

A Case Study

Re-dilation of Coronary Arteries of a Child with H/O Atypical Kawasaki Disease, following Chickenpox: A Case Study

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ABSTRACT

Kawasaki disease (KD) is an acute vasculitis of medium sized arteries in childhood with unclear etiology that leads to coronary artery aneurysm (CAA) and ectasia in up to 25 % of untreated children. Typically, Kawasaki disease has a few traditional diagnostic criteria. Incomplete or atypical Kawasaki disease presents with a complex and variable dimension of clinical features. Though its etiology is unknown, there is evidence for some genetic susceptibility to Kawasaki disease as well as some link to infectious agents like varicella zoster. We are reporting one such child of atypical Kawasaki disease on follow up, who was on low dose aspirin and developed re-dilation of coronary arteries after exposure to varicella virus infection. Initially he was treated with intravenous immunoglobulin (IVIg) and appropriate dose of aspirin during acute stage of Kawasaki disease, six months before the infection of varicella zoster virus. Although the illness happened during COVID-19 pandemic situation, the baby did not have any symptoms of COVID-19 virus and could not do any laboratory test. We suspect the episode of chicken pox to be the probable cause of re-dilatation of coronary arteries in this child.

Keywords: A typical Kawasaki disease, coronary artery re-dilation, varicella zoster virus, COVID-19 pandemic, intravenous immunoglobulin (IVIg).

1. CASE SUMMARY

A three and a half month old male infant weighing 7.5 kg with length 65 cm was admitted in our hospital in late August, 2019 with the complaints of continued fever (103^oF-104^oF) for 5 days, reluctant to feed and oliguria for one day. He was treated by paracetamol at home. On admission, baby was febrile (100^oF) and irritable, had SPO₂ 97% in room air, heart rate 155 b/min, respiratory rate 47 breath/min, blood pressure 75/50 mm of Hg. Precordium examination revealed normal 1st and 2nd heart sound with soft ejection systolic murmur 2/6 at upper left sternal border. Lungs were clear. Abdomen was soft with normal bowel sound. On 3rd day of admission, he

developed red cracked lips with flushed face and faint macular rashes over both limbs. He had no strawberry tongue or congested eye or lymphadenopathy. The baby's anterior fontanelle was normal with no signs of meningism.

He was delivered by LUCS at term. He had patent foramen ovale and PDA diagnosed in his neonatal period. PDA was closed after treating with one course of syrup ibuprofen.

On admission, his lab investigations showed low HB (9.9 gm/dl, n: 11.0-14.0 gm/dl), microcytic hypochromic anemia, neutrophilic leukocytosis (TLC :16.59 x 10⁹/L, n: 5.00 -15.00 x10⁹/L, N:57 %, n: 20-50 %, L:36 %,n: 40-75%), thrombocytosis (462 x 10⁹/L,n:150-400 x10⁹/L), high CRP (63.7mg/L, n : 3.3 mg/dl), high ESR (67 mm in 1st hour), marginally raised serum procalcitonin 0.14 ng/ml , n: 0.05ng/ml), raised fibrinogen (395 mg/dl; normal : 180-350mg/dl), high D-dimer (>2468 µg/L, n :<500 µg/L), low S. albumin (3g/dl, n: 3.5-5.5 gm/dl).

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He had normal S. creatinine (0.3 mg/dl n:0.50-1.1 mg/dl), normal SGPT (25 IU/L ,n: 14-63 IU/L), normal serum electrolytes, Na⁺: 135 mmol/L, K⁺ :4.6 mmol/L, Chloride (Cl⁻):105 m mol/L, HCO₃⁻ : 26 mmol/L and normal S. Ferritin.

Dengue NS1: Negative. Dengue Ab: Negative with normal Widal titer. Chest X-ray revealed normal vascularity with normal cardiac silhouette.

On 3rd day of admission, the 2D and color doppler echo revealed aneurysmal dilation of left main coronary artery (LMCA) and left anterior descending (LAD) and right coronary artery (RCA) with irregular vascular wall of LMCA. No perivascular cuffing or no intra vascular thrombus was noticed.

There was Patent foramen Ovale (2mm) with left to right shunt, normal aortic root, no tricuspid or no mitral regurgitation, normal cardiac chambers and good biventricular function. No pericardial or pleural effusion was noticed.

LMCA: 3.7 mm (Z score + 6.24; n: 0.95-2.27 mm), LAD: 2.9 mm (Z score +5.34 n: 0.63-1.84 mm),

RCA: 3 mm (Z score +4.77; n: 0.72-2.05 mm), (Table 1, Fig 1, Fig 2). LVEF :65%.

He had pyuria (urine R/E: pus cell 8-10/HPF). Urine C/S: Klebsiella Pneumoniae (colony count 11 x 10⁴ CFU/ml). Blood C/S: Coagulase negative Staphylococcus. He was diagnosed as atypical Kawasaki disease with urinary tract infection (UTI). Intravenous immunoglobulin (IVIg, 2 gm /kg as single infusion over 24 hours) plus high dose tab Aspirin (80 mg/kg/day in 4 divided doses) were started immediately. After 36 hours of infusion of IVIg infusion, the baby became afebrile and his activity was improved. The baby was on inj. Ceftriaxone. High dose Aspirin was continued till 48 hours of defervescence of fever. Then the baby was on low dose tab Aspirin (5 mg/kg/dose OD)

2. FOLLOW-UP VISIT

At 8th week of illness (October, 2019) the baby's coronary arteries were normal in caliber, (Table 1, Fig 3, Fig 4). We could stop the low dose tab Aspirin after reviewing the echocardiogram. The baby was under follow up in Paediatric Cardiology and Paediatric OPD in our hospital. He also had follow up visit in Paediatric Cardiology OPD, NUH- Singapore. He had same echocardiogram reports during that visit.

But on 4th month of follow up (early December,2019), the baby's 2 D and color doppler echo revealed dilated coronary arteries while the baby came with the history of lower respiratory tract infection and was on oral antibiotic. LMCA 2.5mm, (Z score+ 2.28), LAD 2.4mm, (Z score: + 3.38) and RCA 2.4mm (Z score +2.63) (Table 1). Tab aspirin at low dose was suggested. After taking tab aspirin for 4 weeks, his echocardiogram (on January, 2020) suggested normal

coronaries except LAD (Z score + 2.77) and his tab aspirin was discontinued.

In early February 2020, the baby was supposed to go to NUH-Singapore for follow up and also come to our center. But he could not be assessed in any center because of lock down situation for COVID-19.

Moreover, on late February 2020, the baby got severe attack of chicken pox and was treated by Paediatrician over telemedicine. The baby had fever (1030F -1040F) for 5 days with typical vesiculopustular rash all over the body which had healed within a few days. He could not do any lab investigations or follow up visit with Paediatric Cardiologist during the illness because of lockdown situation for COVID-19.

The baby came for follow up echo in Paediatric Cardiology OPD after 12 weeks of chicken pox attack in May 2020. On examination, baby was clinically stable, afebrile, active, playful but mildly pale.

Surprisingly, 2-D and color Doppler echocardiogram revealed small aneurysmal dilation of coronary arteries (LMCA, LAD and RCA) with irregular vascular wall of LMCA with normal biventricular function. LMCA: 3.3- 4mm, Z score +3.08 to + 4.83, LAD: 2.75mm, Z score +4.24 and RCA:2.56, Z score +2.56 (Table 1), (Fig 5, Fig 6).

His CBC revealed low Hb: 9.83 gm/dl (n: 11.0-14.0 gm/dl) with microcytic hypochromic anaemia.

He had low absolute count of lymphocytes. He did not have any raised inflammatory markers. CRP: <0.3 mg/dl). [PCV : 28.20% (normal: 40-52 %), MCV :66.20 fl (n : 75-87.00 fl, MCH :20.90 pg (n : 24.00- 30.00) and MCHC : 31.60% (n: 31.00-37.00%) , RDW-CV :17.20%,(n: 11.60-14.00%). His serum iron

level was very low: 19 microgram/dl (n: 65-175 microgram/dl). He had normal total count of WBC

:11.89 x10⁹/L,N: 30.50%(n: 20-50 x10⁹/L),L: 46.30 %(n: 40.00-75.00%),). He had low absolute count of lymphocytes (5.04 x10⁹/L, n:6-9.00 x 10⁹/L)].

We started low dose tab aspirin once daily. Baby had mild fever and strong family history of exposure to COVID-19 after that visit. Although their RT-PCR for COVID 19 reports were negative. We did not know his lab markers during his Varicella zoster infection. However, we had a strong doubt that the baby might have coronary arterial re-dilation because of severe attack of varicella infection which could be the triggering agent or could act as an additional factor to aggravate immune response during this COVID-19 pandemic. Although the baby was COVID-19 negative with mild fever and his parents and other family members had exposure to COVID-19 after that visit, we are assuming that re-dilation of coronary arteries might have association with previous exposure of COVID -19 as well.

The baby is now on follow up in Paediatric Cardiology OPD, so that we can pick up any further changes of coronary arteries on time and take proper measure.

Table 1: Coronary artery changes Evaluated by 2D & color Doppler Echocardiogram

Echocardiogram (Day 9 of illness)	Echocardiogram (8 th weeks of illness)	Echocardiogram (4 th month of illness during LRTI)	Echocardiogram (5 th month of illness)	Echocardiogram (9 th month illness) Post Varicella Zoster+COVID-19 exposure)
<p>LMCA: 3.7 mm (Z score + 6.17) (n :0.97 to 2.28mm)</p> <p>LAD: 2.9 mm (Z score + 5.28) (n:0.64 to1.86mm)</p> <p>RCA: 3 mm (Z score + 4.7) (n:0.73 to 2.06mm)</p> <p>Medium aneurysmal dilatation of left main coronary, left anterior descending and right Coronary Arteries, with irregular vascular wall.</p>	<p>LMCA: 2.02 mm (Zscore+1.05)</p> <p>LAD: 1.79 mm (Z score +1.61) LCX 1.5 mm (Z score + 0.94) RCA: 1.53 mm (Z score +0.28)</p> <p>No coronary artery aneurysm seen. Proximal segments of coronary arteries not ectatic.</p>	<p>LMCA: 2.5 mm (Z score + 2.28) LAD: 2.4 mm (Z score + 3.38) RCA: 2.4 mm (Z score + 2.63)</p> <p>Small aneurysmal dilatation of LAD and RCA. Dilated LMCA No perivascular cuffing.</p>	<p>LMCA: 2.4mm (Z score + 1.8) LAD: 2.29 mm (Z score +2.77) RCA: 2.03 mm (Z score + 1.55)</p> <p>Small aneurysmal dilatation of LAD. Normal caliber of LMCA & RCA.</p>	<p>LMCA 3.3-4mm:(Z score + 3.08-+4.83) LAD:2.75mm(Zscore+4.2) RCA:2.56mm(Zscore+2.7)</p> <p>Small aneurysmal dilatation of coronary artery (LMCA, LAD and RCA) seen. Irregular vascular wall of LMCA noticed.</p>

LMCA- Left main coronary artery, LAD- Left anterior descending Artery, LCX- Left circumflex artery, RCA- Right coronary artery.



Fig 1: Dilated Left main coronary artery and Left anterior descending artery. (Day 9 of illness)

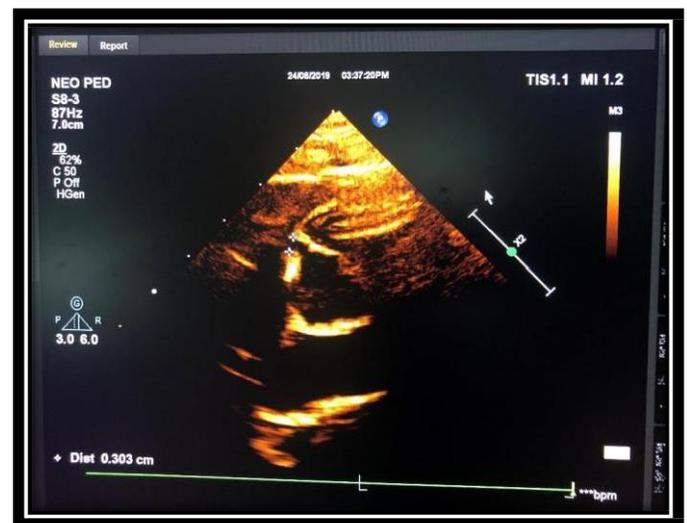


Fig 2: Dilated Right coronary artery. (Day 9 of illness)

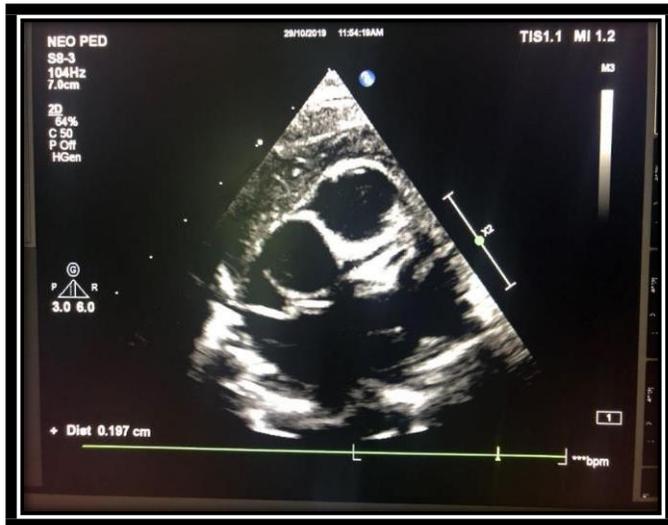


Fig 3: Normal left main coronary artery. (At 8th weeks of illness)



Fig 4: Normal Right coronary artery. (At 8th weeks of illness)

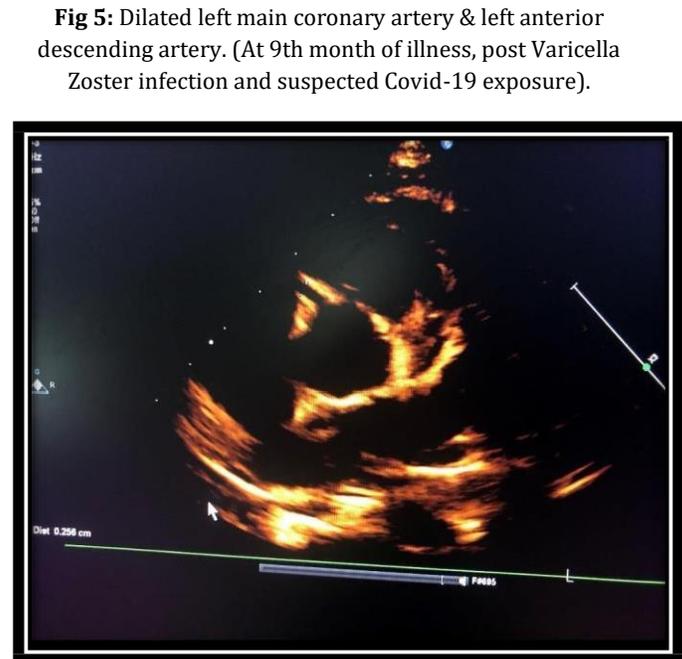


Fig 5: Dilated left main coronary artery & left anterior descending artery. (At 9th month of illness, post Varicella Zoster infection and suspected Covid-19 exposure).

Fig 6: Dilated right coronary artery. (At 9th month of illness, post Varicella Zoster infection and suspected Covid-19 exposure)

3. DISCUSSION

Kawasaki disease (KD) was first described in Japan in 1967 by Dr. Tomisaku Kawasaki. Dr. Kawasaki himself saw his first case in 1961 (1,2). Kawasaki disease was first described in his seminal Japanese series of 50 cases published in the “Japanese Journal of Allergy” (3) and subsequently in English in 1974 (2,4). Kawasaki disease is diagnosed by typical features of fever for at least 5 days with conjunctivitis, oral mucosal changes (eg, strawberry tongue, cracked lips), polymorphous rash, peripheral extremity swelling or peeling and cervical lymphadenopathy.

According to AHA statement (2017) incomplete (atypical) Kawasaki disease is strongly considered in infants, especially <6 months, where fever and irritability may be the only clinical manifestation (5). In this group, <50 % of patients meet the traditional criteria (6). Unfortunately, the infants with very few typical diagnostic criteria except prolonged fever with fussiness, are at high risk of developing coronary artery abnormalities.

Our case, the three-and-a-half-month-old male infant, had high fever for 5 days, irritability and had later developed red cracked lips, skin rashes. He had no strawberry tongue or congested eye or lymphadenopathy. His 2D-color Doppler echo suggested aneurysmal dilation of coronary arteries. The baby was diagnosed as atypical KD and managed with classical treatment and his coronaries became normal in caliber. He was on regular follow up in Paediatric and Paediatric Cardiology OPD which helped us to recognize his further coronary artery re-dilation. His history of severe attack of varicella zoster in

starting time of COVID-19 pandemic situation in Bangladesh pushed us to think in different way whether there is any association of this coronary artery changes with the infectious agents.

Kawasaki disease is a mysterious childhood acute vasculitis initiated by unidentified immunological triggers. It has been hypothesized that there is immune disequilibrium with abnormal and increased inflammatory and allergic manifestation (7,8). Over 4 decades of investigations, the etiology of Kawasaki disease is still unknown. However, surprisingly evidence for some genetic component to Kawasaki disease susceptibility includes infectious trigger which is suggested by the epidemiologic characteristic of this syndrome, especially its tendency to target the children under 5 years, clustering of patients in space, time and predilection for winter and spring months (9).

Because the winter and spring seasons are the time when respiratory viruses abound, it is common for children with KD to have concomitant infection with common respiratory viruses (9,10,11), even one line of investigation suggests infection with novel RNA virus that enters through upper respiratory tract (5). Intracytoplasmic inclusion bodies in bronchial epithelial cells and multiple other types throughout the body appear to contain RNA and could be linked to the KD. Possible association of Kawasaki disease with viral infection as with adenovirus, varicella zoster virus were reported earlier (12). Dao-Hsiung Lee et al focused on the possibility of varicella-zoster virus as one of the triggering agents of KD in genetically susceptible individuals. Their study described two sisters, soon after a primary infection by varicella-zoster virus, manifesting fever and mucocutaneous lesions compatible with the features of KD consecutively. Both siblings had mild dilation of coronary artery on echocardiography. The severe cardiac complication of Kawasaki disease may be prevented by early treatment if clinicians are alert to this possible association in children with chicken pox exhibiting unusual mucocutaneous lesions (12).

Kossiva L, et al also described a 35-day old baby with myocardial infarction with incomplete Kawasaki disease and chicken pox. Infants younger than 6 months with persistent fever and some of the criteria of Kawasaki disease should always raise suspicion for Kawasaki disease early to avoid delayed diagnosis with severe cardiac complications like myocardial infarction (13).

Turkey et al reported a baby 2-year-old girl who was diagnosed as typical Kawasaki disease during concomitant Epstein-Barr virus and varicella-zoster virus infections. But her echocardiogram revealed normal coronary vessels (14). Demet Torak, Özge Serçe described one case report with the review of the literature regarding strong suspicion of varicella zoster an etiological factor in Kawasaki disease (15). Kyun- Yil Lee, Ji-Whan Han et al described in their study that KD may be a

hyperimmune reaction of genetically susceptible children to variants of normal environmental flora (16). Mindy Cheng et al reported a case report of a 3 three years old Asian -American baby boy presented with KD who had a history of vaccine attenuated

Chickenpox one week prior to KD (17). Their observation was that varicella vaccine attenuated infection triggered the Kawasaki disease a week later.

Our baby was already diagnosed as incomplete Kawasaki disease and treated 6 months before the severe infection by varicella zoster and exposure to COVID-19. His coronary artery became normal in caliber at 8th week of illness. However, he had history of coronary artery dilation at 4th month of illness during an attack of lower respiratory tract infection (LRTI). He had the history of severe attack of chicken pox at 6th month of illness at 9 and half months of his age. During varicella zoster infection the baby had fever (103.0F -104.0 F) for 5 days with typical vesiculopustular rash all over body which had healed within few days. Baby did not have any lab investigations or follow up visit with Pediatric Cardiologist during the illness because of lockdown situation for COVID-19.

After 12 weeks of attack with Varicella Zoster during OPD visit clinically the baby had no signs of KD or MIS-C (Multisystem inflammatory syndrome in children) except pallor.

Bur surprisingly his echocardiography showed coronary arterial re-dilation. He had small aneurysmal dilation of coronary arteries (LMCA, LAD and RCA) with irregular vascular wall of LMCA (Table 1, Fig 5, Fig 6).

He had history of mild fever and his parents and other family members had signs and symptoms of COVID-19 after that OPD visit. Although their RT-PCR reports for COVID-19 were negative.

Retrospectively we are correlating the obvious re-dilation of coronary arteries with viral infections. We have a strong suspicion that there is possibility of varicella zoster virus or COVID-19 virus acting as triggering agent for re-dilation of coronary arteries of the baby who was diagnosed as atypical Kawasaki disease and treated with traditional medications 6 months before the exposure of viral infection. Now our baby is on low dose aspirin and on regular follow up in Paediatric and Paediatric Cardiology OPD.

Crystal Phend, senior editor, Med Page reported on May, 2020 of some missed children affected by COVID-19 with mild symptoms, thereafter their fever went away, and they were walking around with coronary artery aneurysm without their concern. These children were reported with coronary artery dilation after that low-lying inflammation and fever for covid-19 (18).

E Tsudal et al reported their study of 562 patients in "Dilated coronary arterial lesions in the late period after Kawasaki disease" that 17 new dilated or expanding lesions were found

in 15 patients (11 boys, 4 girls). The time of detection of new aneurysm after KD ranged from 1.9-19.2 years (median 11.4 years) and their diameters ranged from 2.0-6.5 mm (median 4.4mm).

Thirteen new aneurysms occurred in vessels in which previous aneurysms had regressed and all new aneurysms were associated with localized stenosis. They also described that usually, the diameter of persistent aneurysms may increase slightly because of somatic growth or they may decrease because of intimal thickening of vascular wall (19).

Proper and close follow up would ensure prevention of any sorts of coronary artery complications in KD exposed to further infectious agents.

4. CONCLUSION

Atypical Kawasaki disease is a rare form of acute vasculitis in infants, especially in those less than 6 months, where fever and irritability may be the only clinical manifestation. The consequences of disease process, coronary artery disease is significantly higher in this group which is proven by previous research. In Kawasaki disease, vasculitis is thought to be initiated by unidentified immunological triggers. Although the exact etiology of KD is unclear but association of some infectious agents like varicella zoster and COVID-19 are strongly suspected. Our baby is notable because he is on follow up for atypical Kawasaki disease and echo revealed his coronary artery re-dilation after varicella zoster infection in COVID-19 pandemic situation. It is a matter of concern about the future outcome of coronary artery changes associated with infectious agents. Therefore, regular follow up of KD patients is necessary to prevent any cardiac complications.

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