Case Report

Giant Coronary Aneurysms with Multiple Large Resistant Thromboses in an 8-Month-Old Boy with IVIg-Resistant Kawasaki Disease: A Case Report

Mojtaba Gorji MD[1,3], Maryam Taraz MD[1,3*], Behdad Gharib MD[1,3], Vahid Ziaee MD[2]

[1]*Department of Pediatric Cardiology, Children's Medical Center, Pediatric Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.*
[2]*Department of Pediatric Rheumatology, Children's Medical Center, Pediatric Center of Excellence, Tehran, Iran.*
[3]*Children's Medical Center, Pediatrics Center of Excellence, Tehran, Iran.*

Received 12 May 2023; Accepted 20 June 2023

Abstract

Kawasaki disease is an acute self-limiting systemic vasculitis in childhood, resulting in arterial swelling or inflammation and eventually leading to cardiovascular problems, such as coronary artery aneurysms. Based on previous studies, serum sodium ≤133 mmol/L, albumin ≤3.2 g/dL, alanine transaminase ≥80 U/L, and neutrophil percentage ≥80% at diagnosis are risk factors for intravenous immunoglobulin (IVIg). However, the prevalence of resistance to Ig among children with Kawasaki disease varies among different countries due to diversity in evaluation, treatment, and diagnosis.

Approximately, 10% to 20% of patients have IVIg-resistant Kawasaki disease. As the probability of coronary artery damage associated with IVIg-resistant Kawasaki disease is higher than that with IVIg-sensitive Kawasaki disease, the early detection and appropriate treatment of IVIg-resistant Kawasaki disease can decrease the probability of damage to coronary arteries and hospital lengths of stay and cost.

Kawasaki disease in early infancy is uncommon, and sometimes it occurs with thrombosis and peripheral gangrene. A positive genetic background may play a role in susceptibility to thrombosis.

We herein describe a patient suffering from an IVIg-resistant Kawasaki disease with severe coronary artery thrombosis and positive genetic mutation. Medical treatment resolved the thrombosis, but the coronary arteries remained dilated.

J Teh Univ Heart Ctr 2023;18(3):224-227

This paper should be cited as: Gorji M, Taraz M, Gharib B, Ziaee V. Giant Coronary Aneurysms with Multiple Large Resistant Thromboses in an 8-Month-Old Boy with IVIg-Resistant Kawasaki Disease: A Case Report. J Teh Univ Heart Ctr 2023;18(3):224-227.

Keywords: *Kawasaki disease; Coronary aneurysms; Thrombosis; Thrombophilia*

Introduction

Kawasaki disease is an acute self-limiting systemic vasculitis in childhood predominantly affecting children below 5 years of age.[1] It was first described in 1967; nonetheless; its etiology is still unknown.[2] Patients with

[*]**Corresponding Author:** ***Maryam Taraz,*** *Pediatric Cardiologist, Children's Medical Center (Pediatric Center of Excellence), Tehran University of Medical Sciences, Tehran, Iran. 1419733151. Tel: +98 21 61479. Fax: +98 2166930024. E-mail: maryam.taraz@yahoo.com.*

Kawasaki disease are at risk of coronary artery aneurysms, which can be classified according to their Z score as small-sized (2.5< Z score <5), medium-sized (5< Z score <10), and large (Z score ≥10.0). This Z score uses the body surface area and the luminal diameter of the coronary artery.[3] Larger coronary artery aneurysms correlate with higher risks for clinical complications and major adverse cardiac events since blood flow changes to turbulent flow, facilitating thrombosis.[4] Depending on the classification, prophylactic anticoagulation and/or antiplatelet and intravenous immunoglobulin (IVIg) therapy can be indicated.

Approximately 10% to 20% of patients with known risk factors (serum sodium ≤133 mmol/L, albumin ≤3.2 g/dL, alanine transaminase ≥80 U/L, and neutrophil percentage ≥80%) have IVIg-resistant Kawasaki disease.[5] As the probability of coronary artery damage associated with IVIg-resistant Kawasaki disease is higher than that with IVIg-sensitive Kawasaki disease, the early detection and appropriate treatment of IVIg-resistant Kawasaki disease can diminish the probability of damage to coronary arteries and hospital lengths of stay and cost.

Kawasaki disease in early infancy is uncommon, and sometimes it occurs with thrombosis and peripheral gangrene. A positive genetic background is likely involved in susceptibility to thrombosis.

In this paper, we report the case of an IVIg-resistant Kawasaki disease with severe coronary artery thrombosis and positive genetic mutation. Medical treatment helped resolve the thrombosis, but the coronary arteries remained dilated.

Case Report

An 8-month-old boy with a history of typical Kawasaki disease after COVID-19 was referred to us. The patient was born to consanguineous parents, and his mother and aunts had a history of frequent abortions. His referral to our hospital was because of a relapsing fever. The boy received IVIg, corticosteroid therapy, and infliximab. Nevertheless, 15 days after hospital discharge, he had a fever again.

On readmission, the patient's vital signs were stable except for a fever. His typical Kawasaki disease warranted an echocardiographic examination, which showed multiple coronary aneurysms and thromboses. The laboratory workup was significant for anemia, thrombocytosis, high C-reactive protein, and high erythrocyte sedimentation rate. The blood levels of Igs, complements, troponin, the N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and fibrinogen were within the normal range. Evaluation for thrombophilia was normal, too. Additionally, in the coagulation panel, fibrinogen, factor V Leiden, protein S, and homocysteine were within their normal ranges, whereas D-dimer, cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), and perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) were highly elevated, and protein C was decreased (Table 1).

Table 1. The patient's laboratory test results

White blood cells	11500 /μL	Reference Range
Hemoglobin	8.1 g/dL	9.5-14 g/dL
Platelets	567000 /μL	<450000 /μL
ESR	110 mm/h	<10 mm/h
CRP	64 mg/dL	<5 mg/dL
D-Dimer	3500 ng/mL	<250 ng/mL
c-ANCA	150 AU/mL	Positive≥10 AU/mL
p-ANCA	232 AU/mL	Positive≥10 AU/mL
Protein C	15 IU/dL	70-130 IU/dL

ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; c-ANCA, Cytoplasmic antineutrophil cytoplasmic antibodies; p-ANCA, Perinuclear antineutrophil cytoplasmic antibodies

Echocardiography revealed a giant aneurysmal left main coronary artery (LMCA) 12.5 mm in width and 18.8 mm in length, a dilated left anterior descending (LAD) with a proximal width of 5 mm and a distal width of 5.7 mm, a dilated left circumflex artery (LCX) with a proximal width of 4.1 mm and a distal width of 2.3 mm, and a huge aneurysmal dilation in the right coronary artery (RCA) with a proximal width of 13 mm, an ostial width of 3.2 mm, a mid-width of 4.3 mm, and a distal width of 5.8 mm (Figure 1). Computed tomography angiography also showed a giant aneurysmal LMCA, an ectatic LAD, an ectatic LCX, a giant aneurysmal dilation in the RCA, and large thromboses in the LMCA and the RCA with a linear thrombosis from the LMCA into LAD (Figure 2).

The patient's medical history was insignificant except for affliction by Kawasaki disease 3.5 months earlier. The boy was hospitalized for 8 days, during which he received standard IVIg therapy. Following hospital discharge, the child's fever relapsed, and he was referred to our clinic for persistent Kawasaki disease. His caregivers had positive reverse transcription-polymerase chain reaction (RT-PCR) tests for COVID-19. Since our patient had close contact with COVID-19 and exhibited viral respiratory symptoms before admission for Kawasaki disease, we assessed COVID-19 viral markers. The boy had a negative RT-PCR test for COVID-19 and positive COVID-19 IgG and IgM. Based on these findings, the patient was admitted to the cardiac intensive care unit, where he received clopidogrel (1.2 mg/d), aspirin (30 mg/d), prednisolone (2.5 mg every 8 hours), enoxaparin (7.5 mg every 12 hours), cyclosporin (25 mg/daily), warfarin (1 mg/d), and infliximab. Because of a severe drug reaction, infliximab was stopped. Alteplase injection (0.5 mg/kg/dose: 3 mg in 6 hours) daily for 3 days was also administered.

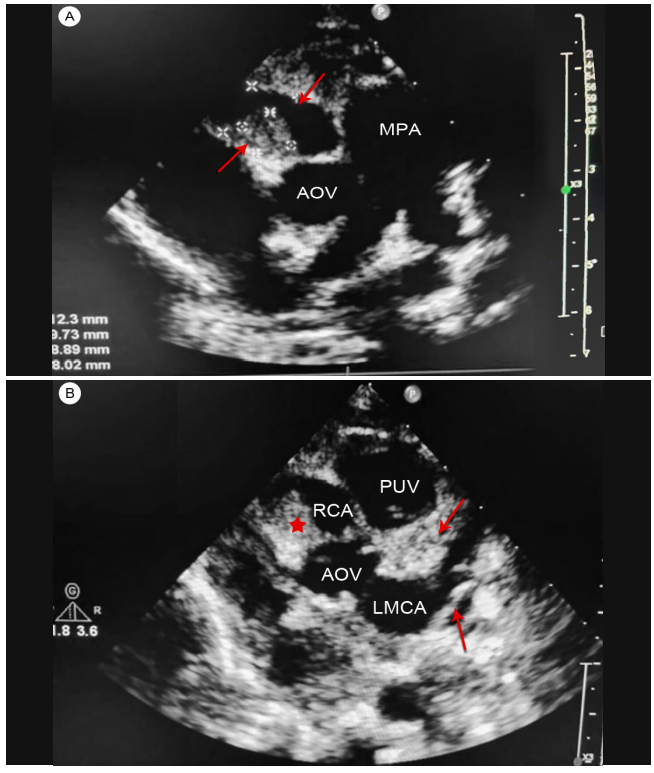

Figure 1. The images illustrate a huge aneurysm and thrombosis. Transthoracic echocardiography in the short-axis view shows the RCA and the LMCA.
A) The image shows the huge RCA aneurysm and (*) thrombosis in the RCA (high parasternal short-axis view), with the arrows indicating the dimensions of the coronary aneurysm.
B) The image depicts the huge LMCA and RCA aneurysms and (*) thrombosis in both coronary arteries (parasternal short-axis view), with the arrows indicating the dimensions of the coronary aneurysms.
AOV, Aortic valve; MPA, Main pulmonary artery; PUV, Pulmonary valve; RCA, Right coronary artery; LMCA, Left main coronary artery

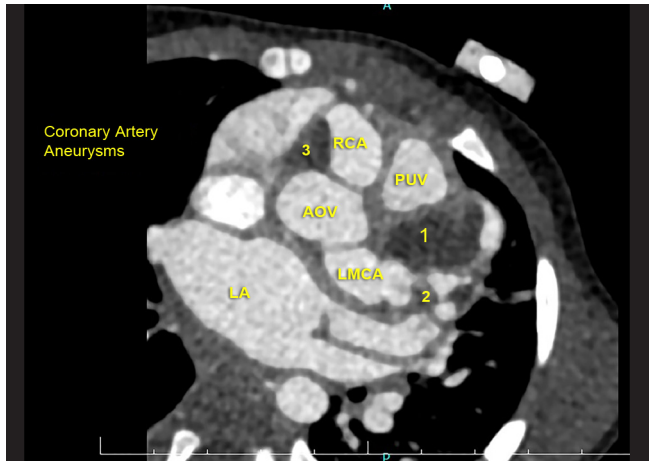

Figure 2. Huge aneurysm in Right coronary artery and left main coronary artery in heart CT angiography and the numbers (1, 2, and 3) represent the number of thrombosis
AOV, Aortic valve; MPA, Main pulmonary artery; PUV, pulmonary valve; RA, Right atrium; LA, left atrium; RV, Right ventricle; LV, left ventricle; RCA, right coronary artery; LMCA, Left main coronary artery

The patient was discharged with prednisolone, cyclosporin, clopidogrel, aspirin, propranolol, and warfarin. Two months later, in the follow-up visit, echocardiography showed a giant coronary aneurysm in both the left coronary artery (11×30 mm) and the RCA (16.5×20 mm, the distal part =7.5×8.8 mm) and mural thromboses in the left coronary artery and the RCA (Figure 3). No significant improvements were observed in the patient's coronary abnormalities, so the treatment was continued.

Due to the unusual manifestation of the disease, we performed a genetic investigation, which revealed a mutation in the THBD gene (exon1 chromosome 20: 20 23030072 23030074 GCG) as an autosomal dominant inheritance. The finding might explain the severe persistent thrombosis in our patient.

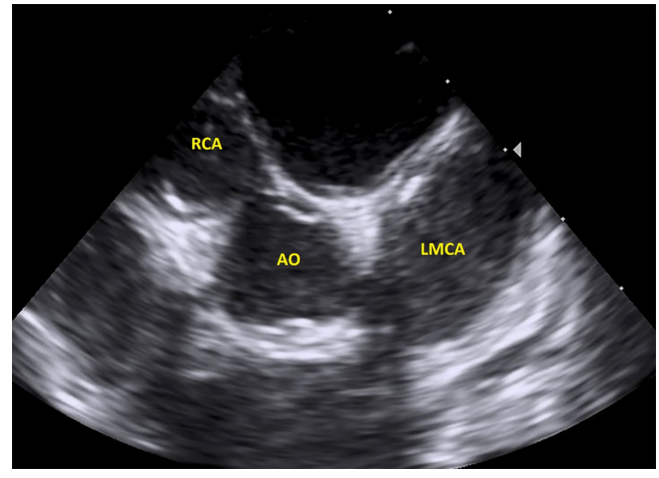

Figure 3. Huge aneurysm without thrombosis in the images of the Right coronary artery and left main coronary artery in short axis view with transthoracic echocardiography.
RCA, right coronary artery; LMCA, Left main coronary artery

Discussion

Kawasaki disease is an acute vasculitis that may involve medium-sized vessels, leading to aneurysms in coronary arteries.[6] Even about 5% of children treated with IVIg can develop coronary aneurysms. Coronary artery aneurysms can also cause obstruction by thrombosis formation. Some risk factors of poor prognoses, such as improper responses to IVIg, male gender, and young age, also existed in our patient. The erythrocyte sedimentation rate can remain elevated for several weeks. According to the Japanese Ministry of Health's classification for coronary artery aneurysms, aneurysms exceeding 8 mm in diameter are considered giant. If the fever does not resolve 36 hours after the completion of IVIg treatment, the disease is regarded as IVIg-resistant Kawasaki disease. Accordingly, other treatment options, such as another dose of IVIg, steroids, infliximab, and cyclophosphamide or cyclosporine (in severely enlarging

aneurysms), can be administered.[7] Cyclophosphamide can stop enlarging aneurysms with an acceptable safety profile.[8]

There have been case reports of giant coronary artery aneurysms in Kawasaki disease accompanied by COVID-19.[9] COVID-19 infection increases the risk of thrombosis and prothrombotic conditions; still, it is rare in children.[10] In some studies on children afflicted by COVID-19, the majority of thromboembolic events occurred in those at a minimum age of 12. Elevated D-dimer is a risk factor heralding the probability of thromboembolic events.[11] COVID-19 may develop Kawasaki-like disease with a tendency toward giant coronary aneurysms and thrombosis,[7] and patients with Kawasaki disease who do not respond to IVIg are at a higher risk of coronary artery aneurysms.[8,9]

We assume that the correlation between Kawasaki disease and COVID-19 produces a synergistic effect on thrombosis and aneurysm formation in coronary arteries, which could explain our patient's lack of a proper response to appropriate treatment. The patient continued the medical treatment and underwent a genetic test for thrombophilia. The results showed a THBD gene mutation. Among the mutations discovered in this patient, NFKB1 (nuclear factor kappa B subunit 1) mutation is associated with susceptibility to and severity of coronary artery disease (specifically in coronary endothelial dysfunction), which verifies the findings of previous articles.[12,13] In treatment-resistant Kawasaki disease, genetic testing is recommended if abnormal manifestations occur.[14]

Moreover, our patient's follow-up echocardiography showed the resolution of the thrombosis in the coronary arteries, while the dilatation of the coronary arteries was still remarkable. Given our patient's risk factors, including very young age, IVIg resistance, close contact with COVID-19, and the aforementioned mutation, there was an ominous chance of disease progression. Crowded health centers, fear of going to hospitals, and poor socioeconomic status caused the delay in seeking treatment for the child on the part of his caregivers.

Conclusion

We herein described an IVIg-resistant Kawasaki disease patient with giant coronary aneurysms and multiple large thromboses in echocardiography. The boy had a mutation in the THBD gene, which could explain his severe thrombosis. Severe aggressive antithrombotic treatment, treatment with biological agents, and corticosteroid pulse therapy may control thrombosis. Genetic studies are advisable in all Kawasaki disease patients with thrombosis in early infancy.

References

1. Mossberg M, Mohammad AJ, Kahn F, Segelmark M, Kahn R. High risk of coronary artery aneurysm in Kawasaki disease. Rheumatology (Oxford) 2021;60:1910-1914.
2. Li W, Zhang L, Wang Z, He X, Lin H, Wang Y, Yuan J, Xie X, Zhang X, Qin Y, Huang P. Predictors for Intravenous Immunoglobulin Resistance in Patients with Kawasaki Disease. Int J Clin Pract 2022;2022:2726686.
3. Tahghighi F, Bakhtiari Koohsorkhi M, Ziaee V. Peripheral Gangerene, an Unusual Presentation of Infantile Kawasaki: A Case Report and Literature Review. Case Rep Rheumatol 2021;2021:6629405.
4. Malekzadeh I, Ziaee V, Sadrosadat T, Moardinejad MH, Sayadpour-Zanjani K. Kawasaki Disease and Peripheral Gangrene in Infancy. Iran J Pediatr 2015;25:e3309.
5. Halyabar O, Friedman KG, Sundel RP, Baker AL, Chang MH, Gould PW, Newburger JW, Son MBF. Cyclophosphamide use in treatment of refractory Kawasaki disease with coronary artery aneurysms. Pediatr Rheumatol Online J 2021;19:31.
6. Navaeifar MR, Shahbaznejad L, Sadeghi Lotfabadi A, Rezai MS. COVID-19-Associated Multisystem Inflammatory Syndrome Complicated with Giant Coronary Artery Aneurysm. Case Rep Pediatr 2021;2021:8836403.
7. Zaffanello M, Piacentini G, Nosetti L, Ganzarolli S, Franchini M. Thrombotic risk in children with COVID-19 infection: A systematic review of the literature. Thromb Res 2021;205:92-98.
8. Cinteză E, Voicu C, Filip C, Ioniță M, Popescu M, Bălgrădean M, Nicolescu A, Mahmoud H. Myocardial Infarction in Children after COVID-19 and Risk Factors for Thrombosis. Diagnostics (Basel) 2022;12:884
9. Duignan S, Doyle SL, McMahon CJ. Refractory Kawasaki disease: diagnostic and management challenges. Pediatric Health Med Ther 2019;10:131-139.
10. Mallik S, Majumder PP. A two-step genetic study on quantitative precursors of coronary artery disease in a homogeneous Indian population: case-control association discovery and validation by transmission-disequilibrium test. J Biosci 2011;36:857-868.
11. Lai HM, Li XM, Yang YN, Ma YT, Xu R, Pan S, Zhai H, Liu F, Chen BD, Zhao Q. Genetic Variation in NFKB1 and NFKBIA and Susceptibility to Coronary Artery Disease in a Chinese Uygur Population. PLoS One 2015;10:e0129144.
12. Lai H, Chen Q, Li X, Ma Y, Xu R, Zhai H, Liu F, Chen B, Yang Y. Association between genetic polymorphism in NFKB1 and NFKBIA and coronary artery disease in a Chinese Han population. Int J Clin Exp Med 2015;8:21487-21496.
13. Luo JY, Li XM, Zhou Y, Zhao Q, Chen BD, Liu F, Chen XC, Zheng H, Ma YT, Gao XM, Yang YN. Mutant DD genotype of NFKB1 gene is associated with the susceptibility and severity of coronary artery disease. J Mol Cell Cardiol 2017;103:56-64.
14. Yoshino S, Cilluffo R, Prasad M, Best PJ, Atkinson EJ, Aoki T, Cunningham JM, de Andrade M, Lerman LO, Lerman A. Sex-Specific Genetic Variants are Associated With Coronary Endothelial Dysfunction. J Am Heart Assoc 2016;5:e002544.