CASE REPORT

Multiple Giant Coronary Aneurysms in an Infant with Prolonged Fever

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Abstract

Kawasaki disease is a systemic vasculitis, sometimes presenting atypically in infancy, often leading to a late diagnosis, and resulting in devastating consequences. We report a 2-month-old baby presenting with fever of unknown origin. Echo showed giant aneurysms in all three coronary arteries with intraluminal thrombus in one artery that required thrombolysis and anticoagulation.

Keywords: Coronary artery aneurysm, Kawasaki disease, Streptokinase, Thrombolysis.

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Introduction

Kawasaki disease (KD) is an acute onset multisystem vasculitis of undetermined etiology presenting as febrile illness in children mostly younger than 5 years of age. The unique clinical symptom complex of this disease was first described by Dr Tomisaku Kawasaki in 1967.[1] European studies have shown the incidence to be 5–10 per 100,000 children under the age of 5 years, but incidence is higher in Asian countries like Japan, Korea, and Taiwan.[2]

The etiology is largely unknown, but genetic, infectious, and immunological factors possibly play a role.

Kawasaki disease is a clinical diagnosis, but all the clinical features may not be present in the same patient or at the same time thus making diagnosis difficult. It affects small and medium sized vessels with a peculiar predilection for the coronary arteries leading to coronary artery aneurysms (CAA) and thrombosis, occasionally resulting in long-term sequelae like stenosis and myocardial infarction.

The standard treatment of 2 g/kg intravenous immunoglobulin (IVIG) together with aspirin (30–50 mg/kg/day), is effective in reducing fever in 80–90% of patients and decreasing the rate of coronary artery aneurysm formation from 20–25% to 3–5%.[3]

Case Description

A 2-month-old male child presented with high fever for 15 days. Clinical examination of the child was unremarkable. Investigations showed hemoglobin of 7.9 g/dL, total leukocyte count of 24,200 cmm with 78% neutrophils, and platelet count of 7.34 lacs/cmm. Cross reacting protein (CRP) was 158 mg/L. Chest X-ray, cerebrospinal fluid (CSF) study, and blood and urine cultures were negative. Fever persisted even on broad spectrum iv antibiotics and a repeat blood test showed platelet count of 10.2 lacs/mm^3 with a CRP of 212 mg/L. To explore the possibility of KD as a cause for the fever with thrombocytosis, echocardiography was performed which showed multiple giant aneurysms involving all major coronaries: left main-coronary artery (LMCA) proximal part 6.3 mm (*z* score +16.1) and proximal left anterior descending (LAD) artery had a giant aneurysm 10 × 12 mm (with sluggish flow) with clot in LAD 4 × 2 mm in size (Fig. 1). There was a huge distal aneurysm 9.2 × 8.4 mm in distal right coronary artery (RCA), left circumflex (LCx) artery was also aneurysmal 3.3 mm (*z* +4.78) (moderate size). Left ventricular function was maintained.

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The baby was promptly started on IVIG 2 g/kg along with aspirin 50 mg/kg and low molecular weight heparin (LMWH). Since fever

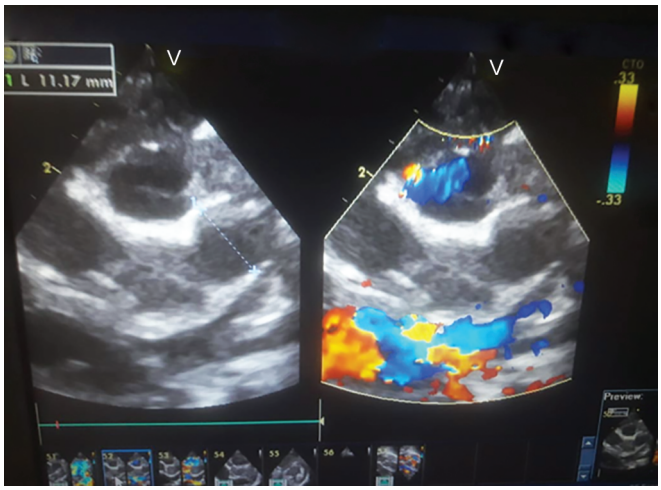

Fig. 1: Giant aneurysms in left main coronary artery and left anterior descending coronary artery with marked increase in perivasacular echogenicity

persisted, and also to intensify therapy in the presence of multiple aneurysms, infliximab 5 mg/kg was administered after 48 hours of completion of IVIG infusion. The child became afebrile within 24 hours of infliximab with normalization of CRP.

Repeat echocardiography after 5 days showed a further increase in the aneurysms with an increased clot size of 7.8 mm × 2.1 mm. In the absence of readily available tissue plasminogen activator, thrombolysis was initiated with Streptokinase at a loading dose of 2000 IU/kg over 30 minutes, followed by a maintenance dose of 500 IU/kg per hour. LMWH and aspirin at 5 mg/kg were continued. Echocardiography on the following day showed a decrease in the clot size. Streptokinase was increased to 700 IU/kg and repeat echocardiography after 24 hours showed complete dissolution of the clot. Streptokinase was stopped after 48 hours of continuous infusion and the baby was finally discharged on LMWH, clopidogrel, and aspirin.

Echocardiography repeated after 2 weeks showed that the size of the aneurysms was unchanged but there was no clot. LMWH was converted to oral warfarin with a target INR of 2–3. At 18 months follow-up, the child continues to have persistent giant aneurysms with minimal regression in size of the aneurysms.

Discussion

KD is diagnosed clinically based on persistent fever ≥5 days in combination with polymorphous rash, cervical lymphadenopathy, bilateral nonpurulent conjunctivitis, changes in the mucous membrane of the tongue and lips (strawberry tongue, dry red cracked lips), and extremity changes (swelling and/or redness of the palms and soles, finger toes desquamation in the subacute phase). "Complete" KD is defined by fever and ≥4 of the five symptoms. It is important to appreciate that all the clinical findings may not be present at a time in a patient: they may appear successively instead of simultaneously. However, in the recent American Heart Association (AHA) guidelines, the diagnosis can be made earlier with only 4 days of fever if four or more of the symptoms are unambiguously present. The AHA has also created an algorithm for diagnosis of "incomplete" KD in case ≤3 criteria are present, which includes CAAs on echocardiography and/or laboratory abnormalities.[4] The diagnosis may be even more difficult in early infancy when incomplete and atypical presentation is commonly seen, thereby resulting in delayed diagnosis.[5] In our case, the baby presented with only persistent fever without any of the other supportive clinical finding. In the absence of negative cultures, the high CRP, neutrophilic leukocytosis, normocytic anemia, progressive thrombocytosis, and the young age of presentation lead to the suspicion of KD, which was confirmed by the presence of significant coronary aneurysms.

Coronary artery dilatation *z*-score ≥2.5 is considered significant and aneurysms with *z*-score ≥10 are considered giant aneurysms. In our patient, the proximal part of LMCA had an aneurysm with *z*-score +16.1 and there was a clot in LAD. These warranted the initiation of anticoagulant therapy with LMWH.

Treatment with 2 g/kg of IVIG, within the first 5–10 days of the illness effectively decreases coronary artery aneurysm formation. IVIG should also be given to patients presenting after the 10th day of illness if they have either ongoing inflammation manifested by persistent fever (after excluding other causes) or elevated CRP/ESR and/or aneurysm formation. Our patient was diagnosed after 15 days of illness and had raised CRP and giant coronary aneurysms, and hence IVIG was initiated immediately.

The majority of patients respond rapidly to IVIG, but about one-fifth of all patients do not respond or have recurrent fever within 36–48 hours after IVIG administration. These patients have an increased risk of developing CAA.

In Japan, scientists have developed risk–score systems to identify patients with an increased risk of developing IVIG resistance.[6] Unfortunately, there is not enough data to conclusively state how far these scoring systems are effective in predicting IVIG resistance in the Indian population. A possible way of decreasing IVIG resistance is intensification of the initial treatment. Dionne et al.[7] have shown that intensifying the treatment with either IFX or corticosteroids independently protect against the progression of coronary artery dilatation in patients with CAA at diagnosis. Since the baby was IVIG resistant and had aneurysms at diagnosis, infliximab was administered.

Giant CAAs may have grave long-term sequelae. There may be thrombosis within the CAA and perfusion abnormalities distal to the CAA, or there may be stenosis just proximal or distal to the CAA. In a study by Friedman et al., in 90 patients with giant CAA at diagnosis (*z*-score ≥10), 21 suffered from major adverse cardiac events (MACE).[8] This shows that patients with giant CAA are at considerable risk for MACE and the risk persists even years after the acute phase.

Anticoagulation in KD is recommended for the following: (1) giant aneurysm, multiple or complex aneurysms, and presence of thrombus; (2) associated stenosis; (3) peripheral gangrene. Initiate with subcutaneous LMWH followed by oral warfarin to maintain INR of 2–2.5. Since maintaining the recommended INR is very difficult in infancy and young children, one may continue with the LMWH for a more stable response.

For arterial thrombosis, peripheral gangrene-thrombolytics have been tried in addition to anticoagulation.[4] Thrombolytic treatment helps in lysing a developing thrombus within a giant CAA and also in preventing distal ischemia due to such thrombus.[9] Urokinase, streptokinase, and tissue-type plasminogen have all been used for the lysis of coronary artery thrombosis. Following thrombolysis, peripheral arterial blood flow is restored, and then perfusion is maintained by heparin followed by oral anticoagulation in the long-term. If these treatments fail, a variety of invasive approaches are tried, including percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. In our patient, there was a giant aneurysm (*z*-score 16.1) and the presence of clot in LAD. Since the clot was increasing in size in spite of LMWH on follow-up echocardiography, fearing an impending MACE, prompt decision was taken to initiate thrombolysis. Post thrombolysis LMWH was continued together with aspirin and clopidogrel, and subsequently on follow-up, LMWH was converted to warfarin.

Usually within the first five years, some CAAs may regress but the degree of return to normalcy seems to be highly dependent on the degree of dilatation.[8,10] While the lumen diameter may regress, the vascular wall elasticity may stay damaged and studies have shown persistent impaired inadequate dilatation in the face of increased cardiac demand.[11] In our patient, though there was resolution of the clot, the baby continues to have persistent giant aneurysms.

Conclusion

Kawasaki disease can have myriad presentations. The patient may not demonstrate all the classic clinical features or the features may be temporally dissociated, confusing the diagnosis. This specially

holds true for patients presenting in early infancy, when they may present with just fever or excess irritability. Timely diagnosis and intervention can save the child from severe cardiovascular accidents and death. Interventions such as thrombolysis and anticoagulation are instrumental in decreasing the mortality and morbidity in special circumstances.

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