemiological and clinical features of KD, it is suggested that KD may be an acute immune-mediated disease that is triggered by substances that are produced after an unknown infection(s), and the immunopathogenesis of KD is more like that of acute rheumatic fever than scarlet fever⁴⁾. Thus, clinical manifestations of KD, including clinical diagnostic signs, can appear as a systemic reaction to similar inflammation-inducing substances produced after infection by various pathogens, not just a single pathogen.

Influenza affects 10% to 40% of children each year in countries with temperate climates. Influenza viruses can cause mild to severe illnesses such as encephalopathy, myositis, carditis, and other organ involvement as extrapulmonary complications. The severity of the illness varies according to influenza strain and the host's immunity, thus suggesting the need for immunization⁵⁾. *Mycoplasma pneumoniae* (MP), which is commonly known as a major causative agent of primary atypical pneumonia, also causes various kinds of extrapulmonary manifestations involving almost all organs of the human body⁶⁾.

In the present case study, we review the case of a pediatric patient with KD who tested positive for two types of pathogens and their corresponding infections.

Case Report

A 27-month-old boy presented with a 2-day history of fever and a 5-day history of cough and rhinorrhea on March 25, 2015. He was brought to the outpatient clinic, and a nasopharyngeal swab was collected for testing as part of a clinical study. For initial testing, a fluorescent immunoassay (Sofia influenza A+B FIA kit, Quidel Inc., San Diego, USA) was performed at the clinic and it revealed an influenza A virus infection,

and he was treated with oseltamivir therapy. Despite administration of the antiviral therapy for 2 days, his fever persisted, accompanied by cervical lymph node enlargement. Thus, he was admitted to the hospital on March 27, 2015.

The patient was born in a hospital through normal spontaneous vaginal delivery with a birth weight of 2,980 g at the gestational age of 40 weeks. His medical history was unremarkable, and he was in good health before the admission. He had no known atopic diseases and had received the seasonal influenza vaccine each year. All members of his family were in good health, none of whom had a contributory medical history or similar symptoms.

Physical examinations revealed a deteriorating general state because of the fever, body temperature of 39.7°C, pulse rate of 120/min, respiratory rate of 28/min, blood pressure of 115/58 mmHg, and pharyngeal erythema without exudates. He had a palpable 1×1 cm lymph node on the right side of his cervix. In a chest auscultation, rough breath sounds were detected, but crackles were not audible and there was no chest retraction. His heart sound was regular, and no cardiac murmur was audible. His abdomen was soft and flat, and showed no signs of hepatosplenomegaly. The results of the other examinations were normal.

The laboratory studies consisted of a complete blood cell count, which yielded the following values: white cell count, 8,200/μL; hemoglobin level, 11.6 g/dL; and platelet count, 211,000/μL. His C-reactive protein (CRP) level was elevated at 7.87 mg/dL. The levels of electrolytes, liver enzymes, lactate dehydrogenase, and urinalysis parameters were within their normal limits.

Chest radiography revealed no acute pulmonary process and showed a normal cardiothymic silhouette. Blood and urine cultures were obtained, both of which eventually yielded no pathogen growth. The result of the reverse transcriptase polymerase chain reaction (RT-PCR) analysis of a nasopharyngeal swab was positive for MP (Anyplex II RB5 Detection kit, Seegene, Seoul, Korea) and influenza A virus (Anyplex II RV16 Detection kit, Seegene, Seoul, Korea). The anti-MP immunoglobulin M (IgM) antibody S/C ratio (enzyme

immunoassay) was 1.4 on hospital day 3 (sample absorbance/cutoff absorbance ratio: negative, <0.9; equivocal, 0.9–1.1; positive, >1.1).

We continued the oseltamivir therapy and added broad-spectrum antibiotics because of the possibility of bacterial coinfection. However, the patient remained febrile over 3 days after hospitalization and his CRP level was elevated to 11.81 mg/dL.

On hospital day 4, physical examination revealed bilateral conjunctival injection, cervical lymph node enlargement, fissured red lips, strawberry tongue, and skin erythema on the Bacillus Calmette–Guérin (BCG) vaccination site. The fever persisted. Echocardiography revealed a 2.5 mm left main coronary artery and mild perivascular brightness around the coronary arteries. A diagnosis of KD was made, and treatment with intravenous immunoglobulin was initiated. The fever eventually subsided on the fifth hospital day, and the patient was discharged on hospital day 9.

On follow-up examination, the anti-MP IgM antibody S/C ratio 1 week after discharge was elevated to 5.9. Follow-up echocardiography revealed a 2.7 mm left main coronary artery and that the previous perivascular echogenicity had disappeared. The patient was continued on clopidogrel therapy and follow-up care.

Discussion

The exact etiology of KD is yet to be identified; but considering its epidemiological and clinical features, it is suspected to be closely associated with infections²⁾. Over nearly a half century, many studies have evaluated the association between KD and various infectious pathogens such as viruses, bacteria, mycoplasma species, and other pathogens. Among reported KD pathogens, we briefly review several pathogens that have historical or clinical relevance to our study.

Several studies have attempted to establish a link between KD and specific respiratory viruses because of its seasonality. Huang et al. investigated the medical records of 15 patients with KD and concomitant influenza infection, and suggested that influenza infection

affects the clinical manifestations of KD⁷⁾. However, they could not detect a significant difference in the coronary artery complications rate between infected and non-infected individuals. Esper et al. conducted RT-PCR on respiratory specimens for coronavirus and reported that samples from 8 of 11 (72.7%) patients with KD and 1 of 22 (4.5%) control subjects tested positive for a novel human coronavirus⁸⁾. Okano et al. analyzed two KD outbreaks, one from 1982 in Kyoto and the other from 1985 in Sapporo, and reported a lower adenovirus antibody positivity rate in the group of patients with KD than in the control group⁹⁾.

Burns et al. reported that retrovirus-associated reverse transcriptase activity was found in culture supernatants of mononuclear cells from KD patients¹⁰⁾. Iwanaga et al. reported a lower Epstein-Barr virus antibody positivity rate in the KD group than in the control group¹¹⁾. Meanwhile, Kikuta et al. reported that 49 of 57 (86%) patients with KD had serological evidence of primary Epstein-Barr virus infection during the first month of illness based on the results of a method of detecting antibodies against the viral capsid antigen¹²⁾.

Many authors have also reported on cases involving bacterial infections that occurred concurrently with KD. Although cases of infection by various pathogens such as *Propriobacterium acnes*, *Leptospira* species, and *Streptococcus sanguis* have been reported to be concurrent with KD, the evidence of their being etiologic agents is insufficient^{13–15)}. Leahy et al. reported on incomplete KD associated with complicated *Streptococcus pyogenes* pneumonia¹⁶⁾. A recent case report introduced a patient with incomplete KD that mimicked a retropharyngeal abscess¹⁷⁾.

The hypothesis that KD is associated with bacterial superantigens was based on the fact that V β T cells engage in selective expansion¹⁸⁾. However, V β expansion was not observed in acute KD in other studies¹⁹⁾. Leung et al. isolated toxin-producing bacteria from 13 of 16 patients with KD²⁰⁾. Although studies have investigated the association of KD with TSST and other superantigenic toxins, their findings have not been confirmed by follow-up studies²¹⁾. *Mycoplasma arthritidis* is known to produce superantigens, and various studies

have examined MP as a KD-causing agent. Greco et al. reported on a case of cutaneous vasculitis induced by mycoplasma infection via immune-complex-mediated mechanisms²²⁾. Lee et al. reported that 12 of 54 (22.2%) patients with concurrent KD and pneumonia had anti-MP antibody titers of $\geq 1:640$ ²³⁾.

The aforementioned authors mostly used a single positive IgM titer as the basis for diagnosing MP infection. However, because there is no IgM response in the early stage of MP pneumonia and a positive IgM titer may persist for several months in some asymptomatic patients, a single serological test may not be suitable for patient selection. Therefore, accurate diagnosis of MP infection is believed to require testing to determine the IgM titers in paired serum samples in the early stages of infection, or testing to determine IgG titers at 2 to 4 week intervals²⁴⁾. However, studies that satisfy these requirements are rare. Moreover, between 1986 and 2004, six MP pneumonia outbreaks occurred at 3 to 4 year intervals in Korean children²⁵⁾, but the annual incidence of KD during the same periods did not increase.

Several hypotheses have been suggested to explain the etiology of KD. Rowley et al. suggested the etiologic agent(s) of KD may be RNA viruses, based on pathological findings from autopsy tissue samples²⁶⁾. The authors were the first to confirm infiltration of oligoclonal IgA plasma cells in inflamed tissues and coronary arteries. Moreover, they confirmed that the synthetic version of such oligoclonal antibodies can detect intracytoplasmic inclusion bodies (ICIs) in the ciliated bronchial epithelium of patients with acute KD. They have also reported that ICIs are composed of aggregates of nucleic acid and viral protein, and that the same ICIs were detected in macrophages of inflamed tissues of patients with KD. Based on the above-mentioned results, they formulated the following hypothesis: ubiquitous RNA viruses that produce granular ICIs enter the respiratory tract to infect the ciliated bronchial epithelium and flow into the bloodstream through macrophages for transport to the target tissues, including the coronary artery, which ultimately results in damage to the coronary arteries by substances such

as matrix metalloproteinase, which are produced during the process of IgA plasma cells and CD8+ T lymphocytes infiltrating the target tissues.

An interesting hypothesis was proposed by Rodo et al. that was based on the synchronicity between Asian and trans-Pacific wind patterns, and seasonal peaks of the incidence of KD in Japan, Hawaii, and San Diego²⁷⁾. They hypothesized that aerosolized microorganisms are propagated by wind from Central Asia to Southern California. According to the authors, physicians can diagnose KD by predicting the KD activity in specific regions even if the specific KD agent is unknown.

Lee et al. hypothesized that the etiologic agents of KD are a group of normal micro flora of the parents/caregivers of infants and young children, and some normal flora have been substituted by variants because of environmental factors such as improved public hygiene or a western lifestyle during industrialization of East Asian countries³⁾. After invasion of KD agents into the host, some immune-immature young children may develop a focus that contains replicating KD agents, the byproducts of the KD agent replication process, and substances from injured host cells. During this process, KD develops when the substances from the focus spread into the systemic circulation. Various clinical signs of multiple organ involvement in KD may originate from these systemically spread substances to target cells, including coronary artery cells, and corresponding immune cells⁴⁾.

Moreover, a recent study suggested that substances that cause inflammation and damage the host cells in infection-associated immune diseases such as KD or infectious diseases are not the viruses or bacteria themselves but rather are smaller-pathogen-derived substances (including pathogen-associated molecular patterns), substances secreted from immune cells that are involved in an immune response (overproduced cytokines), and substances derived from damaged host cells (including damage-associated molecular patterns)²⁸⁾. Therefore, it is possible that KD and its coronary artery lesions can be caused by substances that are produced after any viral, bacterial, or MP infection.

The patient at presentation in this report had fever

and cough consistent with influenza or MP infection, and tests for influenza and MP were initially performed because of the recent influenza season and MP epidemic year in Korea. After admission, clinical signs of KD such as cervical lymphadenitis, conjunctival injection, fissured red lips, strawberry tongue, skin erythema on the BCG vaccination site, and elevated CRP level were observed, which were suggestive of KD. Recently, because the majority of KD patients visit the pediatrician early (within 1-4 days of fever onset) and the phenotype of KD tends to be milder, early diagnosis of KD in Korea has become difficult. The accurate and timely diagnosis of KD is challenging for clinicians in Korea.

Clinicians must rely on the presence of specific clinical criteria and laboratory data and exclude other illnesses that can mimic the disease. Laboratory evaluation for detection of respiratory viruses is occasionally performed before confirmation of a KD diagnosis. In particular, PCR analysis results positive for currently epidemic respiratory viruses should not be used as evidence against the diagnosis of KD. According to a retrospective study, patients with KD who harbor respiratory viruses are more often diagnosed with incomplete presentation of the disease²⁹. Therefore, KD should be considered in patients with unexplained prolonged fever associated with respiratory virus infection.

In conclusion, we report a case of KD with concurrent infection by two pathogens. In view of the fact that the pathogenesis of KD involves immune response to substances produced by infection with certain unknown pathogens, we believe that the symptoms of KD are caused by infections other than the pathogens found in our case study.

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요약

그 동안 다양한 병원체와 가와사키병의 관련성이 제기되어 왔으나 아직 확실한 원인으로 증명된 것은 없다. 본 증례는 가와사키병과 폐렴미코플라스마, 인플루엔자 감염이 동시에 병발한 환자를 소개한다. 27개월 남아가 발열과 기침, 콧물 등의 증상으로 내원하였다. 외래에서 인플루엔자 A 감염을 확인하고 oseltamivir를 복용하였으나 발열이 지속되고 경부 림프절 비대, 양측성 결막 충혈, 입술의 발적과 갈라짐, 딸기혀, BCG 접종 부위의 발진을 보였다. 이에 가와사키병으로 진단하고 면역글로불린을 정맥주사 하였다. 환아는 혈청 항미코플라스마 IgM 항체가 양성하였고 비인두 도말 중합효소 연쇄반응 검사에서 폐렴미코플라스마 양성으로 나타났다. 본 증례와 더불어 가와사키병과의 연관성이 거론되었던 병원체들을 살펴보고 가와사키병의 병인에 대한 가설들을 고찰하여 가와사키병의 증상이나 관상동맥 병변이 폐렴미코플라스마와 인플루엔자 뿐 아니라 다양한 감염에서 발생할 수 있을 것으로 예상하였다.