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CASE REPORT

Two Cases with Kawasaki Diseases and Adenoviral Infection: An Etiology or Association?

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Abstract

Although etiology of Kawasaki disease has not been precisely determined, it has been speculated that there was an association with a variety of bacterial and viral agents because of the seasonality of this disease. Some viruses including human adenovirus have been isolated from patients with Kawasaki Disease. Adenoviral infection may mimic Kawasaki disease clinically but it may also be detected in patients with Kawasaki disease. We have presented two patients with Kawasaki disease who infected with human adenovirus in this case report.

Keywords

Adenovirus, Child, Kawasaki disease

Introduction

Kawasaki Disease (KD), which is also known as "mucocutaneous lymph node syndrome", was first defined in 1967 in Japan [1]. It is diagnosed by clinical symptoms according to American Heart Association criteria [2,3]. This disease is characterized by a suddenly onset systemic inflammatory response. Coronary artery changes including coronary vasculitis are the most important complications in KD, and cardiac findings are present in 25% of the cases [3,4]. It is the most commonly encountered rheumatological heart disease among children in developed countries [5]. It is known that, with early diagnosis, coronary artery changes may be reversible. In our country there is not any clear data about incidence. The incidence differences between ethnical groups lead us to think, it can be caused by genetical factor differences like chemokines and tumor necrosis factor (TNF) receptors, HLA haplotypes. It is shown that in genetically susceptible children, viral and bacterial agents trigger disease onset [3,6]. In our 2 cases, which are diagnosed with KD by physical examination and early echocardiographic findings, human adenovirus are established as responsible agents, and these cases are presented to literature because there is no exact etiological factor defined in KD.

Case 1

A 4-years-old male child was brought to pediatrics clinic with symptoms of fever that began 6 days ago, redness in eyes, mouth and lips, and weakness. There was not special in his background and family history. The patient has been taking antibiotherapy (amoxicillin/clavulanate) for 6 days. In the physical examination, his general condition was exhausted, and he looked pale. The physical examinations findings were fever (39.5 °C), hyperemic and hypertrophic tonsils, strawberry tongue, and dryness and redness in oral mucosa and lips. There were bilateral cervical and submandibular lymphadenopathies, which were 1 × 1 cm in size, painful and mobile. Bilateral nonpurulent conjunctivitis was present in his eyes. In the cardiovascular system examination it was seen that his heart rate was 140/min and there was 2/6 systolic sufl in mitral foci. There were macu-

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lopapular lesions on his extremity surfaces and on the trunk. There was no pathological sign in the abdomen and respiratory system examination. Peripheral blood leukocyte count was 5500/mm^3, hemoglobin: 11 gr/dL, hematocrite rate: 33%, granulocyte: 44.5%, C-reactive protein (CRP): 22 mg/L, erytrocyte sedimentation rate (ESR): 60 mm/h, Epstein-Barr virus (EBV) viral capsid antigen (VCA) IgM and Cytomegalovirus (CMV) IgM were negative and there were no growth in throat, blood and urine cultures (Table 1). Because of his clinical findings which was supported the KH disease and fever that lasted more than five days, echocardiography was performed and polymerase chain reaction (PCR) was performed to detect some viral agents, with the purpose of finding the probable viral upper respiratory infection. The presence of hyperechogenic image in the left coronary artery with echocardiography was evaluated as compatible with coronary arteritis, which is the one of early findings of KD. Intravenous immunoglobulin (IVIG) and acetylsalicylic acid were given to the patient at 2 gr/kg dosage for 1 day, and 90 mg/kg/day, respectively. In the patient's follow up process, after his fever had decreased, acetylsalicylic acid was decreased to a dosage of 5 mg/kg/day. Human adenovirus was determined by multiplex PCR. The patient was followed with echocardiography which was made at the 15th day of therapy, and it was seen that the coronary arteritis had completely regressed and there was no aneurysms.

Case 2

A 3-years-old male child was brought to pediatrics clinic with a complaint of fever for 3 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 2 days. He was looked as pale and exhausted. Fever (39 °C), hyperemic and hypertrophic tonsils, strawberry tongue, painful and mobile bilateral cervical and submandibular lymphadenopathies 1 × 2 cm in size were detected in his physical examination. His heart rate was 128 beats/min and there was no murmur. There were not pathological signs in abdominal and respiratory system examination. Peripheral blood leukocyte count: 16.050/mm^3, hemoglobin: 11.2 gr/dl, %hematocrit: 32.3%, granulocyte: 75.5%, CRP: 94 mg/L, and ESR: 61 mm/h. EBV VCA IgM and CMV IgM were negative, and there were no growth in throat, blood and urine cultures (Table 1). Multiplex PCR was performed on the upper respiratory tract specimen to detect the probable viral respiratory agents. Because his fever had exceeded 4 days and nonpurulant conjunctivitis was clinically visible, echocardiography was performed with suspicion for KD. Hyperechogenic image in the left coronary artery by echocardiography was evaluated to be compatible with coronary arteritis. Therefore, the patient was evaluated as KD, and IVIG was given at 2 gr/kg dosage for the first day. In addition to that, acetylsalicylic acid was started 90 mg/kg/day. After his fever had decreased, acetylsalicylic acid was decreased to a dosage of 5 mg/kg/day. Adenovirus was detected in multiplex PCR. In the follow up period, echocardiography was repeated at the 15th day of therapy and it was seen that the coronary arteritis completely regressed and there were no aneurysms.

Discussion

Although we do not know the incidence of KD in Turkey, and in the United States of America, it makes up for the 23% of rheumatological diseases in children and it is the second most common connective tissue disease, after Henoch-Schönlein vasculitis [3]. In addition, if left untreated, it may cause mortality and morbidity and it has no specific diagnostic test. It is more commonly seen in boys with a ratio of 1.5:1 and 2:1 [3,7,8]. In our study two of our cases were boys.

KD is usually seen in winter, although in some Asian countries it has a peak in summer [9]. Our two patients were admitted in winter. The seasonality of this disease may be related by infectious etiology. Genetic tenden-

Table 1: Laboratory and echocardiographical findings of cases.

	Patient 1	**Patient 2**
Peripheral blood leukocyte count (/mm^3)	5.500	16.050
Granulocyte (%)	44.5	75.5
C-reactive protein (mg/L)	22	94
Erytrocyte sedimentation rate (mm/hour)	60	61
Hemoglobin (g/dL)	11	11.2
Hematocrite rate (%)	33	32.3
EBV-VCA IgM	Negative	Negative
Cytomegalovirus IgM	Negative	Negative
Bacterial cultures (throat, urine, and blood)	Negative	Negative
Multiplex PCR for respiratory viruses	Human adenovirus	Human adenovirus
First echocardiography	Coronary arteritis	Coronary arteritis
Second echocardiography	Normal	Normal

EBV-VCA: Epstein-Barr virus viral capsid antigen; PCR: polymerase chain reaction.

Table 2: Symptoms and signs of KD.

At least five days of fever, which cannot be explained by any other reason
Bilateral non-exudative conjunctival congestion
Changes in oropharynx: Mucosal erythema, red and/or dry lips, a strawberry tongue
Changes in the periphery of extremities: Erythema characteristically in palms and soles, indurations in hands and feet, edema or periungual membranous desquamation
Polymorph exanthema (mainly in trunk, non-vesicular)
Acute nonsuppurative cervical adenopathy (usually unilateral, minimum 1.5 cm in diameter, solitary or multiple)

cies and triggering factors such as infectious agents have been regarded as possible etiologic factors for KD. Some studies found that children who have FC gamma FcyRIIA and ITPKC genes are prone to disease especially in Japanese people, and in North Americans there is a tendency for coroner artery aneurysms [10]. The ITPKC gene is described as a T-cell activity modulator [10]. Infectious agents are considered as environmental causes and that they trigger KD in people with genetic tendencies [11]. Many infectious bacterial and viral agents have been sporadically isolated from patients such as *Staphylococcus aureus*, *Streptococcus pyogenes*, atypical pathogens, Epstein-Barr virus, adenovirus, parvovirus B19, Herpes Simplex virus type 6, parainfluenza type 3, measles, rotavirus, dengue virus, Varicella, 2009 H1N1 pandemic influenza and coxsackie B3 virus, and HIV. Recent studies regarding viral agents suggest that human coronavirus may have an etiological role, but this suggestion has not been validated with ongoing studies. Adenovirus was first found in the autopsy of a patient with fetal KD [12], also it was seen in the nasal swabs of 70 patients with complete or non-complete KD diagnosis by PCR [13]. In our patients with KD, adenovirus was isolated by using PCR in our patients by using PCR.

Diagnosis of KD is made by the presence of at least 5 of the following; fever, changes in the periphery of extremities, polymorphic exanthema, bilateral conjunctival non-purulant congestion, changes in oropharyngeal mucosa and cervical lymphadenopathy (Table 2). If there is a prolonged fever and involvement of coronary arteries in echocardiography, it is defined as an incomplete KD [2,3,14]. Most of the time differential diagnosis can be made with clinical and laboratory findings, although there are some difficulties in incomplete cases. In a study from Japan, 20% of cases did not meet the criteria for diagnosis [15]. EBV and adenovirus infections must be considered in the differential diagnosis. As we know, adenovirus may present with high fever, membranous/exudative tonsillitis, conjunctivitis, signs of gastroenteritis [13,16]. It may also cause leukocytosis, neutrophilia or lymphocytosis, and elevation of acute phase reactants [16]. Adenovirus, which is both an etiological agent and part of the differential diagnosis, can present itself as an incomplete KD. It is difficult to recognize and diagnose incomplete KD as the greatest risk for coronary artery aneurysm which also in these patient group with incomplete KD. One of our patients was diagnosed as complete KD, and other patient fulfills the criteria for incomplete KD with four criteria and echocardiography findings. Bear in mind that incomplete KD has the highest risk for coronary artery aneurysm. There were prolonged fever and lymphoid involvement in our patients. KD is a pediatric vasculitis, which causes a systemic inflammatory response, and if left untreated it will also involve coronary arteries. As a result of that, incomplete KD must be kept in mind as a differential diagnosis in children who are under 5 years of age, who have a high fever for 5 days, and who do not meet the criteria for complete KD and resemble a viral disease with or without exanthemas.

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