

# Four cases with Kawasaki disease and viral infection: aetiology or association?

Tuba Giray<sup>1</sup>, Suat Biçer<sup>1</sup>, Öznur Küçük<sup>1</sup>, Defne Çöl<sup>1</sup>, Zerrin Yalvaç<sup>1</sup>, Yeşim Gürol<sup>2</sup>, Gülden Yılmaz<sup>2</sup>, Ahmet Saç<sup>3</sup>, Yiğit Moğol<sup>3</sup>

<sup>1</sup>Department of Child Health and Paediatrics, Faculty of Medicine, Yeditepe University, Istanbul, Turkey;

<sup>2</sup>Department of Medical Microbiology, Faculty of Medicine, Yeditepe University, Istanbul, Turkey;

<sup>3</sup>Yeditepe University, Faculty of Medicine, 6<sup>th</sup> grade Medical Student, Istanbul, Turkey

## SUMMARY

The aetiology of Kawasaki disease has not yet been precisely determined. It has been associated with a variety of bacterial and viral agents. Some viruses including human adenovirus, coronavirus, and parainfluenza virus type 3 have been isolated from patients with Kawasaki disease. Clinical presentation of patients with human coronavirus and adenovirus infections mimics Kawasaki disease. In addition, these viruses

may also be detected in Kawasaki disease as a coinfection. In this report, we present four Kawasaki disease patients infected with adenovirus, coronavirus OC43/HKU1 and parainfluenza virus type 3.

*Keywords:* Adenovirus, children, Human coronavirus OC43/HKU1, Kawasaki disease, parainfluenza virus.

## INTRODUCTION

Kawasaki disease (KD), which is also known as “mucocutaneous lymph node syndrome”, was first defined in 1967 in Japan [1]. It is characterized by a sudden onset of systemic inflammatory response childhood vasculitis, diagnosed by clinical symptoms according to the American Heart Association criteria [2, 3]. Coronary artery changes are the most important complications in KD, and cardiac findings are present in 25% of the cases [3, 4]. It is the most frequently seen rheumatological heart disease in developed countries [5]. It is shown that in genetically susceptible children viral and bacterial agents trigger disease onset [3, 6, 7]. In our four cases, which were diagnosed with KD by physical examination and early echocardiographic findings, respiratory viruses were

established as responsible agents, and these cases were presented to the literature because there is no exact etiological factor defined in KD.

## CASE DESCRIPTIONS

### *Case 1: Adenovirus and KD*

A four years old male patient was brought to the pediatrics clinic with symptoms of fever that had begun six days before, redness in eyes, weakness, and redness on mouth and lips. The patient has been taking amoxicillin/clavulanate therapy for six days. In the physical examination, his general condition was described as exhausted, and he looked pale. His fever was 39.5°C. His tonsils were hyperemic and hypertrophic, he had a strawberry tongue, and his lips' mucosa was dry and red. There were bilateral cervical and sub-mandibular lymphadenopathies, which were 1x1cm in size, painful and mobile. Bilateral non-purulent conjunctivitis was present in his eyes. At the cardiovascular system examination it was seen that his

*Corresponding author*

Suat Biçer

E-mail: suat.bicer@yeditepe.edu.tr

heart rate was 140/min and there was 2/6 systolic murmur in mitral foci. There were maculo-papular lesions on his extremity surfaces and on the trunk. His acute phase reactants were positive excluding the peripheral blood leukocyte count (Table 1). In addition to the case's clinical findings, his fever lasted more than five days; consequently, echocardiography was performed and viral agents were studied with polymerase chain reaction (PCR) with the purpose of finding the probable viral agent. The presence of hyperechogenic image in the left coronary artery, which was found via echocardiography, was evaluated to be compatible with coronary arteritis, one of KD's early findings. Intravenous immunoglobulin G (IVIG) was given to the patient at 2 gr/kg dosage for 1 day. In addition to that, acetylsalicylic acid was started 90 mg/kg/day. In the patient's follow up process, after his fever had decreased, acetylsalicylic acid was decreased to a dosage of 5 mg/kg/day. Adenovirus was determined by multiplex PCR. On the 15<sup>th</sup> day of therapy the patient was followed with echocardiography, and it was seen that the coronary arteritis had completely regressed and there was no aneurysms.

#### *Case 2: Adenovirus and KD*

A three years old male patient was brought to the pediatrics clinic with a complaint of fever for three days. There was no remarkable feature in the patient's background and family history excluding his treatment with ceftriaxone for his feverish disease in the last two days. His general condition was described as exhausted, and he was pale. His fever was 39°C. His tonsils were hyperemic and hypertrophic, and he had a strawberry tongue. There were painful and mobile bilateral cervical and sub-mandibular lymphadenopathies 1x2 cm in size. His heart rate was 128 beats/min and there was no murmur. There were no pathological signs in the abdominal and respiratory system examination. His acute phase reactants were positive (Table 1). Because his fever had exceeded four days and nonpurulent conjunctivitis was clinically visible, echocardiography was performed with suspicion for KD. Multiplex PCR was performed on the upper respiratory tract specimen to detect a probable viral respiratory agent. Increased echogenicity of the left coronary artery by echocardiography was evaluated to be compatible

with coronary arteritis. Therefore, the patient was evaluated as KD, and treated with IVIG (2 gr/kg, one dose) and acetylsalicylic acid (90 mg/kg/day). Adenovirus was detected in multiplex PCR. In the follow up period, echocardiography was repeated at the 15<sup>th</sup> day of therapy and it was seen that the coronary arteritis completely regressed and there were no aneurysms.

#### *Case 3: Parainfluenza type 3 and KD*

A four years old female patient was brought to the pediatrics clinic with complaints of fever for six days, redness in eyes, cough, and weakness. The medical history of the patient was normal. Her fever was 38.5°C and she was pale. Her tonsils were hyperemic and hypertrophic. Bilateral sub-mandibular, painless and mobile lymphadenopathies were detected as 1x1 cm in size. Bilaterally non-purulent conjunctivitis was detected in the eye examination. Her acute phase reactants were positive (Table 1). Multiplex PCR was performed to detect probable viral agent on upper respiratory tract specimen. Because her fever succeeded five days and the presence of possible findings of KD, echocardiography was performed to detect findings of KD. The presence of increased echogenicity in the left coronary artery by echocardiography was detected and evaluated to be compatible with coronary arteritis, which is one of KD's early findings. She was treated with IVIG (2 gr/kg, one dose) and acetylsalicylic acid (90 mg/kg/day). Parainfluenza virus type 3 was detected in multiplex PCR. Coronary arteritis completely regressed at the 15<sup>th</sup> day of therapy and there were no aneurysms.

#### *Case 4: Coronavirus OC43/HKU1 and KD*

A 17-month-old girl was admitted to our emergency department with a 5-days history of fever, facial pallor and rash. On physical examination, she was irritable with a temperature of 39°C, respiration rate of 44/min, and heart rate of 158 beats/min. Oral mucosa and tongue were hyperemic; she also had bilateral bulbar conjunctival injection without exudate, a maculopapular rash on her trunk and abdomen, oedema on her medial region of feet, and facial pallor. Her BCG scar was exanthematous. Laboratory studies showed elevated CRP (34.2 mg/L, normal range: <2.4 mg/L), neutrophilia (8220/mm<sup>3</sup>, 68.5%) without leukocytosis (11.990/mm<sup>3</sup>), an elevated erythro-

**Table 1 - Laboratory and echocardiographical findings.**

	Case 1	Case 2	Case 3	Case 4
Peripheral blood leukocyte (count/mm <sup>3</sup> )	5.500	16.050	12.790	11.990
Granulocyte (%)	44.5	75.5	70	68.5
C-reactive protein (mg/L)	22	94	90	34.2
Erythrocyte sedimentation rate (mm/hour)	60	61	70	83
Hemoglobin (g/dL)	11	11.2	12	10.3
Hematocrite rate (%)	33	32.3	36	31
Epstein-Barr virus viral capsid antigen IgM	Negative	Negative	Negative	Not determined
Cytomegalovirus IgM	Negative	Negative	Negative	Not determined
Bacterial cultures (throat, urine, and blood)	Negative	Negative	Negative	Negative
Multiplex polymerase chain reaction for respiratory viruses	Human adenovirus	Human adenovirus	Parainfluenza virus type 3	Human coronavirus OC43/HKU1
First echocardiography	Coronary arteritis	Coronary arteritis	Coronary arteritis	Coronary arteritis
Control echocardiography	Normal	Normal	Normal	Normal

cyte sedimentation rate (83 mm/h, normal range: 0–20 mm/h) and hypertransaminasemia (alanine aminotransferase: 89 U/L, aspartate aminotransferase: 85 U/L; normal ranges: 44 and 60, respectively), and pyuria (7 leukocyte per high power field) was seen in urine analysis. Bacterial cultures and multiplex PCR for viral agents were studied. She was hospitalized with the suspicion of KD based on the clinical findings. Coronary arteritis was detected by echocardiographic investigation that showed hyperechogenicity of the pericoronary tissue and no aneurysm was detected. In the first two days of therapy, she received 1 g/kg IVIG with 100 mg/kg acetylsalicylic acid. Although blood, urine and stool cultures were negative for bacterial microorganisms, human coronavirus OC43/HKU1 was detected on the upper respiratory tract specimen by PCR. Her echocardiographic examination became normal on the 14<sup>th</sup> day after hospital admission.

## ■ DISCUSSION

Many infectious bacterial and viral agents have been sporadically isolated from KD patients. The most common bacteria are *Staphylococcus aureus*,

*Streptococcus pyogenes* and atypical pathogens; and viral agents found related to KD are Epstein-Barr virus, adenovirus, parvovirus B19, Herpes Simplex virus type 6, parainfluenza type 3, measles, rotavirus, dengue virus and HIV. Varicella, 2009 H1N1 pandemic influenza and coxsackie B3 virus are also isolated from patients with KD. Recent studies regarding viral agents suggest that human coronavirus may have an etiological role, but this suggestion has not been validated with ongoing studies [3, 6-10]. Adenovirus was first found in the autopsy of a patient with fetal KD [11], also it was seen in the nasal smears of seventy patients with complete or non-complete KD diagnosis by PCR [12]. In two of our patients diagnosed with KD, we found adenovirus and in one of them, we isolated parainfluenza virus type 3 by using PCR. EBV and adenovirus infections must be considered in differential diagnosis. As we know, adenovirus may present with high fever, membranous/exudative tonsillitis, conjunctivitis, signs of gastroenteritis [8, 13]. It can also cause leukocytosis, neutrophilia or lymphocytosis, and elevation of acute phase reactants [13]. Adenovirus, which is both an etiological agent and part of the differential diagnosis, can present itself as an incomplete KD.

In a prospective case-controlled study among children with KD, positive viral isolation and higher positive rates of PCR were described in 7.5% and 50.4% respectively [14]. Human rhinovirus (26.5%), enterovirus (17.7%), adenovirus (8%), coronavirus (7.1%), human metapneumovirus (2.2%), influenza (1.9%), para-influenza type 3 (1.3%) were detected in this study. The authors of this study concluded that several common respiratory viruses were also more frequently detected in cases of KD than in the control children ( $p=0.02$ ). Authors also proposed that viral respiratory agents may trigger KD in young children according to their genetic backgrounds and/or susceptibility [14]. The association of KD and viral respiratory infections may be supported by the winter-spring predominance of KD cases in non-temperate climates likewise Turkey [14-16].

In recent years, common respiratory pathogens including adenovirus, respiratory syncytial virus, rhinovirus, influenza, enterovirus, and para-influenza were reported as viral pathogens in children with KD (11, 12, 17-25). Several detection rates of common respiratory viruses were reported as low as 7.5% and as high as 42% by different authors (17, 19, 21). Adenovirus was detected in 8.8% and 25% among cases with complete and incomplete KD, respectively [12]. In a recent study, rhinovirus/enterovirus were mostly identified (28%) in children with KD by multiplex-PCR (21). Adenovirus, respiratory syncytial virus, and human metapneumovirus were reported equally (5% each) in this report (21). Likewise, rhinovirus (26.5%) and enterovirus (16.8%) were the leading viruses which detected in KD cases in another study conducted in Taiwan (17). Additionally, adenovirus (8%), coronavirus (7.1%), metapneumovirus (2.2%), and influenza B virus (0.9%) were also reported in this study (17). Rhinovirus (32.6%) and influenza virus (26.8%) were most commonly detected viruses in children with KD in South Korea (24). Parainfluenza type 3 was reported as a viral pathogen in children with KD [18]. No single pathogen was consistently detected in patients with KD as in our cases. Common respiratory viral infections including adenovirus, respiratory syncytial virus, rhinovirus, influenza, and parainfluenza were documented in 8.8% of KD cases [19].

Vascular endothelium may be damaged by cytokines or inflammatory mediators, which may

cause coronary artery complications in KD [26]. It is suggested that a tumor necrosis factor may be responsible from the formation of coronary artery damage [26]. The large amounts of proinflammatory cytokines and chemokines including interferon and tumor necrosis factor are produced by influenza-infected cells [27]. Huang et al. detected influenza viruses in 4.8% of cases with KD [20]. Among these 34 cases, 15 cases were only infected with influenza A ( $n=11$ ) and B ( $n=4$ ) virus, and other cases ( $n=19$ ) were also infected with other pathogens, including mycoplasma, chlamydia, adenovirus, respiratory syncytial virus and Epstein-Barr virus. Huang et al. demonstrated that CRP and ESR values of cases with KD and influenza were higher than cases with only influenza and only KD [20]. This finding is interpreted as the indication of more serious inflammation in KD with influenza infection. For these reasons, the longer duration of fever in cases with influenza or other viruses may be a warning about KD. Although clinical presentation, laboratory findings, number of days of illness before treatment, response to treatment, and development of coronary artery abnormalities were not different between virus-positive and virus-negative patients, there was an interesting finding among children with adenovirus and KD which coronary artery aneurysm had developed in three of the nine cases (21). We think that this is an incidental finding. There was not relationship between viral agents and coronary artery aneurysm in other reports about children with Kawasaki disease. KD (12, 17-25). Coronary artery aneurysm was not detected in our cases.

In conclusion, we propose that common respiratory viruses including adenovirus, human coronavirus OC43/HKU1 and parainfluenza type 3 in our cases were associated with KD. Clinicians should be aware about concomitance of respiratory viruses and KD. Development of more economical and faster methods to diagnose viral agents and wider use of these virological diagnostic methods in cases of KD may contribute to new evidence about this possible concomitance.

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