

## Case Series

# COVID-19 and multi-system inflammatory syndrome in children: keep a high index of suspicion in all inflammatory disorders

Fatima Afreen Ahmad<sup>1</sup>, Munesh Tomar<sup>1\*</sup>, Umang Arora<sup>2</sup>

<sup>1</sup>Department of Pediatrics, LLRM Medical College, Meerut, Uttar Pradesh, India

<sup>2</sup>Department of Pediatrics, Hope Hospital, Meerut, Uttar Pradesh, India

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**\*Correspondence:**

Dr. Munesh Tomar,

E-mail: [drmunesh tomar@gmail.com](mailto:drmunesh tomar@gmail.com)

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### ABSTRACT

COVID-19 pandemic put many challenges for the health care professionals and one of that is the multi-system inflammatory syndrome in children (MIS-C). This syndrome shares its features with other inflammatory conditions including Kawasaki disease and toxic shock syndrome. We are reporting 4 cases from a tertiary care center in COVID-19 hotspot area in the state of Uttar Pradesh who presented with multiple organ system involvement.

**Keywords:** COVID-19, MIS-C, Kawasaki disease, Transverse myelitis, Intravenous immunoglobulins

### INTRODUCTION

As the global pandemic of COVID-19 took over, it was seen that children were less affected than adults, and had milder clinical course when affected. However, the multi-system inflammatory syndrome in children (MIS-C) has emerged as a recent challenge for pediatricians all over the world due to later manifestation in course of SARS CoV-2 infection and atypical clinical presentations in children.<sup>1</sup>

Kawasaki disease is an acute vasculitis involving medium sized vessels. The exact etiology is unknown but some infectious trigger is implicated. MIS-C shares common patho-physiology with Kawasaki disease. Its actual incidence is unknown. The clinical spectrum includes Kawasaki disease, atypical Kawasaki disease, and shock syndromes.

Despite the differences in clinical spectrum most patients respond quickly with appropriate therapy with intravenous immuno-globulins, steroid and supportive care.

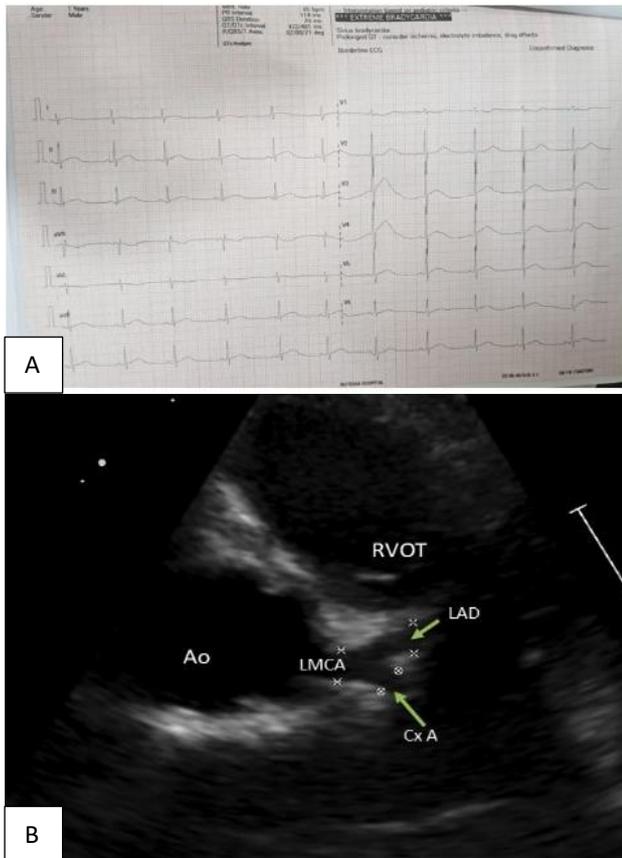
We are reporting 4 cases from a tertiary care center in COVID-19 hotspot area in the state of Uttar Pradesh who presented with multiple organ system involvement. Three of the four cases recovered and discharged while one left against medical advice.

### CASE SERIES

#### Case 1

A 14-month-old male, weighing 10 kg, presented in pediatric emergency with shock and respiratory failure. Child was immediately intubated and was put on ventilatory support. He was started on inotropic agents (dobutamine and dopamine intravenous infusion), empirically broad-spectrum antibiotics (injection ceftriaxone and injection amikacin) and intravenous fluid. There was history of high-grade fever, cough and respiratory distress for 3 days. On examination, child was febrile (temperature 103F), anemic, cold periphery with feeble peripheral pulses. He was having relative bradycardia (heart rate 80/minute, regular). Per abdomen examination revealed soft abdomen, normal bowel sounds, liver enlargement (3 cm below costal margin) but

no splenomegaly. On chest auscultation there were bilateral crepitations. Arterial blood gas (ABG) revealed severe respiratory acidosis with type 2 respiratory failure. Chest X-ray frontal view showed bilateral upper and middle zone haziness with prominent broncho-vascular markings and no cardiomegaly. Twelve lead ECG showed bradycardia (heart rate 75/minutes) with 1:1 atrioventricular conduction, normal QRS axis and normal intervals. To note 'P' wave is of small amplitude, not like a normal wave suggestive of ectopic origin of atrial impulse in acute inflammatory stage (Figure 1A).



**Figure 1: (A) Twelve lead ECG of patient 1 showing bradycardia with 1:1 atrioventricular conduction, normal QRS axis and duration, normal corrected QT interval. To note 'P' wave is of small amplitude, not like a normal wave suggestive of ectopic origin of atrial impulse in acute inflammatory stage. (B) Two-dimensional echocardiography from parasternal short axis view showing dilated coronaries. Ao-aorta, RVOT-right ventricular outflow tract, LMCA-left main coronary artery, Cx A-circumflex artery, LAD - left anterior descending artery, RCA-right coronary artery.**

Laboratory tests revealed low Hb, high total leucocyte counts (TLC) with lymphocytosis, normal platelets, high C-reactive protein (CRP), high ESR. D-dimer was raised with normal serum ferritin levels (116.5 mg/dl). SARS CoV-2 was not detected by RT-PCR in nasopharyngeal

and oropharyngeal swab. However, COVID-19 IgG antibody was highly positive.

Echocardiography was done with Phillips's affinity 50 with the use of broad band transducers and findings included left main coronary (LMC) and left anterior descending artery (LAD) dilatation, normal circumflex artery (Cx A) and right coronary artery (RCA), no structural heart defect and mild pulmonary arterial hypertension (mild TR with pressure gradient 34 mmHg) (Figure 1B). There was mild biventricular dysfunction but no wall motion abnormality. The patient was diagnosed with post COVID MISC, Kawasaki disease with bilateral pneumonia. Child was treated on the line of Kawasaki disease with intravenous Immunoglobulins (IVIG) at 2 g/kg over 24 hours, high dose Aspirin (50 mg/kg in three divided doses) and subcutaneous low molecular weight heparin (LMWH) for 5 days. Packed red blood cell (PRBC) transfusion was given in view of low Hb. Broad-spectrum intravenous antibiotics were given for 5 days. Blood culture was sterile. Patient was extubated after 3 days of mechanical ventilation and was kept on moist oxygen by nasal prongs for 3 more days.

Repeat hemogram after 6 days showed normal Hb, TLC and differential counts but high platelets. CRP and D-dimer showed decreasing trend. Aspirin was changed to antiplatelet dose (3-5 mg/kg once daily) after 48 hours of afebrile period and discharged on oral aspirin after 9 days of hospital stay.

### Case 2

A 7-year-old female presented in emergency with weakness of both lower limbs for one week and loss of bladder bowel control for 5 days. It started manifesting as difficulty in walking and now unable to sit without support. There was no history of sore throat or fever. She had history of diarrhea 15 days ago lasting for 3 days which was treated by the local physician. On examination, an average built child (weight 20 kg), afebrile, anemic, but no icterus or cyanosis. Her vitals were stable (HR 98/minute, RR 20/minute regular, BP 100/60 mmHg). Neurological examination revealed spinal tenderness without gibbus, kyphosis or surgical scar. Power was grade 1 in both lower limbs and so coordination could not be tested. There were no involuntary movements. No sensation was present below umbilicus, deep tendon reflexes were absent in both lower limbs and planter was bilateral mute. Upper limb sensory and motor system was intact. All cranial nerves were intact. Bladder and bowel both were involved with unable to pass urine and stool voluntarily. On laboratory examination, acute phase reactants (ESR, CRP, serum ferritin), d-dimer were elevated while hemogram revealed borderline low hemoglobin, normal total leucocyte counts and differential leucocyte count and normal platelet count, normal liver and renal function tests. RTPCR for SARS CoV-2 on nasopharyngeal swab sample was negative but IgG antibody for SARS CoV 2 was high.

Patient was diagnosed with SARS CoV-2 induced acute transverse myelitis, and was started on high dose intravenous methyl-prednisolone (30 mg/kg/day once daily for 5 days), LMWH and supportive care. She was planned for MRI spine but parents took the child Leave against medical advice.

**Case 3**

A 5-year-old male presented with high grade continuous fever without chills and rigor, maculopapular erythema (on day 2 of fever), non-purulent bilateral conjunctival injection and strawberry tongue. On examination, he was an average built child and was in hemodynamically stable stage. He was febrile, cervical lymph nodes were enlarged (multiple both sided, 8-15 mm non-matted). There were ophthalmic and oral cavity changes. A clinical suspicion of Kawasaki disease was made and evaluation was started on that line. His laboratory findings included mild anemia, raised total leucocyte count, normal platelet counts, and high levels of acute phase reactants. Covid RTPCR was negative while serological testing for IgG antibodies for SARS CoV-2 was positive. CXR frontal view did not reveal any abnormality. On twelve lead ECG there was sinus tachycardia with normal intervals and complexes. Echocardiography done with Phillips Affinity 50 showed dilated left main and LAD, normal RCA and Cx A, mild left ventricular dysfunction and small pericardial effusion (Figure 2 A and B). Pulmonary artery pressures were mildly elevated. Patient was diagnosed with MIS-C post COVID 19 infection and was managed with Intravenous Immunoglobulins (IVIG) at 2 gm/kg/day along with subcutaneous LMWH, high dose aspirin till 48 hours of afebrile period. Repeat hemogram showed high platelet counts. Patient was discharged after 5 days of hospital stay on Ecosprin in antiplatelet dose. Follow up echocardiography done after 1 weeks showed persistence of coronary changes as in previous echo, normal ventricular function, normal PA pressure and no pericardial effusion.

Echocardiography at 4 weeks post illness showed normal findings. Ecosprin in antiplatelet dose was given for total duration of 8 weeks.

**Case 4**

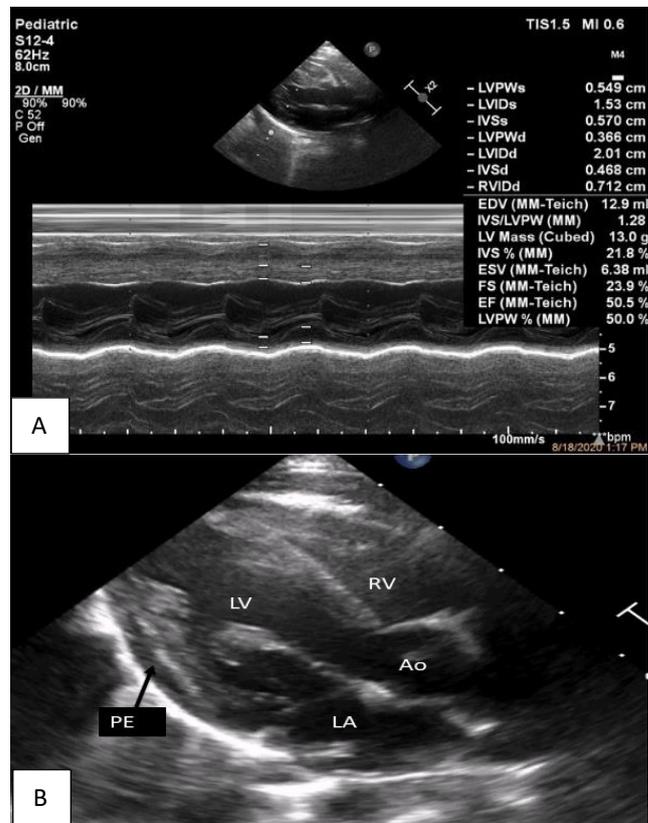
A 21-month-old boy, known case of trisomy 21, came to emergency with complains of high-grade fever, maculopapular erythematous rash all over body along with strawberry tongue and conjunctival injection for 2 days. On general physical examination, child was very irritable, febrile (temperature 104-degree F), there was tachycardia (Heart rate 150/min), tachypnea (respiratory rate 50/min) and SPO2 was 94 % on room air. Chest X-ray frontal view showed bilateral lung infiltrates and no cardiomegaly. Hemogram showed anemia, low total leucocyte counts with normal platelet counts. CRP and D-Dimer were raised. To find out the cause of fever,

RTPCR for COVID-19 was also done which was negative. LFT, RFT along with urine routine examination were within normal limits. Blood culture was sterile. He was diagnosed with Kawasaki disease due to fever and accompanying findings like conjunctival injection, changes in lips and oral cavity and rash. IgG antibodies for SARS CoV-2 was done and it came out to be positive. Echocardiography showed normal coronaries, normal ventricular function, mild AR, mild pulmonary arterial hypertension and no pericardial effusion.

Patient was treated with high dose Intravenous Immunoglobulin, high dose aspirin, LMWH along with supportive care.

Echo was repeated after 4 days and revealed similar findings except for development of small pericardial effusion. Repeat hemogram showed decreasing level of ESR and CRP but rising platelets (5.8 lac/cumm on day 10 of illness and 7.6 lac/cumm on day 14 of illness). Once he remained afebrile for 48 hours, low dose aspirin was started and was continued for 8 weeks.

Clinical manifestations along with investigations at presentation and on 10<sup>th</sup> day of presentation of all 4 patients are shown in Table 1-3.



**Figure 2: Echocardiography of case 3 (A) M-mode showing mild LV dysfunction. (B) Parasternal long axis view on 2D showing small pericardial effusion (PE) posterior to LV. LV-left ventricle, RV-right ventricle, LA-left atrium, AO-aorta.**

**Table 1: Clinical presentation, investigation and treatment of MIS-C COVID-19 patients**

Age/sex	Presentation	CBC (Hb-gm/dl) (TLC-/cumm)	Platelets (/cumm)	D-dimer (n=<250 ng/ml)	CRP (n<5 mg/liter)	ESR (N<10 mm/hour by Westergreen method)	Covid RTPCR	Covid IgG	Cardiac involvement	Treatment
14 months/M	Fever, shock, respiratory failure	Hb-7 TLC-14,000 P80L17	2,40,000	1241	24	25	Negative	80	Yes	IVIg, Aspirin, LMW heparin
7 year/F	Lower limb weakness, bowel-bladder incontinence	Hb-10 TLC-10,000 P70L27	2,80,000	521	22	28	Negative	20	No	Injection Methylpredni solone
5 year/M	fever, rash, vomiting	Hb-11 TLC-21000 P30L66	2,10,000	1927	94	30	Negative	22	Yes	IVIg, Aspirin, LMW heparin
21 months/M	Fever, rash, irritability, refusal to feed	Hb-8 TLC-4600 P63L30	3,50,000	2500	60	20	Negative	13.9	Yes	IVIg, Aspirin, LMW heparin

**Table 2: Echocardiographic findings of children with MIS-C COVID-19.**

Patient	Ventricular function	Valve Regurgitation (mmHg)	Coronaries Z score	Pulmonary artery pressure	Structural defect	Pericardial effusion
1	Mild dysfunction (EF 45%)	Mild TR (gradient 32), mild MR	Dilated LMCA + 2.7 Cx +1.9 LAD +2.56, RCA +2	Mild PAH PAP 32 +RAP	none	Mild
2	Normal (EF 60%)	Mild TR (gradient 20)	LMCA +1.5 Cx +1 LAD +1.2, RCA +1.1	Normal PAP 20+RAP	none	None
3	Mild dysfunction (EF 45-50%)	Mild TR (gradient 30)	Wall of coronaries bright LMCA +2 Cx +1.5 LAD +2.4, RCA +1.6	Mild PAH PAP 30+RAP	none	Mild
4	Normal (EF 60%)	Mild TR (gradient 32), mild AR	LMCA +1 Cx +1 LAD + 0.5, RCA +1.1	Mild PAH PAP 32+RAP	None	None

EF -ejection fraction, LMCA-left main coronary artery, LAD-left anterior descending artery, Cx A- circumflex artery, RCA-right coronary artery, PAP-pulmonary artery pressure, PAH-pulmonary arterial hypertension, RAP-right atrial pressure, TR-tricuspid regurgitation

**Table 3: Clinical and investigation findings on day 10 of illness.**

Clinical	CBC (Hb-gm/dl) (TLC-/cumm)	Platelets (/cumm)	D-dimer (ng/ml)	CRP	ESR	Cardiac involvement	Outcome
<b>Afebrile No distress</b>	Hb-11 TLC-10,300 P55 L40	7,60,000	normal	Negative	Normal	Ventricular function normal No effusion LMCA +2.2 Cx +1.5 LAD +2.5 RCA +1.8	Recovered
<b>NA</b>	NA	NA	NA	NA	NA	NA	Left against medical advice
<b>Afebrile No distress Skin peeling of hand</b>	Hb-11 TLC-7,300 P50 L46	6,50,000	Mildly elevated (550)	Negative	normal	EF normal No PE Brightening of wall of coronaries, diameters normal	Recovered
<b>Afebrile No distress skin peeling all over body</b>	Hb 10 TLC-12,430 P45 L50	5,80,000	Mildly elevate (650)	Negative	normal	EF normal No PE Normal Coronaries	Recovered

PE- pericardial effusion, LAMA- left against medical advice, NA- not available.

## DISCUSSION

SARS-CoV -2 related multisystem inflammatory syndrome has emerged as global concern in children. This syndrome shares its features with other inflammatory conditions including Kawasaki disease and toxic shock syndrome. The world is in dire need of uniform diagnostic criteria for MIS-C, so that the cases are not missed or diagnosed late. The first case of Covid related Kawasaki disease in India was reported by Rauf et al in April 2020.<sup>2</sup>

World health organization defines a case of pediatric MIS-C as children and adolescents 0-19 year of age with fever >3 days and 2 of the following<sup>3</sup>: 1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet). 2. Hypotension or shock. 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP). 4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers). 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, *Staphylococcal* or *Streptococcal* shock syndromes. Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19

Laboratory findings of MIS-C are suggestive of elevated inflammatory markers such as abnormal fibrinogen, absence of potential causative organisms (other than

SARS-CoV-2), high CRP, high D-dimers, high ferritin, hypo-albuminemia, lymphopenia, neutrophilia in most and normal neutrophils in some, coagulopathy, high IL-10, high IL-6, raised CK, raised LDH, raised triglycerides, raised troponin, thrombocytopenia, and transaminitis.<sup>4</sup>

The mechanisms which lead to MIS-C are not well understood. Certain triggers such as adenovirus and Coronaviruses have been identified which can lead to manifestations of a clinically apparent Kawasaki disease.<sup>5</sup> Another proposed mechanism is through triggering of a host inflammatory response either through formation of immune complexes or direct cellular activation.<sup>6</sup> There is a lag period of 2-4 weeks between COVID-19 infection and MIS-C, which further supports its immune response trigger etiology.

Most reported patients were negative for virus detection by RTPCR but positive for antibody against SARS-CoV-2. It implies that past asymptomatic infection with formation of antibodies could be the case as these patients resided mostly in COVID hotspot areas, or they were in contact with adults who were COVID-19 positive. It is possible that the disorder may involve acquired immunity similar to antibody enhancement of viral entry seen in dengue infection.<sup>7</sup>

Our case series comprised of 4 patients, 3 male and 1 female in age group 1-7 years, of MIS-C-COVID 19 infection with varied clinical presentation. None of the patient or family member had history of COVID-19 infection. SARS CoV-2 RTPCR was negative in all four

patients while all four children had high COVID-19 IgG. All children had elevated inflammatory markers. One patient presented in shock with respiratory failure, one with features of acute transverse myelitis while two had clinical features of Kawasaki disease. Three children were managed with high dose IVIG, high dose aspirin, low molecular weight heparin followed by antiplatelet dose of aspirin while one with ATM was treated with high dose methylprednisolone along with supportive care in all. Three patients recovered while one with ATM left against medical advice.

Acute flaccid palsy as a manifestation of COVID-19 infection in acute stage and also as a late manifestation.<sup>8-10</sup> Curtis et al reported 1<sup>st</sup> case of GBS with COVID-19 infection in a 8 year old child.<sup>8</sup> Review article by Rahimi highlighted possible link between GBS and COVID-19 infection from case reports around the world. The age of patients ranged from youngest 5 years to oldest 84-year-old.<sup>9</sup> Abdelhady et al reported 1<sup>st</sup> case of transverse myelitis in a 52-year-old male patient with acute COVID-19 infection.<sup>10</sup>

Our patient presented with flaccid symmetrical paralysis involving both lower limbs along with bladder and bowel involvement favoring clinical diagnosis of ATM though we could not further investigate her as the patient went LAMA.

High index of clinical suspicion should be maintained for early diagnosis of the disease as it requires aggressive treatment. The patients may require IVIG, pulse steroid therapy, low molecular weight heparin, aspirin along with supportive care. With coronary artery involvement, a long-term watch and continuation of antiplatelet is needed.

## CONCLUSION

We present patients in pediatric age group with post COVID-19 MISC with varied presentation that includes shock, atypical KD like disease and ATM. The general pediatrician needs to be aware of the atypical presentations so as to promptly suspect and start early and specific treatment.

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