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A Case Study

Kawasaki disease with COVID-19 positive children, evaluation of multi-system inflammatory syndrome in children (MIS-C): A Case Study

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ABSTRACT

K*awasaki disease is a rare Paediatric inflammatory condition that results in swelling throughout the body's medium sized vessels, including coronary arteries. It also affects skin, mucus membranes and lymph nodes. Early symptoms include fever for 5 days, conjunctivitis, oral mucosal changes, polymorphous rash, peripheral extremity swelling or peeling of skin and cervical lymphadenopathy as the disease progresses gastrointestinal symptoms and joint pain may develop.*
Even though the relationship of Kawasaki disease to COVID-19 is not yet defined, a new serious COVID-19 cardiovascular presentation emerges in the form of Paediatric multisystem inflammatory syndrome, which includes feature similar to Kawasaki disease. But this COVID positive child having Kawasaki disease presented with more acute respiratory and cardiac failure than usual Kawasaki diseases. Rapid recovery with the use of immune globulin and steroids were observed. Early diagnosis and management appear to lead to favorable outcome using classical therapies. Delaying of proper diagnosis and management can lead to multisystem hyper-inflammatory syndrome or Kawasaki disease shock syndrome.

Keywords: *Kawasaki disease, inflammatory syndrome, COVID -19, lymphadenopathy.*

CASE SUMMARY:

On 27th May, 2 years old baby weighing 12 kg, height 90 cm was admitted in our hospital with the complaints of fever for 8 days 101-105 *F followed by rash, conjunctival congestion with cracked lips, severe myalgia, respiratory distress and loose motion for last 5 days which was gradually increasing in frequency.

Baby was at home and treated with only suppository paracetamol. Because the parents were afraid to come to the hospital because of lockdown situation for Corona virus.

The baby developed 105 * F temperature with frothy secretion from mouth on 27th May, hence immediately they rushed to this hospital with the baby having severe respiratory distress and anuria for few hours.

On admission, baby was febrile (103*F), dyspneic (RR :40/min), tachycardia (145/min),BP was bellow 50th centile (70/40 mmHg, 50th centile :85/55mmHg), SPO2 93% in room air ,mild conjunctivitis, cracked lips, blotchy erythematous rashes on lower limbs with pedal edema, mild ascites with severe irritability with some dehydration. His weight and height were 12 kg and 90 cm respectively.

On admission his lab investigations showed low HB (9.9 gm/dl>9.2gm/dl), microcytic hypochromic anemia, low albumin (2 gm/dl>1.9 gm/dl), neutrophilic leukocytosis with lymphopenia (N:72 %,L :24.40 %, TLC 13.13 x 10^9/L), gradual thrombocytosis (159x10^9/L on d 8th day,659x10^9/L on 14th day,801 x 10^ 9/L on d 17th of fever). He had electrolytes imbalance, s. Na+ 135 mmol/L (n : 135-145 m mol/l), s. K+ 2.1 m mol/l (n : 3.5-5 mmol/l),Cl- 104 mmol/L (n:98-108 m mol/L), HCO3- 22 mmol/L (n: 24-32 mmol/L), high ferritin (859 ng/ml; normal : 12-140 ng/ml), high CRP

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(130 mg/dl, normal ,0.33mg/dl), high D-dimer (>4400 µg/L, n :<500 µg/L), high Troponin I (38ng/L, n :<34.2 ng/L), normal S. creatinine (0.52 mg/dl n:0.50-1.1 mg/dl), normal S. SGPT (27 IU/L ,n: 14-63 IU/L), normal S. (LDH :238U/L, n:<250U/L).

The baby's RT-PCR COVID test report was positive one days after admission in hospital.

Widal test : negative, Dengue IgG and IgM were also negative.

Chest x-ray revealed, huge patchy opacity with nodular ground glass opacifications on both lung fields with cardiomegaly.

2D and color Doppler Echocardiogram revealed, coronary artery aneurysm (CAA of LMCA, LAD and RCA) with dilated all cardiac chambers. Severe pulmonary hypertension. Fair biventricular function (LV EF 53%). Trace pericardial effusion. No pleural effusion.

Dilated Left main coronary artery 3.87mm, Z score + 4.13 (n:1.63-2.91mm), Left anterior descending artery 2.48mm, Z score + 2.67 (n:1.37-2.22mm), Right coronary artery 2.83mm, Z score +3.20,(n : 1.24-2.32mm). Dilated all cardiac chambers with severe tricuspid regurgitation and severe pulmonary regurgitation with severe pulmonary hypertension. Fair biventricular function (left ventricular ejection fraction was 53%) was noted in echocardiogram.

We started oxygen therapy first 3- Li/min which increases up to 7-8 lit/min in MICU. Baby got intravenous cholera saline and thereafter o.45 % NaCl with 5% Dextrose saline for correction of fluid and electrolytes imbalance and after correction of dehydration he was on 20-30 % restriction of fluid. He was also on injection Meropenem and inj. Vancomycin. We immediately started IVIg @ 2 gm/kg/dose over 24 hours, IV Methyl prednisolone 1 mg/kg/dose 12 hourly, inf. Dobutamine, inf. Albumin slowly with inj. Lasix support. Within 38 hours of treatment with IVIg and methyl prednisolone and high dose tab Aspirin (tab Aspirin 50 mg/kg/day, 6 hourly, baby became afebrile. We also started inj Lasix, tab ACEI (tab. Enalapril) and tab Digoxin judiciously after correction of fluid and electrolytes imbalance. His SPO2 was 97-98 % with minimal oxygen support within 2 days of treatment. We reduced the dose of tab Aspirin after the child had been afebrile for 72 hours. Continuous monitoring of HR, BP and SPO2, RR, intake and output chart were maintaining in MICU. Repeat chest x-ray and s. electrolytes were done to guide the management. Gradually baby's, loose motion, rashes and cracked lips, ascites and edema also subsided. Baby was also on vit D, Vit C, zinc, vit B-complex with protein rich food.

On 4th to 5th day of treatment, we observed cardiac improvement with stability of BP and reducing cardiac size, although x-ray revealed few patchy opacities on both lungs. We could shift the baby on 6th day from MICU to cabin with continuous monitoring. By 10th day of admission baby's all inflammatory markers were within normal range. Follow up echo revealed dilated coronary arteries (reducing in calibers on admission echo) reducing sizes of cardiac chambers with mild pulmonary hypertension and good biventricular function. No pericardial or pleural effusion were noticed. On 14th day baby got discharged with advice. On discharge, Baby was stable and was on low dose tab. Aspirin, syp Frusemide, tab. Enalapril, tab Digoxin, low dose tab Prednisolone, H2 blocker, vitamins and minerals and iron to be started after one week of discharge.

Further follow up will be done in OPD Paediatric Cardiology and Paediatrics after one week.

Well organized teamwork of Paediatric Cardiologist, Paediatricians and Intensivists are praiseworthy in this current situation to handle the challenge in health service.

DISCUSSION

Kawasaki disease (KD) is an acute medium vessel vasculitis of still unclear an etiology which typically afflicts children under 5 years. (1,2) The peak onset is between 18 and 24 months, with an ethnic predilection for Asian populations. It is associated with long-term coronary artery abnormalities, such as coronary artery aneurysm (CAA) and ectasia in up to 15-25% of untreated children. (1,2) It has been postulated that there is immune disequilibrium with abnormal and increased inflammatory and allergic manifestations. (3,4)

A new, serious COVID-19 Cardiovascular presentation emerged in late April and early May 2020 in the form of pediatric multi-system inflammatory syndrome, which includes features similar to Kawasaki disease. It was first reported in the United Kingdom and then cases began to appear in New York City and elsewhere in the United States. (5)

The U.S Centers for Disease Control (CDC) first issued a health advisory statement on the new COVID-19 (SARS-CoV-2) presentation May 14 (5).The CDC is calling the new presentation in kids **multi-system inflammatory syndrome in children (MIS-C).** The CDC called for health care providers report any patient who meets the case definition to local, state and territorial health departments so data can be collected to enhance knowledge of risk factors, pathogenesis, clinical course and treatment of this syndrome.

On April 26, 2020, clinicians in UK recognized increased reports of previously healthy children presenting with severe inflammatory syndrome with Kawasaki disease-like features. (6)

2 years old baby was admitted in our hospital with the complaints of fever for 8 days 101-105 *F followed by rash, conjunctival congestion with cracked lip, severe myalgia, respiratory distress and loose motion for last 5 days which was gradually increasing in frequency.

One day after admission baby was reported as Covid-19 in our hospital. The baby was diagnosed clinically as classic Kawasaki disease with Covid-19-severe Pneumonia with heart failure. The team of Paediatric Cardiologist, Paediatrician and Medical ICU were highly concerned about baby's multisystem involvement and rapid management started in MICU. He was evaluated by laboratory investigations, chest x-ray and 2D-color doppler echocardiogram study.

The first known published case of classic Kawasaki disease associated with Covid-19 was reported in *Hospital Pediatrics* in late April. A 6- month-old seen in Sandford, California, screened positive for COVID-19 after presenting with fever, blotchy rash, and minimal respiratory symptoms. She had initially been sent home from urgent care. (7)

Dr.Veena Goel Jones, an Assistant Professor at Stanford School of Medicine, and her team tested the baby girl for COVID-19 mainly out of hospital protocol, l-"not necessarily because we felt very strongly like she must have the virus," Jones said. But the girl did test positive for COVID-19, despite never developing a cough and having only minor congestion. Struck by the possible combination of COVID-19 and Kawasaki, Jones and her colleagues published a case report in Hospital Paediatrics in April. (7)

Crystal Phend Senior Editor Med Page Today reported on 8th May that week, the New York City Health Department announced finding 15 cases between April 29 and May 3. The "full spectrum of disease is not yet known," it noted. "Only severe cases may have been recognized at this time."

The New York State Department of Health expanded that to 64 cases statewide and issued an advisory on what is being called "Pediatric Multi-System Inflammatory Syndrome Temporarily Associated with COVID-19." (7)

Crystal Phend reported that two children died of in New York by 8th May with the syndrome, a 5-year old boy and a 7-year-old boy.

Deepika Thaker, MD, medical director for the cardiac inpatient unit at Nemours Children's Health System in Wilmington, Delaware noted "What's really unusual about this particular presentation is that they are older". Kawasaki disease typically affects children age 5 years and younger, but many of these cases reported have been in teens, she pointed out. (7)

Although our 2 years old boy had the sign and symptoms of Kawasaki disease, we send the RT-PCR for COVID test because he was highly suspected case of COVID-19 according to our hospital protocol in the current situation. Moreover, the baby was dyspneic, desaturated (SPO2 93% in R/A) with loose stool and had typical radiological findings of COVID-19.

Italy, Spain, and the U.K. had noted an uptick in Kawasaki-like disease among children coincident with the COVID-19 outbreaks there (7).

On admission, our baby was febrile (102*F), dyspneic (RR :40/min), tachycardia (145/min),BP was below 50th centile (70/40 mmHg, 50th centile :85/55mmHg), SPO2 93% in room air, mild conjunctivitis, cracked lips, blotchy erythematous rashes on lower limbs with pedal edema, mild ascites and severe irritability with some dehydration.

The baby had all four criteria of typical Kawasaki disease although his cervical lymph nodes were not significantly enlarged.

Crystal Phend reported that British health authorities warned about a small rise in children with severe COVID-19 and features consistent with toxic shock syndrome and atypical Kawasaki disease." Abdominal pain and gastrointestinal symptoms have been a common feature as has cardiac inflammation." (7)

Our baby also had obvious gastrointestinal symptoms like uncontrolled loose motion leading to some dehydration, on his admission.

Royal College of Paediatrics announced in a statement most kids are asymptomatic or exhibit mild symptoms when infected with covid-19. This rare syndrome attacking kids shares common features with other pediatric inflammatory condition including Kawasaki disease, staphylococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndromes. It can also present unusual abdominal symptoms with excessive inflammatory markers. (6)

The U.K. Pediatric Intensive Care Society also issued a statement April 27 about increasing numbers of reported cases of novel presentation of MIS-C and COVID-19 infection. (8)

A study in London published May 7 highlights what researchers called an" unprecedented cluster" of 8 children with MIC-C during a period of 10 days in mid-April. (9) The study said typically London sees one or two children per week with hyper-inflammatory shock, similar to atypical Kawasaki disease shock syndrome or toxic shock syndrome. This case cluster formed the basis of the U.K. national alert.

Michael Levin, MBF, PhD, FRCPCH, FMedSci, Professor of Paediatrics and international child health Imperial College London explained that they looked 37 patients in London and other cities in southern England. The reviews varied, but most had prolonged fever, sore throat, headache and particularly with abdominal pain (in 57 percent of patients) and vomiting. Some also had rash and conjunctivitis. Levin said the children progressed rapidly to shock and organ dysfunction. All of the patients had similar lab results with elevated C-reactive protein, neutrophils, profoundly lower lymphocytes and

elevated D-dimers , and some had elevated troponin and brain natriuretic peptide (BNP) levels, suggesting cardiac injury, he explained.

About 38 percent of patients had acute kidney injury with raised creatinine levels, but only one patient required renal replacement therapy (RRT).

"Unlike adults with COVID, only a third had respiratory symptoms," Levin said.

Shock occurred in 75 percent of the children and 51 percent had clear myocardial impairment. (7)

Our baby had fever with more cardiac, respiratory and gastrointestinal signs and symptoms. He had myocarditis with heart failure with tachycardia, tachypnea, desaturation, low BP, cold periphery with pedal edema, mild ascites and some dehydration, rash, conjunctivitis, myalgia with suggestive laboratory, radiological and echocardiographic findings. The baby had started COVID-19 mediated cytokine storm with elevated C-reactive protein, neutrophils, profoundly lower lymphocytes, elevated D-dimers, elevated ferritin, elevated troponin-I, on x-ray ground glass appearance of both lung fields with dilated coronary arteries by z-score, cardiomegaly and fair left ventricular function on echocardiogram. The baby had clear acute myocardial impairment, pulmonary interstitial inflammation, and also gastrointestinal impairment with myalgia. His serum creatinine was normal. The baby had thrombocytosis which reached to the peak at 3rd week of illness.

Thrombocytosis is a characteristic feature of KD but generally does not occur until the second week. Peaking in the 3rd week (mean 7,00000 per mm3) and normalizing by 4-6 weeks after onset in most cases according to the "Scientific Statement for Health Professionals from the American Heart Association". (10)

A study in Circulation published online May 17 reports a series of pediatric patients with acute heart failure potentially associated with SARS-CoV-2 infection and MIS-C. The study looked at 35 paediatric patients from France and Switzerland over a two-month period who had been exposed to COVID-19 and had an emerging condition with features overlapping toxic shock syndrome. The patients ages 2-16 (11).

MIS-C shares similarities with atypical Kawasaki disease, but prominent clinical signs are largely different. Myocardial involvement with acute heart failure is likely due to myocardial stunning or edema rather than inflammatory myocardial damage.

Our baby's x-ray showed bilateral patchy opacity with ground glass appearance on both lung fields with cardiomegaly. We could not do chest CT.

Radiological studies of MIS-C patients in UK had mixed results. Levin said some of the of the chest X-rays showed smaller bilateral pleural effusions, patchy consolidation, focal consolidation or a partial collapse of entire lungs (atelectasis). Chest CT included the same findings as on chest x-rays, but all included some areas of nodular ground glass opacifications. (7)

On admission our baby's 2D and color doppler echo cardiogram revealed left main coronary artery dilation or aneurysm, dilation of left anterior descending artery and right coronary artery, dilated all cardiac chambers with severe pulmonary hypertension. Fair left ventricular function (left ventricular ejection fraction was 53%). Trace pericardial effusion was noted. The baby did not have any pleural effusion.

"The cardiac findings were striking, with 8 out of 19 patients who had echocardiograms having evidence of impaired left ventricular function. Coronary artery dilation or aneurysms were present in 5 of the 19 patients. One patient had a giant left coronary artery aneurysm," said Levin regarding the studies of MIS-C patients in UK. (7)

Crystal Phend also noted in open questions that despite the chronological connection between COVID-19 and Kawasaki disease like cases " at present, there is no definitive evidence that COVID-19 induced shock is related to Kawasaki disease," cautioned Anne Rowley, MD, an infectious diseases specialist studying Kawasaki disease at Northwestern University in Chicago (7).

"Some clinical symptoms of both these disorders—Kawasaki disease and COVID-19—such as fever, rash, eye redness (conjunctival injection) are present in many childhood illnesses. However, the laboratory testing of these two groups of children seems quite different, and in particular, the children with COVID-19 infection have inflammation of the heart muscle rather than the characteristic swelling of the coronary arteries that is observed with Kawasaki disease."(7).

Our COVID-19 positive child presented with Kawasaki disease with heart failure had typical features of myocardial inflammation and coronary artery dilation.

MIS-C shares similarities with atypical Kawasaki disease, but prominent clinical signs are largely different. Myocardial involvement with acute heart failure is likely due to myocardial stunning or edema rather than inflammatory myocardial damage (7,11).

To treat our baby, In MICU, we immediately started intravenous immune globulin (IVIg), IV methyl prednisolone and high dose tab Aspirin to control the storm of inflammation along with ionotropic agent, preload and afterload reducing agents for heart failure management. The baby also got other supportive management for correction of fluid and electrolytes imbalance, hypoalbuminemia, anemia and micronutrients supplementation subsequently.

A study in Circulation published online May 17 reports a series of Paediatric patients with acute heart failure potentially associated with SARS-CoV-2 infection and MIS-C. The study looked at 35 paedaitric patients from France and Switzerland over two-month period who had been exposed to COVID-19 and had an emerging condition with the features overlapping toxic shock syndrome. (11) All patients presented with fever, unusual lethargy (asthenia) lasting approximately two days, and 83% of patients(n=29) presented with gastrointestinal symptoms. Left ventricular systolic dysfunction was present in all patients in association with low systolic blood pressure. Almost all patients required respiratory assistance (n=33). Ten patients treated with extracorporeal membrane oxygenation (ECMO) for 3-6 days were successfully weaned.

The majority of patients received intravenous immune globulin treatment (n=25), and 12 patients were treated with intravenous steroids. Three children were treated with an interleukin 1 receptor antagonist due to persistent severe inflammatory state. There were 23 patients treated with a therapeutic dose of heparin. No deaths were observed. (11)

"The majority of patients recovered within a few days of following intravenous immune globulin with adjunctive steroid therapy used in one third. Treatment with immune globulin appears to be associated with recovery of left ventricular systolic function," researchers reported (11).

On May 14 to include information about a new study from Italy published in the journal The Lancet **stated that** Children diagnosed as Kawasaki disease are given a high dose of aspirin to prevent blood clots and turn down the rampant inflammation in the body. They also receive immunosuppressants, to tamp down the inflammation even further, and intravenous immunoglobulin (IVIG), a cocktail of antibodies collected from donors and used to treat a wide variety of conditions. IVIG may help to clear the child's underlying infection, as physicians don't know which pathogen might be to blame, but the therapy also serves as an inflammatory treatment (12).

According to Circulation published online May 17, whereas the initial presentation may be severe with some patients requiring circulatory and respiratory mechanical assistance, rapid recovery with the use of immune globulin and steroids is currently observed. (11,13)

Demetre C. Dakalakis,MD, MPH, deputy commissioner, Division of Disease Control, New York City Health Department said pediatrician to report and refer to pediatric infectious disease, rheumatologist and or critical care any patients who seem to have MIS-C having criteria as younger than age 21 with persistent fever (four or more days), and either incomplete Kawasaki disease, typical Kawasaki disease, and / toxic shock syndrome-like presentation; and no alternative etiology identified that explains clinical presentation, including those regardless of SARS-CoV-2 PCR test result. He also said that early diagnosis and treatment of patients meeting full or partial criteria for Kawasaki disease is critical to preventing end - organ damage and other long-term complications.(13)

He reported patients meeting criteria for Kawasaki disease should be treated with intravenous immunoglobulin and aspirin.(13)

Above all "early diagnosis and management appear to lead to favorable outcome using classical therapies". (11)

There is big discussion about "Kawasaki disease from COVID-19 in kids: How common?" by Crystal Phend.(7) Kawasaki disease has long been believed to be an immune response triggered by infection, but its etiology is still not clear and not all viruses predispose to Kawasaki disease, noted by Deepika Thaker, MD, medical director for the cardiac inpatient unit at Nemours Children's Health System in Wilmington, Delware.(7)

And despite the chronological connection between COVID-19 and these cases, "at present, there is no definitive evidence that COVID-19 induced shock is related to Kawasaki disease," cautioned Anne Rowley, MD,an infectious diseases specialist studying Kawasaki disease at Northwestern University in Chicago.(7)

To better understand what's going on, the AHA council called for enrolling affected children in COVID-19 studies that obtain serum or plasma samples(7).

Michael Portman, MD, of Seattle Children's Hospital and a member of the American College of Cardiology committee that set benchmarks for care of Kawasaki disease that even under normal circumstances, it can be difficult to sort out Kawasaki Disease from other childhood diseases that cause similar symptoms given that there are no definitive blood tests.

Portman's group is looking to track Kawasaki disease patients to see if they were exposed to COVID-19, to look for genetic susceptibility, and to see what happens to their immunity to the corona virus. (7)

"What is the relationship between Kawasaki disease and COVID-19?", that is still under investigation.

Dr. R. Mathew, jones' colleague and a Paediatric infectious disease specialist at Stanford's Lucile Packard Children's Hospital, said" the general thought is this is a post-infectious trigger causing the immune system to hyper-react." Infections of any kind can cause inflammation in the body. So, it's possible that SARS-CoV-2, the virus that causes COVID-19, is kickstarting inflammatory responses in small numbers of children, she said.(7)

But as our child was diagnosed with the typical features of Kawasaki disease with COVID-19 we succeeded in treating the baby accordingly without any delay. Reducing inflammation or "putting out the fire" is key in the management of KD. This is achieved with the use of pharmacological "fire extinguishers", for which the efficacy of IVIg has been well described by Newburger and colleagues in 1986. (14)

CONCLUSION

Kawasaki disease with COVID -19 presented as multi-system inflammatory syndrome in children (MIS-C) should be picked up without any delay. It needs urgent evaluation clinically and also by lab investigations along with radiological support and echocardiogram. Early diagnosis and management appear to lead to rapid recovery and favorable outcome using cocktail of classical therapies. However, we need more data to lift the veil of the mystery between MIS-(C) and the relationship of Kawasaki disease with COVID-19, we should be highly concerned about early diagnosis and management of every different cases of Kawasaki disease with COVID-19 children with various presentation.

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13. Kawasaki-like Inflammatory Disease Affects Children With COVID-19

What we know about multi-system inflammatory syndrome in children (MIS-C)

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