Giant Coronary Artery Aneurysms in an Infant Diagnosed With Kawasaki Disease

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INTRODUCTION

Kawasaki disease (KD) is a systemic vasculitis that is predominantly a clinical diagnosis as defined by the American Heart Association. Kawasaki disease has become the most common cause of acquired heart disease in children due to a predilection for targeting the coronary arteries, with approximately 25% of untreated cases developing coronary artery aneurysms (CAAs). Although it is a self-limited diagnosis, early diagnosis and treatment is the key to reduce inflammation and potential for damage to the arterial wall with risk for developing coronary artery ectasia and CAAs. Complications of this include but are not limited to stenosis formation, coronary thrombosis, myocardial infarction, and sudden death. Giant aneurysms (≥8 mm) have the fatal risk of rupture. In this case report, we present a case in which a pediatric patient developed prominent enlargement of coronary arteries with associated giant aneurysms, which was managed with aspirin and rivaroxaban.

CASE PRESENTATION

A 5-month-old previously healthy Caucasian infant presented with 1-week history of fever and new onset of full body rash, with symptoms of dehydration including decreased oral intake and decreased wet diapers. On examination, the patient was found to have tongue and lymph node swelling with full-body squamous rash. Laboratory results were significant for elevated inflammatory markers, erythrocyte sedimentation rate of 125 mm/hour, and C-reactive protein of 14.6 mg/dL. Of note, N-terminal pro-BNP was markedly elevated at 2,020 pg/mL. A clinical diagnosis of KD was made.

Transthoracic echocardiogram (TTE) was performed using a standardized imaging protocol for accurate and complete assessment, including obtaining a specific sequence of imaging views in order to delineate all segments of the coronary arteries. A high-frequency transducer was used to optimize resolution. Coronary artery luminal diameters were measured in two-dimensional images from inner edge to inner edge in all segments. Complete characterization of coronary artery involvement was performed including quantitative assessment as *Z* scores to ensure proper prognostication and calibration of follow-up surveillance and treatment. Normal color-flow Doppler is laminar and antegrade in systole and diastole. Aliasing or requiring a higher Nyquist limit suggests possible stenosis. Normal spectral Doppler display profiles for the coronary arteries consists of a biphasic pattern with a late systolic peak followed by diastolic flow. The pattern should return to baseline between systole and diastole with no flow reversal. Initial TTE performed at day of illness 8 showed normal cardiac anatomy and function with no evidence of coronary artery dilation.

Treatment was initiated for KD with aspirin at 100 mg/kg/day divided every 6 hours and intravenous immunoglobulin (IVIG) at 2 g/kg. The patient failed initial treatment with IVIG since fever persisted and inflammatory markers remained elevated 36 hours after the initial dose of IVIG. Therefore, the patient was treated with a second dose of IVIG at 2 g/kg, after which fever resolved and the inflammatory markers were within normal limits. Repeat TTE performed on day of illness 13 (Figure 1 and Video 1) showed evidence of right coronary artery (RCA) aneurysm measuring at least 16.5 × 24.4 mm (white arrow in Figure 1) with a *Z* score of +47.2. Proximal left main coronary artery (LMCA) measured normal. Left anterior descending artery (LAD) measured 6.9 mm (blue arrow, Figure 1) with a *Z* score of +22.5. Aneurysms were measured in all dimensions, and there was no evidence of intraluminal thrombus or flow disturbance noted. Retrospectively gated cardiac computed tomography (CCT) with functional analysis was performed, which confirmed dilated coronary arteries with aneurysms (Figure 2 and Video 2). The proximal LMCA measured normal at 1.7 × 1.3 mm. A large saccular aneurysm was noted in the distal LMCA to proximal LAD origin measuring 7.5 × 6 mm. The LAD and the left circumflex coronary artery beyond the aneurysm measured normal. A giant fusiform aneurysm was seen in the proximal RCA measuring 22.0 × 14.0 mm in the maximal, orthogonal dimensions. Given the findings of giant CAAs, the patient was started on a prophylactic dose of low molecular weight heparin (LMWH) at 0.5 mg/kg/dose twice a day and continued on a low-dose aspirin at 5 mg/kg/day.

The patient was monitored closely as an outpatient with serial TTE every few weeks to assess the progression of the aneurysms and for possible thrombus formation and was then transitioned from LMWH to rivaroxaban at 4 months after diagnosis. However, at the 7-month serial TTE evaluation, a possible thrombus was suspected in the proximal LAD, and the patient was restarted on a therapeutic dose (1 mg/kg) of LMWH twice daily. Repeat CCT was suboptimal for distal coronary visualization but demonstrated that the proximal LAD aneurysm was patent without an intraluminal thrombus. Invasive coronary angiography was discussed in a shared decision-making setting and not performed. The patient was transitioned to rivaroxaban and continued on aspirin. Serial TTE has demonstrated stable CAAs without thrombus and normal biventricular systolic function at 20 months.

DISCUSSION

Kawasaki disease, first described by Tomikasu Kawasaki in 1967,[1] is a multisystem medium vessel vasculitis with a predilection for coronary

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Keywords: Kawasaki disease, Severely dilated coronary arteries, Giant coronary artery aneurysms, Case report

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2468-6441
https://doi.org/10.1016/j.case.2024.10.004

VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, basal parasternal short-axis view, demonstrates a giant RCA fusiform aneurysm and a normal proximal LMCA with distal LMCA/proximal LAD saccular aneurysm.

Video 2: Three-dimensional CCT, rotational cine-loop of the volume-rendered reconstruction display, demonstrates a giant fusiform aneurysm of the proximal RCA and a large saccular aneurysm in the distal LMCA/proximal LAD.

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artery involvement, making it the most common cause of acquired heart disease in children. Kawasaki disease is a clinical diagnosis as defined by the American Heart Association guidelines. Classic KD is diagnosed in the setting of fever greater than 5 days with 4 out of the 5 clinical features, which include erythema of oropharyngeal mucosa or strawberry tongue, conjunctival injection, diffuse maculopapular or erythema multiform type rash, erythema/edema of hands and feet, and/or unilateral cervical lymphadenopathy.[2] However, in several cases it may be difficult to diagnose based on these criteria as some patients will not present with full clinical features, in which case, they may be diagnosed with incomplete KD (also referred to as atypical KD),[2] commonly seen in patients under 1 year or older than 10 years of age.

Coronary involvement can be in the form of ectasia, which is defined as diffuse dilation of a coronary artery, with dilation exceeding more than one-third of the coronary artery length with the diameter of the dilated segment measuring more than 1.5 times the diameter of a normal adjacent segment. A CAA is defined as focal enlargement of the coronary artery exceeding the 1.5-fold diameter of the adjacent normal segment. There are 2 types of CAAs: saccular, where the longitudinal diameter is less than the transverse diameter; and fusiform, where the longitudinal diameter is more than the transverse diameter. Giant CAA is defined as aneurysm ≥8 mm in diameter or with a *Z* score ≥10.

Although the etiology has been unclear, KD is prominently divided into 2 phases, acute and chronic.[2] The acute phase involves the febrile phase, leading to systemic inflammation of medium sized arteries and in multiple organs with associated clinical findings including hepatitis, interstitial pneumonitis, abdominal pain with vomiting/diarrhea, gallbladder hydrops, aseptic meningitis, myocarditis, pericarditis, valvulitis, pyuria, pancreatitis, lymphadenopathy, and other nonspecific symptoms. Recent proposed models of KD show that there is first development of necrotizing arteritis with synchronized neutrophilic process within the first 2 weeks after onset of fever.[2] During this period, immunomodulation with high-dose IVIG with aspirin is used to reduce inflammation and prevent clot formation. The acute phase is followed by a subacute/chronic vasculitis process with asynchronous infiltration of lymphocytes, plasma cells, eosinophils, and macrophages, which can persist for months to years after initial onset. Along with this, a third process known as progressive luminal myofibroblastic proliferative phase sets in, which has been attributed to the development of persistent coronary artery abnormalities, including coronary artery stenosis.

Echocardiography has become the central modality for following the progression of CAA in patients diagnosed with KD and is preferred given the minimal need for sedation and lack of radiation exposure.[2-4] Echocardiography does not exclude coronary involvement as distal aneurysms are more difficult to evaluate and may be missed on echocardiography. Furthermore, the role of echocardiography is unclear for stenotic lesions or thrombosis. Therefore, CCT and cardiac magnetic resonance imaging are increasingly used.[2,4]

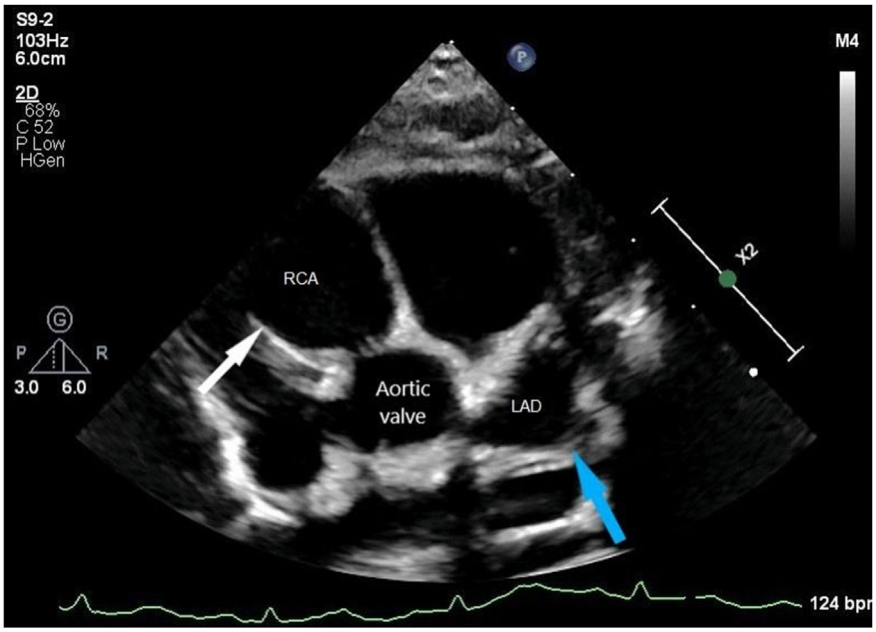

Figure 1 Two-dimensional TTE, basal parasternal short-axis view, demonstrates a giant RCA fusiform aneurysm (*white arrow*; 16.5 × 24.4 mm; *Z* score +47.2) with a *Z* score of +47.18 and normal proximal LMCA with distal LMCA/proximal LAD saccular aneurysm (*blue arrow*; 6.9 mm; *Z* score +22.5).

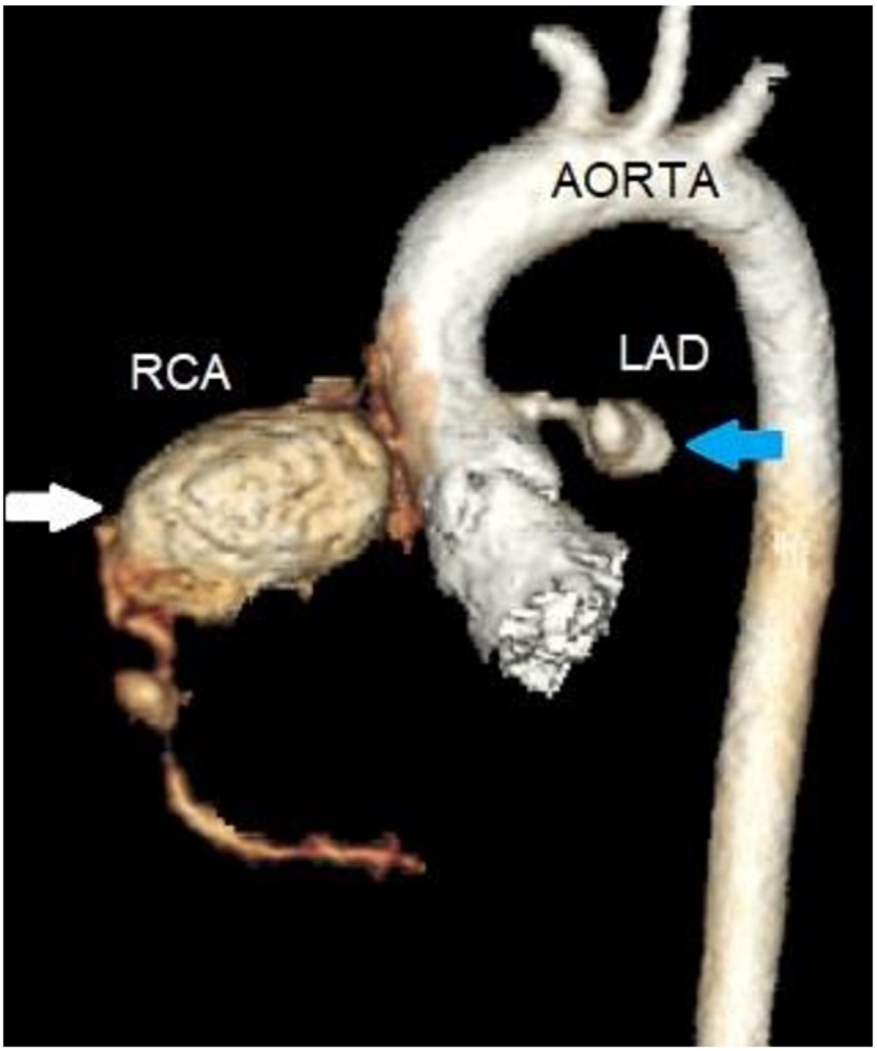

Figure 2 Three-dimensional CCT, volume-rendered reconstruction, oblique sagittal display, demonstrates a giant fusiform aneurysm of the proximal RCA (*white arrow*; 22.0 × 14.0 mm) and a large saccular aneurysm in the distal LMCA/proximal LAD (*blue arrow*; 7.5 × 6.0 mm).

The mainstay treatment to prevent CAA in patients with KD is IVIG, in an attempt to rapidly reduce inflammation. Introduced in 1980, IVIG reduces the incidence of CAA in patients with acute KD to approximately 4% from a prior incidence of 24.6%.[5] Prior to IVIG, approximately 49% of patients with CAA in acute KD had regression; however, IVIG increased the rate to 71%. Resistance to IVIG is defined as persistent or recrudescent fever ≥36 hours after completion of the initial IVIG infusion. For patients who were IVIG-resistant, had CAA at diagnosis (CA *Z* score >3 or Japanese Ministry of Health Criteria), and/or were deemed to be at high risk by clinical criteria, second-line therapy has varied over time and by site and has included repeat IVIG (2 g/kg),[2] oral or intravenous steroids (varying dosing and duration regimens),[6] infliximab,[7] cyclosporine, cyclophosphamide, and/or anakinra.[8]

The strongest predicting factor for CAA regression was found to be the initial aneurysm size in the acute stage, with smaller aneurysms having a greater likelihood of regression.[5,9] Long-term complications include persistent CAA, stenosis, or thrombosis. Predictors for formation and persistence of CAA include male sex, onset at less than 1 year or more than age of 9 years, and IVIG resistance.[4,10] Laboratory findings including elevated CRP, leukocytosis, anemia, thrombocytopenia, low albumin, and hyponatremia indicating severe inflammatory state and, when present, are associated with an increased risk of CAA development.[2] Predictors for coronary thrombus formation in KD with CAA include male gender, LAD involvement, and giant CAA (defined as aneurysms ≥8 mm in diameter or with a *Z* score ≥10). Furthermore, patients with bilateral giant CAAs of the left and right coronary arteries have a fourfold increased risk of death. Giant CAAs do not resolve, regress, or remodel; however, they act as a nidus for layered mural thrombosis formation requiring intervention, or they rarely rupture.[11] Aspirin along with either warfarin or LMWH has been the standard of care.[2,12] Direct oral anticoagulants are increasingly being used for anticoagulation and can be considered in the setting of CAA as well.[13,14] Rupture is rare but is noted in patients with giant CAA.[15]

CONCLUSION

This case report demonstrates that despite early treatment based on guidelines, the clinical course of this infant was severe. There are

currently no randomized controlled studies to guide anticoagulation therapy in patients with giant CAA, but they would benefit from further study in randomized controlled clinical trials. Direct oral anticoagulants appear to be safe and effective for thromboprophylaxis in infants with giant CAA; however, they merit randomized controlled studies to substantiate the same.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

CONSENT STATEMENT

The authors declare that since this was a non-interventional, retrospective, observational study utilizing de-identified data, informed consent was not required from the patient under an IRB exemption status.

FUNDING STATEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE STATEMENT

The authors report no conflict of interest.

ACKNOWLEDGMENTS

We thank the sonographers who acquired echocardiographic images. We also thank the cardiac imaging team who acquired the computerized tomographic images.

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