Case Report / Olgu Sunumu

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Kawasaki Disease Shock Syndrome: Think Earlier, Treat Intensively

Kawasaki Şok Sendromu: Erken Tanıyın, Agresif Tedavi Edin

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Abstract

Kawasaki disease shock syndrome (KDSS) is a rare disease characterized by cardiovascular collapse that requires aggressive supportive and immunomodulatory therapy. The purpose of this report is to highlight our management strategies in KSSS patients. Patients who were followed up with a diagnosis of Kawasaki disease in intensive care unit and those who met the criteria for Kawasaki disease shock syndrome were included in the study. Data were obtained retrospectively from hospital records. Between 2005 and 2020, 5 patients with Kawasaki disease were followed up in the pediatric intensive care unit. Three children in the adolescent age group were diagnosed with Kawasaki disease shock syndrome. Two patients had severe coronary artery dilatation, one patient required therapeutic plasma exchange due to multiple organ failure. Kawasaki disease shock syndrome is a serious, life-threatening form of Kawasaki disease and should be suspected in children with severe inflammation and significant cardiac involvement. Administration of plasmapheresis in addition to steroid therapy appears to be effective in controlling severe disease and should not be delayed.

Keywords: Kawasaki disease, vasculitis, shock, steroid therapy

Öz

Kawasaki şok sendromu, agresif destekleyici ve immünomodülatör tedavi gerektiren kardiyovasküler kollaps ile karakterize nadir görülen bir hastalıktır. Bu raporun amacı, Kawasaki şok sendromu hastalarında tedavi stratejilerimizi vurgulamaktır. Kawasaki hastalığı tanısı ile yoğun bakımda izlenen ve Kawasaki şok sendromu ölçütlerini karşılayan hastalar çalışmaya alındı. Veriler geriye dönük olarak hastane kayıtlarından elde edildi. 2005-2020 yılları arasında Kawasaki hastalığı nedeniyle 5 hasta çocuk yoğun bakım ünitesinde izlendi. Ergen yaş grubundaki üç çocuğa Kawasaki şok sendromu tanısı konuldu. İki hastada ciddi koroner arter dilatasyonu vardı, bir hastada çoğul organ yetmezliği nedeniyle terapötik plazma değişimi gerekti. Kawasaki şok sendromu, Kawasaki hastalığının ciddi, hayatı tehdit eden bir şeklidir ve şiddetli enflamasyonu ve belirgin kardiyak tutulumu olan çocuklarda şüphelenilmelidir. Steroid tedavisine ek olarak plazmaferez uygulaması şiddetli hastalığı kontrol etmede etkili görünmektedir ve geciktirilmemelidir.

Anahtar Kelimeler: Kawasaki hastalığı, vaskülit, şok, steroid tedavisi

Introduction

Kawasaki disease (KD) is the most common cause of acquired heart disease causing coronary artery aneurysms.[1,2] It is mostly seen in early childhood (<2 years). The main pathology of the disease is vasculitis of medium and small-sized arteries associated with increased immune response, often triggered by a viral infection, environment and vaccine associated toxins.[3] It is generally a self-limiting disease with a good long-term prognosis that responds well to intravenous immunoglobulin (IVIG) therapy.[4] However, there is also a subgroup which is resistant to IVIG and associated with coronary artery involvement and poor prognosis.[5,6] Kawasaki disease shock syndrome (KDSS) refers to a subgroup of patients with KD who present with cardiovascular dysfunctions and other organ system dysfunctions. The aim of this report was to

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investigate the characteristic features of children diagnosed with KDSS which is a rare but life-threatening disease, and its clinical presentation is often atypical.

Results

Between 2005-2020, five patients required intensive care treatments; one was admitted for giant aneurysm resulting myocardial ischemia and four for severe organ dysfunction and one for septic shock after immunomodulating treatments. Three patients were met the KDSS criteria. Patient 1 was an 8-year-old boy who suffered from fever at least five days, maculopapular rash, and unilateral painless cervical lymphadenopathy. A strawberry tongue, bilateral non-purulent conjunctivitis, desquamation of fingertips, tachypnea, gallop rhythm along with tachycardia, weak peripheral pulses and hypotension were detected on physical examination. Echocardiography (ECHO) revealed diffuse dilatation of the coronary arteries. The ejection fraction (EF) was 62%. He was admitted to the intensive care unit and received high-dose inotropes, IVIG (2 gr/kg, single dose), acetylsalicylic acid (ASA). After IVIG and ASA therapy, the fever resolved but need of inotropes persisted. Thus, a course of oral prednisolone treatment (2 mg/kg/day) was started. The patient showed clinical improvement after steroid treatment and was discharged on the 10th day of hospitalization (Table 1).

Patient 2 was a 16-year-old girl who had fever for at least five days, generalized rash and abdominal pain. Conjunctival hyperemia, strawberry tongue and maculopapular rash were detected on her physical examination. The laboratory investigations showed increased C-reactive protein (CRP), hypoalbuminemia, elevated creatinine and liver transaminase levels and thrombocytopenia but normal erythrocyte sedimentation rate (ESR). The chest X-ray revealed bilateral pleural effusion, and hydrops of bile sac was detected on abdominal ultrasound. She had decompensated shock requiring high dose inotropes and mechanical ventilation. ECHO studies showed diffuse dilatation of coronary arteries. Figure 1 and Figure 2 show the coronary artery dilatation on reconstructed 3-dimensional (3D) cardiac computerized tomography (CT) scan. She was diagnosed with KDSS and after IVIG therapy with a single dose of 2 gr/kg fever resolved but she remained hypotensive, so high dose methylprednisolone (500 mg/day, 5 days) therapy was initiated. On the second day of steroid therapy, inotropes were stopped. She was

Table 1. General information of the patients' demographic data, laboratory investigations and clinical course

	Patient 1	Patient 2	Patient 3
Age	8 years	16 years	13 years
Sex	Male	Female	Female
Symptoms	Fever Rash Lymphadenopathy Strawberry tongue Non-purulent conjunctivitis	Fever Rash Abdominal pain Conjunctival hyperemia Strawberry tongue	Fever Vomiting abdominal pain Rash Conjunctival hyperemia
Serum CRP level (mg/dL)	29.1	33	9.2
ESR (mm/h)	19	8	2
Ferritin level (µg/L)	-	1.330	1.061
Thrombocyte count (cell/mm^3)	454.000	309.000	204.000
Serum albumin level (gr/dL)	3.05	3.24	2.83
Z-scores of CAs LCA LADA RCA	 1.9 2.7 0.83	 2.5 - 6.3	 0.13 3.07 6.8
Need of mechanical ventilation	No	Yes	Yes
Need of inotropic agents	Yes	Yes	Yes
Immunomodulatory treatment	IVIG (2 gr/kg) Oral prednisolone (2 mg/kg/d)	IVIG (2 gr/kg) IV methylprednisolone (500 mg/d, 5 days) infliximab	IVIG (2 gr/kg) IV methylprednisolone (20 mg/kg/d, 5 days) TPE
Length of stay in PICU	5 days	5 days	5 days
Length of stay in hospital	10 days	18 days	13 days
Mortality	No	No	No

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, CA: Coronary artery, LCA: Left coronary artery, LADA: Left anterior descending coronary artery, IVIG: Intravenous immunoglobulin, TPE: Therapeutic plasma exchange, PICU: Pediatric intensive care unit

discharged from the intensive care unit after five days with infliximab for persistent proteinuria.

Patient 3 was a 13-year-old-girl who presented with fever, vomiting and abdominal pain. Four days after the onset of the fever, a maculopapular rash that appeared from neck to trunk. Conjunctival hyperemia, rash, decreased respiratory sounds, weak pulses and poor perfusion findings were detected on physical examination. Laboratory findings showed increased CRP, hypoalbuminemia, anemia, pyuria but normal ESR. ECHO showed diffuse dilatation of coronary arteries. Figure 3 shows the coronary artery dilatation on reconstructed 3D cardiac CT scan. EF was 42%. She was mechanically ventilated and treated with IVIG (2 gr/kg single dose) and intravenous methylprednisolone (20 mg/kg/day, for five days). Fever resolved with combined IVIG and steroid therapy but need of vasoactive agents persisted. One episode of therapeutic plasma exchange (TPE) with the amount of plasma volume of the patient was applied. She clinically improved in a short time, inotropic treatments were discontinued, and she discharged from intensive care on the 5th day.

To use clinical data for this case series an informed consent was obtained from the parents of all the patients.

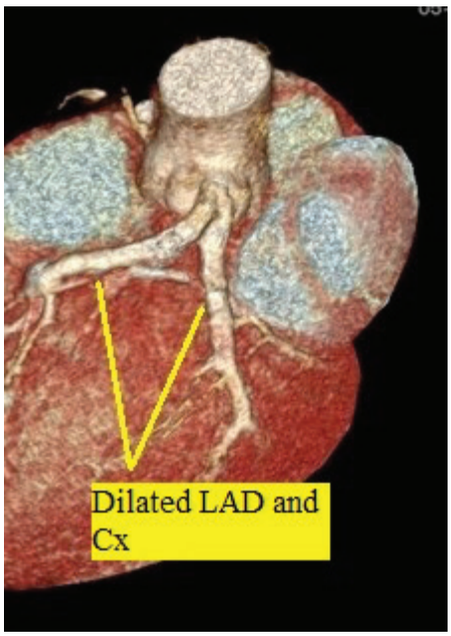

Figure 1. The left coronary artery and left ascending coronary artery of the patient 2 on reconstructed 3D cardiac computerized tomography (CT) scan

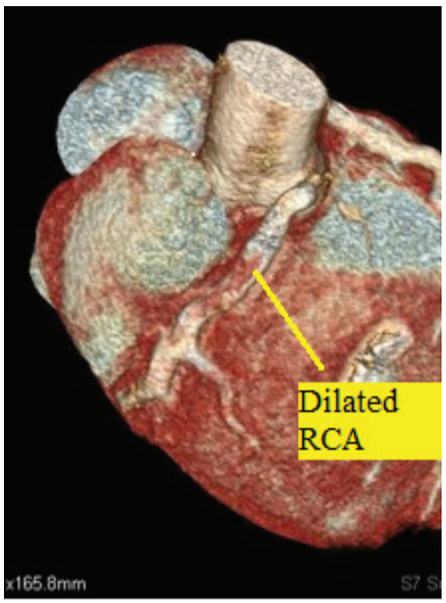

Figure 2. The right coronary artery and circumflex artery of the patient 2 on reconstructed 3D cardiac CT scan
CT: Computerized tomography

Discussion

There is no definitive diagnostic test for KD; thus, diagnosis relies on clinical criteria and laboratory findings. The American Heart Association-AHA (2017) diagnostic criteria are fever lasting five days or more and four of the five major clinical criteria.[7] There is a group of patients who do not fully meet these criteria but still have KD and are at risk for coronary artery disease. For this reason, the single hub and access point for pediatric rheumatology in Europe-SHARE initiative recommends that KD diagnosis and treatment should not be delayed if: 5/6 diagnostic criteria of KD are present before day 5 of fever, coronary artery aneurysms or coronary dilatation are present and there is evidence of persistent (4 days) elevation of inflammatory markers and/or persistent

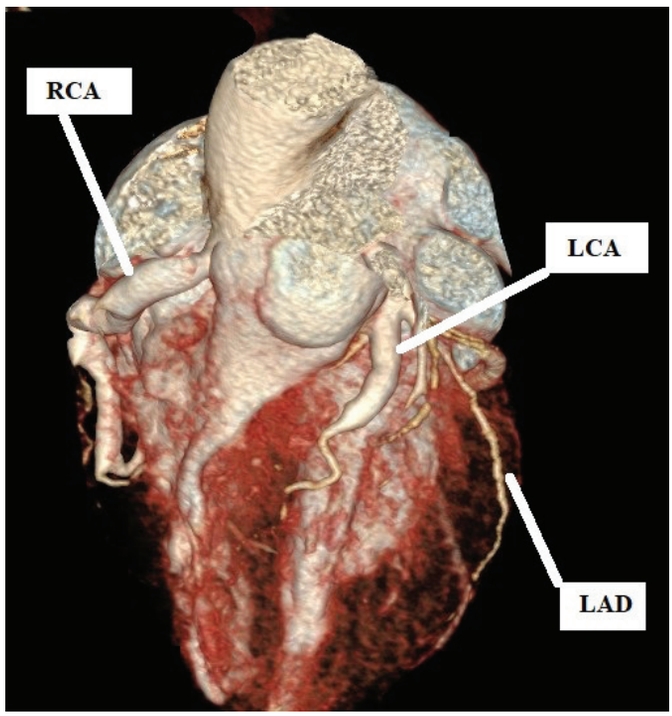

Figure 3. The CA dilatation of the patient 3
CA: Coronary artery, LCA: Left coronary artery

fever, especially in infants or younger children without other explanation.[4] Hypoalbuminemia and thrombocytosis as a late phase finding are minor criteria. As shown in Table 1, all patients had elevated CRP levels, but normal ESR and platelet counts. Only one of them had hypoalbuminemia. The last two of our patients conform to the definition of incomplete or atypical KD and ECHO findings provided the KD diagnosis. The EFs were normal and/or close to normal but multiple organ failure prevailed with severe hypotension and poor perfusion findings. Therefore, it can be said that the severe clinical conditions of these patients were not only associated with coronary artery involvement. In a retrospective study, KDSS was defined as follows; sustained hypotension, need to transfer to an intensive care setting and clinical signs of inadequate organ perfusion.[8] In another large retrospective data of 2.203 patients with KD, the incidence of KDSS reported as 1.23% and the patients with KDSS were older than those with classical KD.[9]

The SHARE initiative recommends that corticosteroid treatment should be given to patients with severe KD which characterized with IVIG resistance, features of hemophagocytic lymphohystiocytes, shock and presentation with coronary and/or peripheral aneurysm.[2] There are no definitive recommendations about the steroid dosing. Both low (1-4 mg/kg/day) and high dose (10-40 mg/kg/day) methylprednisolone seem to be equally effective.[10]

During the Coronavirus disease-2019 pandemic, which is a disease in which adult respiratory distress syndrome is at the forefront in adults, the number of pediatric patients increased with time. We learned from the pandemic that the virus associated hyperinflammatory state showed similarity with KD.[11] It is reported that advanced treatments such as IVIG and plasma exchange can potentially provide immunomodulation in these patients.[12] Although it was not possible to determine the immunological profile of our patients, the obvious clinical improvement with early steroid treatment supports these findings. KDSS is a kind of cytokine storm condition and tighter regiments of immunomodulation are required for success. In a Cochrane review, the authors conclude that the use of steroids in the acute phase of KD can be associated with improved coronary artery abnormalities, shorter length of stay and decreased duration of clinical symptoms.[13] In more severe cases even without coronary artery involvement, early administration of steroid combined IVIG therapy may help to stabilize the patient.[14] Monoclonal antibodies such as infliximab can be used in cases with refractory inflammation.[15] Therapeutic plasma exchange is an alternative third-line treatment for IVIG refractory KD. It is reported that early administration of TPE improves coronary artery involvement when there is IVIG resistance.[16,17] In patient 3, TPE allowed us to withdraw inotropes.

Conclusion

KDSS is severe and acutely life-threatening form of KD and should be suspected in children who do not meet all the criteria of classical KD but have severe inflammation findings and significant coronary artery involvement. Early administration of immunomodulatory treatment is crucial when KDSS is suspected. Steroid treatment and plasmapheresis seem to be effective for controlling disease progress and should not be delayed in patients unresponsive to the initial immunomodulatory treatment.

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Ethics

Informed Consent: Informed consent was obtained from the parents of all the patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.S.N., A.Ü.Y., Y.B., Concept: S.K., B.B., Design: S.K., Data Collection or Processing: Ö.S.N., Y.B., S.Ö., B.B., Analysis or Interpretation: S.K., Y.B., S.Ö., B.B., Literature Search: Ö.S.N., S.Ö., Writing: Ö.S.N., S.K., S.Ö., B.B.

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