EMJ THE EWHA MEDICAL JOURNAL

Original Article

Ewha Med J 2018;41(3):45-52
https://doi.org/10.12771/emj.2018.41.3.45
eISSN 2234-2591

Comparison of Clinical Manifestation and Laboratory Findings between Adenoviral Infection with or without Kawasaki Disease

Yu Jin Kwak, Yi Kyung Kim, Ji Eun Ban, Sejung Sohn, Young Mi Hong

Department of Pediatrics, Ewha Womans University College of Medicine, Seoul, Korea

Objectives: Adenovirus infection, which has been known to mimic Kawasaki disease (KD), is one of the most frequent conditions observed during differential diagnosis when considering KD. Accordingly, it is essential to being able to differentiate between these two diseases. Therefore, we performed multiplex reverse transcriptase-polymerase chain reaction and tissue-Doppler echocardiography to distinguish between adenovirus patients and KD patients.

Methods: A total of 113 adenoviral infection patients (female 48, male 65) diagnosed from January 2010 to June 2016 were evaluated. We divided adenoviral infection patients into two groups: group 1, which consisted of individuals diagnosed with KD according to the KD American Heart Association criteria (n=62, KD with adenovirus infection); and group 2, which comprised individuals only diagnosed with adenovirus infection (n=51). Laboratory data were obtained from each patient including N-terminal pro-brain natriuretic peptide. Echocardiographic measurements were compared between two groups. In addition, reverse transcriptase-polymerase chain reaction was performed using nasopharyngeal secretions to diagnose adenoviral infection.

Results: Conjunctival injection, cervical lymphadenopathy, polymorphous skin rash, abnormalities of the lip or oral mucosa and abnormalities of extremities were significantly higher in group 1 than group 2. Moreover, group 1 had significantly higher C-reactive protein and alanine aminotransferase levels, as well as lower platelet counts and albumin levels than group 2. Coronary artery diameter was significantly greater in group 1 than group 2.

Conclusion: In patients with adenoviral infection with unexplained prolonged fever, echocardiography and C-reactive protein can be used to differentiate KD with adenoviral infection from adenoviral infection alone. **(Ewha Med J 2018;41(3):45-52)**

Received March 27, 2018
Revised April 16, 2018
Accepted April 18, 2018

Corresponding author
Young Mi Hong
Department of Pediatrics, Ewha Womans University College of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea
Tel: 82-2-2650-2841, Fax: 82-2-2653-3718
E-mail: ymhong@ewha.ac.kr

Key Words
Mucocutaneous lymph node syndrome; Adenoviridae; Polymerase chain reaction; Echocardiography

Introduction

Kawasaki disease (KD), which is an acute systemic vasculitis also known as mucocutaneous lymph node syndrome [1,2], is the most common cause of acquired heart disease in children [3]. Potentially serious complications from KD include coronary artery inflammation, aneurysm and possible aneurysm rupture, myocarditis, thrombotic occlusion of the aneurysm, and congestive heart failure [2,3]. According to previous studies, up to 25% of children with KD who go untreated may develop coronary artery abnormalities [4].

Numerous studies have investigated the role of infectious

pathogens as potential agents for KD [5,6]. Moreover, studies have attempted to establish a link between KD and specific respiratory viruses including adenovirus, human coronavirus and human bocavirus [7-9]. However, the diagnosis of KD continues to be a challenge and there is still no definitive diagnostic test; accordingly, it is currently being guided based on clinical patient characteristics and the support of laboratory data. Although the etiology of KD remains unknown, some experts believe that infectious exposure leads to the illness [10].

Nevertheless, the role of respiratory viruses in the pathogenesis of KD is still not fully understood [10]. Detection of incidental adenovirus in KD is important to its differentiation from acute adenovirus disease. In a previous study, patients with adenovirus disease were found to have less than 4 KD-like features, predominance of species B or E and higher viral burden compared to those with KD and incidental adenovirus detection [11]. Moreover, Jordan-Villegas et al. [5] reported that human adenoviruses are responsible for 7% to 8% of all pediatric respiratory illness and can lead to prolonged fever, elevated inflammatory markers [11], and clinical features that mimic KD [12]. Acute adenoviral infections have been known to mimic KD, and adenovirus and KD share a number of clinical characteristics; therefore, it can be difficult to distinguish between the two illnesses because the signs and symptoms usually noticed in adenovirus may overlap with those of KD [12,13].

Previous studies have shown that adenovirus might be one of the pathogens that trigger KD [10]. Fukuda et al. [14] reported that simultaneous development of KD followed acute adenovirus infection in monozygotic twins. Moreover, KD can be triggered by adenovirus-3 infection, indicating that specific immune responses to some pathogens such as adenovirus arising from genetic susceptibility may play a critical role in the pathogenesis of KD [14].

Differences in clinical presentations or outcomes have not yet been observed according to positive or negative respiratory viral PCR tests in children with KD [15]. Accordingly, we cannot rule out a diagnosis of KD with a positive respiratory viral PCR or presence of respiratory symptoms at the time of presentation [15]. Because we do not yet have a confirmatory laboratory test that can be used to diagnose KD directly, the diagnostic dilemma is to distinguish adenovirus infection mimicking KD from KD with accompanying adenovirus detection.

Therefore, this retrospective study was conducted to compare the clinical characteristics, laboratory data and echocardiographic findings between simple adenovirus infection and KD with adenovirus infection.

Methods

1. Subject

A retrospective study of 1,403 adenoviral infection patients who were hospitalized at Ewha Womans University Mokdong Hospital from January 2010 to June 2016 was conducted. Only adenoviral infection patients who performed echocardiography was included, and the number of them was 115. And adenoviral infection patients under other respiratory virus coinfection status were also excluded. The enrolled 113 (female 48, male 65) patients were divided into two groups: group 1, which consisted of individuals diagnosed with KD according to the American Heart Association (AHA) criteria (n=62, KD with adenovirus infection); and group 2, which comprised individuals diagnosed only with adenovirus infection (n=51).

This study was approved by the ethics committee of Ewha Womans University Mokdong Hospital Institutional Review Board (2018-03-055-002). The parents of all patients agreed to this study with written informed consent.

2. Definition

1) Diagnosis of adenoviral infection

All patients diagnosed with adenoviral infection were identified by multiplex reverse transcriptase-polymerase chain reaction (RT-PCR), which is a highly sensitive and specific assay. The PCR assay was performed on nasopharyngeal (NP) swabs.

2) Diagnosis of KD

The classical diagnostic criteria for KD as defined by the AHA include the existence of high fever for more than 5 days and the presence of at least 4 of the 5 following criteria: changes in extremities; polymorphous exanthema; bilateral bulbar conjunctival injection without exudates; changes in lips and oral cavity; and cervical lymphadenopathy (>1.5 cm diameter). Incomplete KD can also be diagnosed by the AHA guidelines based on prolonged fever for over 5 days and 2 to 3 of standard clinical features of KD [1].

3. Laboratory data

The following parameters were measured: hemoglobin, white blood cell count, neutrophils percentage, erythrocyte sedimentation rate (ESR), and levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), total protein and albumin. We performed the laboratory examination at the first day of admission to hospital.

4. Echocardiographic parameters

The enrolled patients were evaluated by echocardiogram using an IE33 machine (Philips Medical System, Andover, MA, USA) with S8 and S5 transducers during their admission period. Echocardiography approximately performed within 7 to 10 days of onset of fever. Standard parasternal and apical views were acquired. Two dimensional and M-mode echocardiogram, pulsed color-flow Doppler and tissue Doppler imaging (TDI) were obtained. The following left ventricular (LV) parameters were measured by M-mode echocardiography: interventricular septal wall thickness, posterior wall thickness, and LV end diastolic dimension at the chordae tendinae level. The ejection fraction (EF) was determined using the biplane Simpson formula, and fractional shortening (FS) was calculated using LV internal dimensions. The diastolic function was assessed in pulsed Doppler mode from the apical window. Early diastolic velocity (E), late diastolic velocity (A) and E/A ratios were measured using conventional pulsed wave Doppler echocardiography.

The TDI velocities were obtained at the basal septum from the apical four-chamber view. The Doppler beam was aligned as parallel as possible to the direction of the maximum annular motion. TDI was conducted to obtain longitudinal myocardial velocity with high quality. A narrow sector angle was used, and image depth was adjusted to allow for a high frame rate (130 to 160 frames/sec) with care taken to avoid angulations. The sweep speed was at least 100 mm/sec. The peak systolic myocardial velocity (S'), early diastolic myocardial velocity (E'), and late diastolic myocardial velocity (A') were obtained (Fig. 1).

The Tei index, which combines systolic and diastolic LV time intervals, was then calculated from the TDI using the formula (a-b)/b, where a is the interval between the closing and opening of the mitral valve, and b is equal to the left ventricle ejection time (Fig. 1). The isovolumetric relaxation time was measured from the end of the S' wave to the onset of the E' wave, and the isovolumetric contraction time was measured from the end of the A' wave to the onset of the S' wave (Fig. 2). The coronary artery was measured at the parasternal short axis view (Fig. 3). Coronary arteries were considered abnormal if (1) the internal lumen diameter was >3 mm in children younger than 5 years of age and ≥4 mm in children aged ≥5 years; (2) the internal diameter of a segment was ≥1.5 times that of an ad-

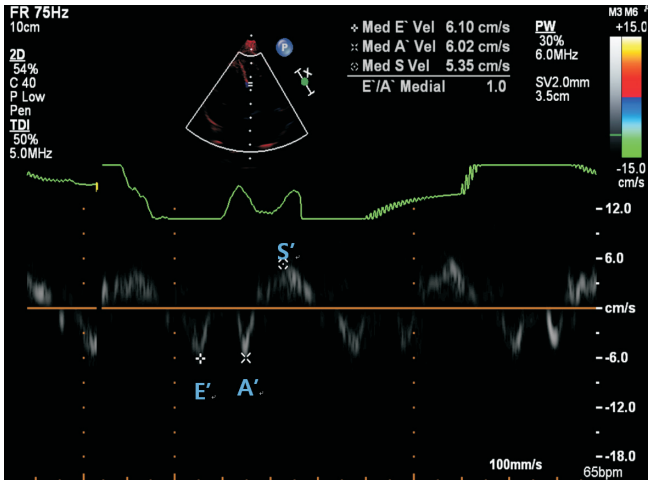

Fig. 1. Myocardial velocity by tissue Doppler imaging in Kawasaki disease patient. E', early diastolic myocardial velocity; A', late diastolic myocardial velocity; S', systolic myocardial velocity.

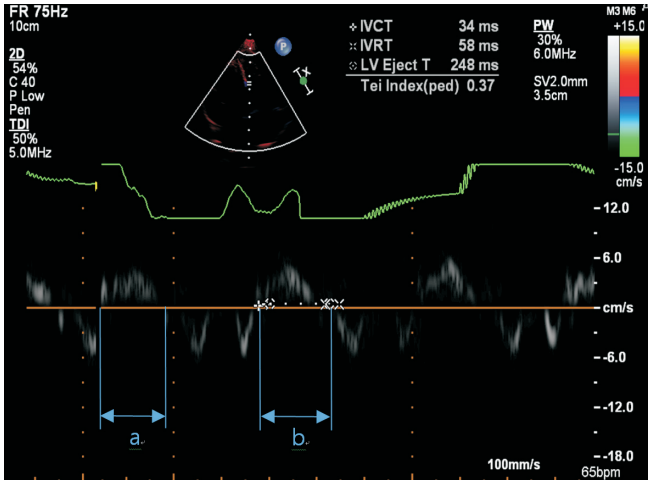

Fig. 2. Tei index by tissue Doppler imaging in Kawasaki disease patient. Tei index=(a-b)/b=(IVCT+IVRT)/LVET. IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; LVET, left ventricle ejection time.

jacent segment; or (3) the coronary lumen was clearly irregular [16].

5. RT-PCR

NP secretions were collected from patients with respiratory symptoms using nasal swabs on the first day of hospitalization. RT-PCR was performed using an AdvanSure RV Real-time PCR kit (LG Life Sciences, Seoul, Korea) with Taqman chemistry technology. This kit consisted of a primer/probe set with sequences specific to each type of viral pathogen. Specifically, the kit targeted 14 strains of RNA virus (corona virus 229E/OC43/NL63, parainfluenza virus 1/2/3, influenza A/B virus, respiratory syncytial virus A/B, rhinovirus A/B/C, and human metapneumovirus) and two strains of DNA virus (adenovirus and bocavirus). The kit enabled sequential RT and multiple PCR within one PCR tube, and was capable of detecting the DNA regions of the bocavirus and the adenovirus. The RNA regions of specific genes of the 14 strains of the RNA virus synthesized complementary DNA through RT, after which complementary DNA created each real-time target PCR product along with specific primers. The Taqman probe fluoresced, and fluorescence intensity was measured using a RT-PCR detection system (SLAN-96P Real-time PCR System; Shanghai Hongshi Medical Technology, Shanghai, China) 0.

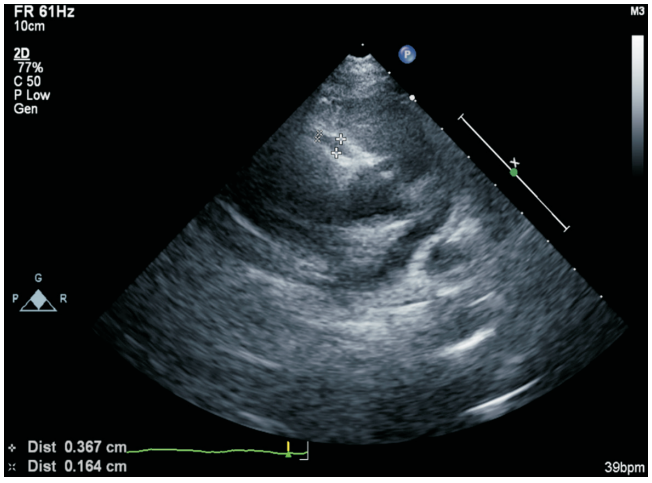

Fig. 3. Right coronary artery dilatation by echocardiography in Kawasaki disease patient.

6. Statistical analysis

PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Numerical data were expressed as the median (interquartile range) and categorical data were expressed as the number of subjects and percentage. The chi-square test, Fisher exact test and the Mann-Whitney U-test were used to compare between two groups. A P-value <0.05 was considered statistically significant.

Results

1. Comparison of clinical characteristics between two groups

In this study, a total of 113 patients (female 48, male 65) were divided into two groups. Group 1 consisted of those who had KD with adenoviral infection and group 2 only had adeno-

Table 1. Comparison of clinical characteristics between group 1 and group 2

Clinical characteristics	Group 1 (n=62)	Group 2 (n=51)	P-value
Boys	37 (59.7)	28 (54.9)	0.609
Girls	25 (40.3)	23 (45.1)	0.703
Age (year)	4 (2-4)	3 (1-4)	0.045†
Fever duration (>5 days)	38 (61.3)	26 (51.0)	0.271
Conjunctival injection	39 (62.9)	16 (31.4)	0.001
Cervical lymphadenopathy	20 (32.3)	2 (3.9)	<0.001
Polymorphous skin rash	22 (35.5)	1 (2.0)	<0.001
Abnormalities of lip or oral mucosa	19 (30.6)	2 (3.9)	<0.001
Abnormalities of extremities	8 (12.9)	1 (2.0)	0.039‡

Values are presented as number (%) or number (range).
†P value obtained from the Mann-Whitney test.
‡P value obtained from the Fisher's exact test.
Group 1, KD with adenoviral infection; Group 2, adenoviral infection.

Table 2. Comparison of laboratory data between two groups

Laboratory data	Group 1 (n=62)	Group 2 (n=51)	P-value
Hb (g/dL)	11.4 (11.0–12.1)	11.8 (11.2–12.3)	0.116
WBC (/μL)	9,570 (7,417–12,677)	10,030 (7,500–12,440)	0.892
Neutrophil (%)	59.1 (49.9–65.7)	57.0 (46.5–67.0)	0.604
Platelet (x10^9/L)	230.0 (193.0–282.2)	257.0 (215.0–302.0)	0.044
ESR (mm/hr)	36.0 (26.0–49.5)	31.0 (18.5–41.0)	0.063
CRP (mg/dL)	5.65 (2.81–7.66)	2.52 (1.09–5.12)	<0.001
AST (IU/L)	26.5 (17.5–32.3)	32.0 (28.0–35.0)	<0.001
ALT (IU/L)	16.5 (13.0–29.3)	15.0 (12.0–18.0)	0.044
Total protein (g/dL)	6.5 (6.3–6.7)	6.5 (6.1–6.7)	0.858
Albumin (g/dL)	3.7 (3.6–3.9)	3.8 (3.7–4.0)	0.006
NT-pro BNP (pg/mL)	192.0 (82.5–316.5)	144.5 (144.0–220.0)	0.089

Values are expressed as the mean (range).
Group 1, KD with adenoviral infection; Group 2, adenoviral infection.
Hb, hemoglobin; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; RCA, right coronary artery.

viral infection. Overall, 62 patients (54.8%) were included in group 1 and 51 patients (45.2%) were included in group 2.

The mean patient age was higher in group 1 than group 2 (P=0.045). The sex and fever duration were similar in both groups. However, the following signs were significantly more severe in group 1 than in group 2: conjunctival injection (62.9% vs. 31.4%, P=0.001), cervical lymphadenopathy (32.3% vs. 3.9%, P<0.001), polymorphous skin rash (35.5% vs. 2.0%, P<0.001), abnormalities of lip or oral mucosa (30.6% vs. 3.9%, P<0.001), and abnormalities of extremities (12.9% vs. 2%, P=0.039) (Table 1).

2. Comparison of laboratory finding between two groups

There were no significant differences in hemoglobin, white blood cell count, neutrophils percentage, ESR, serum total protein and NT-proBNP between groups. However, the platelet count (230.0 vs. 257.0 ×10^9/L, P=0.044), AST (26.5 vs. 32.0 IU/L, P<0.001) and albumin (3.7 vs. 3.8 g/dL, P=0.006) levels were significantly lower in group 1 than group 2. However, the CRP (5.65 vs. 2.52 mg/dL, P<0.001) and ALT (16.5 vs. 15.0 IU/L, P=0.044) levels were significantly higher in group 1 than group 2 (Table 2).

3. Comparison of echocardiographic findings between two groups

The right coronary artery (RCA) diameter was significantly higher in group 1 than group 2 (2.30 vs. 1.70 mm, P<0.001). The EF and FS were not significantly different between groups. E' velocity was slightly decreased in group 1 compared with group 2 (9.9 vs. 10.83 cm/sec, P=0.02). There were no significant differences in A' velocity or S' velocity. Finally, the Tei index did not differ significantly between two groups (Table 3).

Discussion

Several studies have been conducted to identify the infectious agents responsible for KD [10,17,18]. Respiratory symptoms are frequently observed in children with KD in the acute phase [10]. Turnier et al. [15] reported that 86% of patients with KD had respiratory viral PCR results and 41.9% of them had a positive result in the respiratory viral PCR. The most common virus was rhinovirus/enteroviruses, which was followed by adenovirus, human metapneumovirus and respiratory syncytial virus [15]. Chang et al. [10] suggested that several viruses, including enteroviruses, adenoviruses, rhinoviruses and coronaviruses, were associated with KD. The KD patients in their studies had significantly higher positive rates for virus isolation and PCR than those in the control group (50.4% vs. 16.4%). Jordan-Villegas et al. [5] showed that 8.8% of KD patients had respiratory viruses identified in the upper respiratory tract. Moreover, they reported that patients with KD who had respiratory viruses more

Table 3. Comparison of echocardiographic finding between two groups

Echo findings	Group 1 (n=62)	Group 2 (n=51)	P value
RCA (mm)	2.30 (1.75–3.95)	1.70 (1.30–2.00)	<0.001
LCA (mm)	1.80 (1.50–2.00)	1.60 (1.50–1.90)	0.067
EF (%)	69.45 (65.25–75.10)	71.55 (65.08–76.73)	0.392
FS (%)	38.15 (35.10–42.75)	39.60 (35.03–44.20)	0.423
TDI			
E' (cm/sec)	1.80 (1.50–2.00)	9.73 (8.68–11.13)	0.020
A' (cm/sec)	69.45 (65.25–75.10)	4.56 (3.86–6.52)	0.805
S' (cm/sec)	38.15 (35.10–42.75)	5.47 (4.91–6.34)	0.066
Tei index	1.80 (1.50–2.00)	0.43 (0.38–0.47)	0.302
IVCT (msec)	69.45 (65.25–75.10)	66.00 (54.00–79.00)	0.277
IVRT (msec)	38.15 (35.10–42.75)	48.00 (41.00–58.00)	0.834
LVET (msec)	1.80 (1.50–2.00)	277.00 (252.50–298.00)	0.696

Values are expressed as the mean (range).
Group 1, KD with adenoviral infection; Group 2, adenoviral infection.
RCA, right coronary artery; LCA, left coronary artery; EF, ejection fraction; FS, fractional shortening; TDI, tissue Doppler imaging; E', early diastolic myocardial velocity; A', late diastolic myocardial velocity; S', systolic myocardial velocity; IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; LVET, left ventricle ejection time.

frequently showed coronary artery dilatation and were more often diagnosed with incomplete KD. Lee et al. [17] published a study in which the incidence of KD with respiratory symptoms was 31.8%.

The duration of fever was significantly longer and coronary artery diameter was larger in KD with respiratory symptoms compared to KD without respiratory symptoms. Some studies reported an association between specific respiratory viruses and KD [5,18]. However, other authors insisted that the detection of viruses in KD may not have any associative implications [19].

In KD, adenovirus detection by PCR is not uncommon; therefore, quantitative PCR may be helpful in distinguishing adenovirus disease mimicking KD from that with concomitant adenovirus detection [18,20]. Primary infections with adenovirus C species commonly occur in children younger than age 5. After initial infection, adenovirus C can also persist in the tonsils for several years with low grade replication [9]. Jaggi et al. [18] suggested that detection of adenovirus in a patient with suspected KD should be interpreted cautiously because detection of adenovirus is not uncommon; therefore, a diagnosis of KD should not be excluded. PCR is an important diagnostic tool because it is highly sensitive and can detect low-level viruses [18].

Other clinical or laboratory data that are useful in distinguishing KD from adenoviral disease include neck swelling, distal extremity changes and presence of pyuria and/or hepatitis [18]. A positive result for a respiratory virus, regardless of the virus detected, should not be used to exclude the diagnosis of KD [18]. Continued research is needed to elucidate the etiology and discover a more sensitive and specific diagnostic test for this important KD [15].

Human adenoviruses are detected in 7% to 8% of all pediatric respiratory illnesses [9]. Adenovirus species C is a cause of pediatric illness. Because it is commonly detected in the nasopharynx incidentally because of persistence in the tonsil and adenoid tissue, its presence can lead to misinterpretation of a positive result in an acute illness [21]. Additionally, PCR has replaced adenoviral culture as a diagnosis, which has also led to confusion in diagnosis between adenoviral infection and KD because of the highly sensitive PCR test. This incidental detection by PCR of adenovirus has been observed in patients with KD, some of whom developed coronary artery abnormalities [5].

Adenoviruses have been reported in the NP secretions of 2% to 9% of patients with KD [5,10,18]. Song et al. [11] reported that 8.8% of patients with complete criteria for diagnosis of KD were also found to have adenovirus in the respiratory tract upon

PCR analysis. Furthermore, they found that their patients with complete KD had lower viral burden and a higher percentage of species C than those with adenoviral infection. Adenoviruses have been detected by PCR in the NP secretions of up to 11% of healthy children;[11] therefore, detection of adenovirus by PCR in the NP secretion does not mean infection.

Some patients developed coronary artery aneurysm [5], clearly indicating that detection of adenovirus in the respiratory tract does not exclude the diagnosis of KD. However, adenovirus illness can also mimic KD with prolonged fever, other similar clinical features and elevated inflammatory markers [22,23]. Ideal diagnostic tools to make a completely accurate diagnosis may not be available, but we found certain clinical, laboratory, and virologic characteristics that aid in differentiation of these two conditions.

Children with acute adenovirus disease are very likely to have less than four KD-like clinical features. Adenovirus conjunctivitis includes unilateral onset, prominence of tearing more frequently than purulence and follicular hyperplasia [11]. However, as noted in previous studies, the least common finding was changes in the extremities [1,24]. In our study, the adenoviral infection group most commonly had fever (100%) and conjunctival injection (31.4%). However, cervical lymphadenopathy (3.9%), abnormality of lip or oral mucosa (3.9%) and rash (2%) were rare in adenoviral infection compared with the KD group. The signs were more severe in KD compared than only adenoviral infection such as conjunctival injection (62.9% vs. 31.4%, P=0.001), cervical lymphadenopathy (32.3% vs. 3.9%, P=0.000), polymorphous skin rash (35.5% vs. 2.0%, P=0.000), abnormalities of lip or oral mucosa (30.6% vs. 3.9%, P=0.000) and abnormalities of extremities (12.9% vs. 2%, P=0.039).

The AHA algorithm is very useful in diagnosing incomplete KD. However, the current guidelines suggest that a finding of CRP of ≥3 mg/dL or ESR ≥40 mm/hr [1,2] indicates a diagnosis of incomplete KD. Nevertheless, several studies have documented higher levels of these inflammatory markers in adenovirus patients [22-24]. In the present study, the mean CRP level was 3.35 mg/dL in the adenoviral group. We believe this suggests that this CRP level may be inadequate for discriminating between the two diseases. These findings are consistent with those of Song et al. [11], who reported that CRP was consistently higher in subjects with KD compared with those who had adenovirus, but that both had a median CRP of ≥3 mg/dL, suggesting this threshold for discrimination may lack specificity for KD. In our study, CRP, ALT and RCA diameter were significantly higher in group 1 than group 2. Although the level of ALT don not have clinical difference on account of within the normal range in both groups, the other significant findings, CRP and dilated RCA, can be helpful to differential diagnosis. In addition, making a correct diagnosis is necessary because untreated cases may lead to coronary artery damage. Because adenoviral infection has similar clinical symptoms, laboratory findings and echocardiography are needed to differentiate between these two diseases [25].

It should be noted that there are some limitations to this study. Specifically, the sample size was relatively small. PCR was only performed on KD patients with respiratory symptoms because of the relative expense of the PCR test. For a complete analysis, PCR should have been performed on all patients; however, not all parents of the patients agreed to the test. Moreover, this study was a retrospective analysis. Accordingly, further prospective studies are needed to clarify the differential diagnosis between adenoviral infection and KD with incidental adenoviral detection.

In conclusion, in patients with adenoviral infection with unexplained prolonged fever, if patients represent typical KD features, we can diagnosis by clinical manifestations. Otherwise we need to consider another way to make a correct diagnosis. We should consider performing echocardiogram to find out whether coronary arteries are dilated. The dilated RCA or high level of CRP can be used to differentiate KD with adenoviral infection from adenoviral infection alone.

References

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017;135:e927-e999.
2. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004;114:1708-1733.

3. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986;315:341-347.
4. Burns JC, Glode MP. Kawasaki syndrome. *Lancet* 2004;364:533-544.
5. Jordan-Villegas A, Chang ML, Ramilo O, Mejias A. Concomitant respiratory viral infections in children with Kawasaki disease. *Pediatr Infect Dis J* 2010;29:770-772.
6. Rowley AH, Baker SC, Shulman ST, Garcia FL, Fox LM, Kos IM, et al. RNA-containing cytoplasmic inclusion bodies in ciliated bronchial epithelium months to years after acute Kawasaki disease. *PLoS One* 2008;3:e1582.
7. Okano M, Thiele GM, Sakiyama Y, Matsumoto S, Purtilo DT. Adenovirus infection in patients with Kawasaki disease. *J Med Virol* 1990;32:53-57.
8. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. *J Infect Dis* 2005;191:499-502.
9. Shike H, Shimizu C, Kanegaye JT, Foley JL, Schnurr DP, Wold LJ, et al. Adenovirus, adeno-associated virus and Kawasaki disease. *Pediatr Infect Dis J* 2005;24:1011-1014.
10. Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, et al. Viral infections associated with Kawasaki disease. *J Formos Med Assoc* 2014;113:148-154.
11. Song E, Kajon AE, Wang H, Salamon D, Texter K, Ramilo O, et al. Clinical and virologic characteristics may aid distinction of acute adenovirus disease from Kawasaki disease with incidental adenovirus detection. *J Pediatr* 2016;170:325-330.
12. Ferone EA, Berezin EN, Durigon GS, Finelli C, Felicio MC, Storni JG, et al. Clinical and epidemiological aspects related to the detection of adenovirus or respiratory syncytial virus in infants hospitalized for acute lower respiratory tract infection. *J Pediatr (Rio J)* 2014;90:42-49.
13. Rocholl C, Gerber K, Daly J, Pavia AT, Byington CL. Adenoviral infections in children: the impact of rapid diagnosis. *Pediatrics* 2004;113(1 Pt 1):e51-e56.
14. Fukuda S, Ito S, Fujiwara M, Abe J, Hanaoka N, Fujimoto T, et al. Simultaneous development of Kawasaki disease following acute human adenovirus infection in monozygotic twins: a case report. *Pediatr Rheumatol Online* J 2017;15:39.
15. Turnier JL, Anderson MS, Heizer HR, Jone PN, Glode MP, Dominguez SR. Concurrent respiratory viruses and Kawasaki disease. *Pediatrics* 2015;136:e609-e614.
16. Japan Kawasaki Disease Research Committee. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Tokyo: Ministry of Health and Welfare;1984.
17. Lee SB, Choi HS, Son S, Hong YM. Cardiac function in Kawasaki disease patients with respiratory symptoms. *Korean Circ J* 2015;45:317-324.
18. Jaggi P, Kajon AE, Mejias A, Ramilo O, Leber A. Human adenovirus infection in Kawasaki disease: a confounding bystander? *Clin Infect Dis* 2013;56:58-64.
19. Kim JH, Yu JJ, Lee J, Kim MN, Ko HK, Choi HS, et al. Detection rate and clinical impact of respiratory viruses in children with Kawasaki disease. *Korean J Pediatr* 2012;55:470-473.
20. Heim A, Ebnet C, Harste G, Pring-Akerblom P. Rapid and quantitative detection of human adenovirus DNA by real-time PCR. *J Med Virol* 2003;70:228-239.
21. Edwards KM, Thompson J, Paolini J, Wright PF. Adenovirus infections in young children. *Pediatrics* 1985;76:420-424.
22. Tabain I, Ljubin-Sternak S, Cepin-Bogovic J, Markovinovic L, Knezovic I, Mlinaric-Galinovic G. Adenovirus respiratory infections in hospitalized children: clinical findings in relation to species and serotypes. *Pediatr Infect Dis J* 2012;31:680-684.
23. Colvin JM, Muenzer JT, Jaffe DM, Smason A, Deych E, Shannon WD, et al. Detection of viruses in young children with fever without an apparent source. *Pediatrics* 2012;130:e1455-e1462.
24. Barone SR, Pontrelli LR, Krilov LR. The differentiation of classic Kawasaki disease, atypical Kawasaki disease, and acute adenoviral infection: use of clinical features and a rapid direct fluorescent antigen test. *Arch Pediatr Adolesc Med* 2000;154:453-456.
25. Kawasaki Y, Hosoya M, Katayose M, Suzuki H. Correlation between serum interleukin 6 and C-reactive protein concentrations in patients with adenoviral respiratory infection. *Pediatr Infect Dis J* 2002;21:370-374.