Kawasaki Disease Triggered by Epstein-Barr Virus Infection: A Case Report

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Abstract- Kawasaki disease (KD) is the most common cause of acquired heart disease today. An important and enduring complication of KD is a coronary aneurysm, whose early diagnosis and treatment can reduce the risk from 25% to 3%. Diagnosis of this disease is mainly clinical, although leukocytosis, increased erythrocyte sedimentation rate, and echocardiography are helpful in diagnosis. The cause of KD remains unknown, but the most common hypothesis is an abnormal immune response that is likely caused by an infectious agent, possibly in a favorable genetic background, and leads to vasculitis of the middle arteries, especially coronary arteries of the heart. Numerous infectious agents have been suggested in this regard. Co-infection with KD can also delay diagnosis. In this article, we introduce five years and seven months child who developed Kawasaki disease within a few days of the onset of Epstein-Barr virus infection.

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Introduction

Kawasaki disease (KD) is a systemic vasculitis syndrome that occurs acutely for no apparent reason. It is most common in children under the age of five years and is more common in late winter and early spring. Symptoms of the acute phase include fever over five days, non-purulent bilateral conjunctivitis, inflammation of the mucous membranes of the mouth and throat with redness and cracking of lips and strawberry tongue, cervical lymphadenopathy, swelling of the back or erythema of the palms of the hands and feet. The most important complication of KD is coronary artery aneurysm, which can lead to thrombosis and sudden death. The etiology of KD is not yet known, although it has been linked to infections and genetic predisposition (1). Some of its epidemiological and clinical features support infectious origin, including the young age of patients with the disease, occurrence of epidemics with wave geographic propagation, self-limiting fever, and acute course of KD and its clinical features, including fever, skin rash, enanthema, conjunctival redness, and cervical lymphadenopathy. Further evidence of the role of infection as a stimulus for the disease includes rare disease in infants under three months of age, possibly due to maternal antibodies in the baby's blood, and rare disease in adults, probably due to exposure to various and frequent infections and immunity to them. However, there are features that are not compatible with the source of the infection, at least alone. For example, it is uncommon for several cases of Kawasaki disease to occur simultaneously in a family or childcare center. In addition, no definitive infectious agents have been identified to date, although various factors have been identified in recent years, such as Parvovirus B19, Neisseria meningitides, Bacterial toxin-mediated superantigens, Mycoplasma pneumoniae, Klebsiella pneumoniae, Adenovirus, Cytomegalovirus, Parainfluenza type 3 virus, Rotavirus, Measles, Epstein-Barr virus, Human lymphotropic virus, Mite-associated bacteria, Tick-borne diseases, Rickettsia, Propionibacterium acnes (2-4).

The role of genetics in the development of KD disease is very likely. The higher risk of the disease in Asian children has been proven regardless of the country of residence, as well as in siblings and children of people with a history of Kawasaki disease (5-9). In addition, family linkage studies and genome-wide association studies (GWAS) have shown a significant potential link between polymorphism in the ITPKC (Inositol 1,4,5-

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trisphosphate 3-kinase C) gene, which regulates T cells with increasing risk of developing KD, as well as more severe types of it (10). Other genes that may be effective in causing Kawasaki disease known by GWAS include CASP3, BLK, FCGR2A, and CD4 (11-13). Finally, a link between single-nucleotide polymorphism (SNP) in class II human leukocyte antigen (HLA-DQB2 and HLA-DOB) has been reported with KD (13). The concordance rate between identical twins is approximately 13% (14).

Using optical and electron microscopy, the researchers identified RNA-containing cytoplasmic bodies in 85% of death cases of acute and late Kawasaki disease and 25% of the adult control group. Based on this finding, it is assumed that the infectious agent of this disease can be a common RNA-containing virus, which in most people leads to asymptomatic infection but in genetically predisposed people leads to Kawasaki disease. It is also possible that many infectious agents create a final common pathway in susceptible hosts, leading to KD (15). In other words, an abnormal immune response to an infectious trigger in a favorable genetic background is still the most important hypothesis for KD pathogenesis. Due to the significant prevalence of this disease and its irreversible cardiac complications, which has made it one of the most common causes of acquired cardiovascular disease in the world, and the ambiguous aspects of this disease, including its causes, we report here a case of KD following Epstein-Barr virus (EBV) infection.

Case Report

The patient was a five year and seven months old boy who had symptoms of fever, nausea, and sore throat four days before hospitalization. He did not respond to acetaminophen and amoxicillin. At the time of admission, the child had a fever of 39˚ C, icteric sclera, bilateral and extensive exudate of the tonsils, submandibular bilateral lymphadenopathy 3 cm in size, and high erythrocyte sedimentation rate (ESR) and leukocytosis. Urine analysis was normal, and blood and urine cultures were negative. (Table 1 shows the patient's laboratory data according to the hospitalization days). Abdominal ultrasound showed only a slight increase in gallbladder diameter (50 mm) with a slight accumulation of fluid in the Morrison space. Primary echocardiography was also normal. In the subsequent diagnostic survey, IgM antibody to viral capsid antigen-VCA was positive, and the presence of EBV DNA sequence in peripheral blood was confirmed by polymerase chain reaction (PCR).

Table 1. Patient's laboratory data according to hospitalization days

Admission Days	1	2	3	5	6	7	8	9	10	11	12	13	15	17
Lab data														
WBC/mm^3	17810			18400	20200	27100	20220	19810	20520	18520		9670	8660	8420
Neutrophils (%)	90			84	84	87	78	86	84	82		74	70	72
Lymphocytes (%)	5.7			5	11	9	18	10	11	13		19	22	21
PLT×1000/mm^3	197				202	242	253	299				580	674	614
Hb (g/dL)	11.3			8.5	9.9	10.3	9.9	11.6	11.5	11.2			11.6	10.2
ESR (mm/hr)	93			115						92				79
AST (IU/L)	22		59	133	88	45	36				30	22		26
ALT (IU/L)	11		93	86	82	55	30				13	10		10
ALP (U/L)	274		333	273	228	293	-				-	208		213
Albumin (g/dL)			3.1	2.6	2.6	2.3	2.8		3.5	2.6	3.1		3.3	
Calcium (mg/dL)	9.2									7.5	8.7		8.6	
BUN (mg/dL)	8					8	7.9						7.9	7.7
Creatinine (mg/dL)	0.7					0.4	0.5						0.5	0.5
TBil (mg/dL)			3.1	5.4	5.2		2							1
DBil (mg/dL)			3	5.2	4.7		1.3							0.6
Amylase (U/L)			55									70		
Lipase (U/L)			20									83		

On the fourth day of hospitalization, the patient developed a rash on the chest and abdomen together with bilateral non-purulent conjunctivitis. In the second echocardiography, coronary artery dilatation was seen

with aneurysmal changes, dilatation of the heart cavities, and a decrease in left ventricle ejection fraction (LVEF) to 47%. The patient was transferred to the intensive care unit (ICU), and treatment began with a high dose of intravenous immunoglobulin (IVIG: 2 gr/kg of body weight) and aspirin (60 mg/kg/day). Captopril, Lasix, Aldactone, and Digoxin were prescribed by a pediatric cardiologist. Due to the continuation of fever for three days, the second dose of IVIG was prescribed on the seventh day of hospitalization.

Over the next five days, coronary aneurysms persisted, but the size of the heart and its cavities were normal in the third echo and LVEF=61%. Liver enzymes were high at the onset of the disease and returned to normal with treatment. The ESR did not decrease significantly until the end of hospitalization but returned to normal within a month. Prothrombin time disorder and decreased hemoglobin, albumin, and calcium were treated. The patient was discharged on the twenty-first day with a good general condition and recommendations to outpatient follow-up and medication instructions. CT angiography after discharge revealed diffused dilatation and spindle-shaped aneurysm in the main left anterior descending (LAD) and giant aneurysm in the right coronary artery.

Discussion

The relationship between KD and EBV infection had previously been reported. Kikuta *et al*., showed the EBV virus in 86% of KD patients by serology (IgM antibody to viral capsid antigen-VCA). EBV DNA sequence was also shown in the peripheral blood of 56% of these patients versus 18% in the control group by PCR (16). Kanegane *et al*., reported a 2-year-old child with primary EBV infection (tonsillitis, splenomegaly, and atypical lymphocytosis) and KD co-occurrence (17). Maggio *et al*., also reported a 3-year-old boy with Mediterranean fever who also developed EBV infection at the same time as the onset of atypical KD (18). Our patient was five years and seven months old, first showing signs of acute mononucleosis due to EBV infection and then gradually developing typical KD, which progressed to coronary aneurysms and heart failure. Ariza *et al*., showed in-vitro that EBV-encoded protein called deoxyuridine 5'-triphosphate nucleotidohydrolase (dUTPase) stimulates monocyte-derived macrophages through a signal dependent on Toll-like receptor 2 (TLR2). This increases the production of interleukin 6 (IL-6), which in turn activates endothelial cells and platelets (19). Certainly, there is also conflicting information about the association of EBV and KD (20).

As a result, although more studies are needed, in the case of an abnormal course of a primary EBV infection, especially bilateral conjunctivitis and erythema of the lips and mouth, Kawasaki disease should be considered. In addition, although it is unlikely that tonsillar exudate will be seen in a patient with suspected KD, the physician should not rule out its diagnosis altogether.

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