Multisystem inflammatory syndrome in Indian adolescents associated with SARS-CoV-2 infection: a case report

Rahul D. Bhiwgade*, M. C. Nischitha, Bhushan Shahare and Shobhna Bitey

Abstract
Background: Adolescents with coronavirus disease 2019 (COVID-19) associated multisystem inflammatory syndrome (MIS) can present with shock and myocardial injury and mimic Kawasaki disease.

Case presentation: We describe 4 previously well adolescents (age 13–14 years), presenting with clinical features of MIS in children (MIS-C). All patients had nearly similar clinical presentation. Hematological investigations revealed elevated inflammatory markers, anemia, thrombocytopenia, and decreased neutrophil:lymphocyte ratio. All patients were negative on real-time polymerase chain reaction against severe acute respiratory syndrome coronavirus 2, but had elevated immunoglobulin G titers. Two patients had atypical Kawasaki disease. Three patients had severe disease with hypotensive shock and required intensive care with fluids and inotropes. Two patients required non-invasive respiratory support for dyspnea and one patient had biventricular dysfunction. All received empiric antibiotics, low-molecular weight heparin, steroids, and intravenous immunoglobulin. One patient succumbed, while others recovered well.

Conclusions: MIS-C may be a late presentation in adolescent with COVID-19. Individualized treatment with empiric antibiotics, immunomodulation, and thromboprophylaxis can result in significantly better outcome.

Keywords: Adolescents, COVID-19, Inflammatory markers, Multisystem inflammatory syndrome, SARS-CoV-2, Shock

Background
The coronavirus disease 2019 (COVID-19) pandemic has affected all the countries and age-groups alike. However, during initial part of pandemic, COVID-19 affected children with milder form of disease and had better clinical outcomes than adults [1, 2]. Subsequently, a rising number of previously well children with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induced hyperinflammatory states resembling macrophage activation syndrome or hemophagocytic lymphohistiocytosis, toxic shock syndrome (TSS), and Kawasaki disease (KD) were reported [3–5]. The Centers for Disease Control and Prevention termed this condition as multisystem inflammatory syndrome in children (MIS-C) [6].

Here, we describe 4 adolescents with COVID-19-associated MIS-C presenting to a tertiary care center in Central India between 17 May and 17 June 2021. They had distinct clinical features, but similar laboratory and radiological findings. Though, none of them were positive for SARS-CoV-2 nucleic acid on real-time polymerase chain reaction (RT-PCR), all of them had elevated immunoglobulin G (IgG) titers against SARS-CoV-2.

Case presentation
Four previously well adolescents, aged 13–14 years, including equal number of males and females, presented with the disease onset over the past 5–10 days. They had a variety of presenting symptoms, of which fever with rash were common. Though the rash involved overall...
abdomen in every patient, entire upper limb and hands were additionally affected in patient 1 and 2, respectively (Fig. 1). Patients 2 and 4 had conjunctival congestion (Fig. 2). None of the patients had comorbidities, except patient 2, who was a known case of type 1 diabetes mellitus and was receiving Huminsulin. Two months back, patient 1 had a history of contact with COVID-19 positive mother, while other patients had no history of contact with COVID-19 patients. All patients had visited private clinics and received antibiotics (azithromycin, doxycycline), hydroxychloroquine, and symptomatic treatment; however, there was no relief.

At presentation, patients 2 and 3 were stable, while patients 1 and 4 were critical due to the presence of hypovolemic shock with hypotension and dyspnea. All patients, except patient 3, had tachypnea. In all patients, electrocardiography suggested sinus tachycardia and non-specific findings. Two dimensional echocardiography (2D ECHO) was normal in patients 1 and 2, while there was mild global hypokinesia with mild tricuspid and mitral regurgitation in patient 3, and biventricular dysfunction (ejection fraction: 54%) with mild pericardial effusion in patient 4. X-ray chest in all patients revealed normal lung fields. High-resolution computed tomography (HRCT) of chest in patients 1 and 2 was unremarkable.

Laboratory investigations revealed negative fever profile for malaria, dengue, scrub typhus, and leptospira in all the patients. Similarly, urine and blood culture were negative, and liver and renal function tests were within normal limits. Of 4 patients, 3 had anemia. Among them, patient 2 had moderate anemia, and patients 3 and 4 had mild anemia. Leukocytosis was present in patients 1 and 2, with neutrophilia and lymphocytosis observed in every patient. All, except patient 2, had thrombocytopenia. International normalization ratio was raised in patients 1 and 2. All patients had negative RT-PCR for SARS-CoV-2. While the levels of COVID-19 IgG antibody, C-reactive protein, D-dimer, lactate dehydrogenase, erythrocyte sedimentation rate, and procalcitonin were raised. Given the complaint of joint pain and residence of patient 1 in an area endemic to sickle cell disease (SCD), solubility test was done and this led to an incidental diagnosis of AS pattern SCD.

As patients 1 and 4 had critical disease, they were managed in medicine intensive care unit (MICU), while
patient 2 and 3 were managed in wards. On day 2, patient 2 developed hypotensive shock and was shifted to MICU. The shock was managed with fluids and inotropes (Intravenous Noradrenaline (4–8 mg) infusion in 50 cc Normal Saline), and dyspnea was managed with 6–8 L O2 through bag-mask-ventilation, which improved arterial blood saturation. Additionally, in all the patients, MIS-C was suspected and intravenous immunoglobulin (IVIG, 2 mg/kg), Intravenous methylprednisolone (40 mg once daily), low molecular weight heparin (0.4 cc subcutaneously once daily), broad spectrum antibiotics (Intravenous Piperacillin-Tazobactam (4.5 gm thrice daily) in patient 1 and Ceftriaxone (1 gm twice daily) in all other patients), fluid therapy, and supportive care was initiated.

In patient 1, despite ongoing treatment, hypotension did not improve and patient developed cardiorespiratory arrest during intubation. Resuscitation was done but patient could not be revived back, while other patient responded well over next 48–72 h with gradual decrease in titters of inflammatory markers. In patient 4, bedside 2D ECHO suggested improved ventricular function. Patients were shifted out of MICU. Steroids were slowly tapered off and patients were discharged. The length of hospital stay was 2–10 days. Table 1 depicts the demographic and clinical characteristics with examination findings.

Discussion

The presentation and laboratory findings in our patients suggest that the occurrence of MIS-C may intensify in adolescents towards the later part of SARS-CoV-2 infection. The patients, in our report, highlight that SARS-CoV-2 infection may provoke a severe inflammatory syndrome despite seroconversion, when the virus may not be identified in upper respiratory tract [7]. All patients had negative RT-PCR and raised IgG titters, suggesting that they, especially patient 1, were asymptomatic for many days following the onset of disease. Similar to our report, other authors have described RT-PCR negative and SARS-CoV-2 IgG positive children with MIS-C [8, 9]. Based on these findings, we assume that a probable delayed mechanism linked to COVID-19 that may present as a late secondary hyperinflammatory syndrome.

As per the available literature, gastrointestinal symptoms and fever are predominantly reported in patients with MIS-C, and our patients had similar presenting symptoms [8, 10, 11]. Though these studies and our patients, in this report, had features of KD and TSS, only a limited number of children with MIS-C have been documented to satisfy KD diagnostic criteria and none of our patients fulfilled all criteria of classic KD. In our report, two patients had fever, rash, and conjunctival congestion and resembled the presentation of atypical KD. As per the available literature, shock, inflammation, and myocardial involvement are observed more frequently among patients with KD related to MIS-C than among patients with classic KD not related to MIS-C [10–12]. Additionally, this former group of patients have certain presenting feature of classic KD, probably because both KD and MIS-C are mediated by an unrestrained inflammatory response.

Half of the patients had normal respiratory status, while remaining half had dyspnea at presentation. However, chest radiography and HRCT chest were unremarkable. Both patients received non-invasive respiratory support and improved. Other studies have reported children with COVID-19, without MIS-C, who required MICU admission for respiratory distress [13, 14]. In a case report, of the two children with SARS-CoV-2 associated MIS-C, one developed dyspnea, but had normal chest radiography. The child responded well to non-invasive ventilation [9]. This finding highlights that patients with MIS-C can present with respiratory distress and still have normal lung fields.

MIS-C is related to shock and myocardial injury. Three of our patients had hypotensive shock. Additionally, one patient had heart failure with preserved ejection fraction. They were managed with fluids and inotropes, and the blood pressure normalized gradually. A study described 8 children with hyperinflammatory shock resembling KD
or TSS. All had myocardial injury, with myocardial dysfunction, for which all received inotropic support and recovered well [8]. Another study reported 35 patients with cardiogenic shock or acute left ventricular dysfunction associated with multisystem inflammatory state. More than three quarter of them required inotropic support and improved [11]. In patients with MIS-C associated myocardial injury, with or without shock, cardiac Troponin is used as a marker [10, 12]. The patients, in this report, had hypovolemic shock and estimation of Troponin I could have led to false positive results, so it was not performed to assess myocardial injury.

Inflammatory markers were elevated in our patients, and published studies involving adults with severe COVID-19 suggest that immunomodulatory drugs have a role in improving the outcome. Increased levels of inflammatory markers are also described in other studies reporting children with MIS-C [8, 10, 11].

### Table 1: Demographic and clinical characteristics and findings on investigations

| Clinical characteristics | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|--------------------------|-----------|-----------|-----------|-----------|
| Age, years               | 13        | 14        | 14        | 14        |
| Sex                      | Male      | Male      | Female    | Female    |
| History of contact       | Present   | Absent    | Absent    | Absent    |
| Comorbidities            | No        | Type 1 DM | No        | No        |
| Time to presentation, days | 5        | 6         | 10        | 7         |
| Disease severity         | Severe    | Mild      | Mild      | Severe    |
| Body temperature, °F     | 102.3 (↑) | 101.3 (↑) | 100.4 (↑) | 101.7 (↑) |
| Respiratory rate, per min| 32 (↑)    | 30 (↑)    | 22 (N)    | 28 (↑)    |
| Heart rate, per min      | 130 (↑)   | 110 (↑)   | 108 (↑)   | 118 (↑)   |
| Blood pressure, mmHg     | 80/60 (↓) | 100/60 (N)| 90/60 (N) | 70/40 (↓) |
| SpO2 on RA, %            | 85 (↓)    | 95 (N)    | 99 (N)    | 83 (↓)    |
| COVID-19 RT-PCR          | Negative  | Negative  | Negative  | Negative  |
| COVID-19 IgG Titer, U/ml | 250 (↑)   | 131 (↑)   | 88 (↑)    | 72 (↑)    |
| Hb levels, gm/dl         | 12.4 (N)  | 9.9 (↓)   | 10 (↓)    | 10.7 (↓)  |
| Leucocyte count, cells/μl| 15700 (↑) | 16300 (↑) | 1700 (N)  | 5400 (N)  |
| Platelets, cells/μl      | 95000 (↓) | 151000 (N)| 71000 (↓) | 97000 (↓) |
| Neutrophils, cells/μl    | 20.8 (↑)  | 80 (↑)    | 56 (↑)    | 83 (↑)    |
| Lymphocytes, cells/μl    | 9.16 (↑)  | 16 (↑)    | 38 (↑)    | 113.3 (↑) |
| C-reactive protein, mg/L | 110 (↑)   | 107.9 (↑) | 84.1 (↑)  | 123 (↑)   |
| ESR, mm/hr               | 54 (↑)    | 60 (↑)    | 47 (↑)    | 56 (↑)    |
| Procalcitonin, ng/ml     | 0.10 (↑)  | 0.16 (↑)  | 0.08 (N)  | 0.12 (↑)  |
| LDH, IU/l                | 352 (↑)   | 888 (↑)   | 628 (↑)   | 560 (↑)   |
| D dimer, μg/l            | 4060 (↑)  | 9640 (↑)  | 2633 (↑)  | 1300 (↑)  |
| INR                      | 1.44 (↑)  | 1.21 (↑)  | 1.1 (N)   | 1.12 (N)  |
| Fever profile            | Negative  | Negative  | Negative  | Negative  |
| Blood culture            | Negative  | Negative  | Negative  | Negative  |
| Urine culture            | Negative  | Negative  | Negative  | Negative  |
| Liver function test      | WNL       | WNL       | WNL       | WNL       |
| Renal function test      | WNL       | WNL       | WNL       | WNL       |
| X-ray chest              | WNL       | WNL       | WNL       | WNL       |
| HRCT chest               | WNL       | WNL       | ND        | ND        |
| ECG                      | Sinus Tachycardia | Sinus Tachycardia | Sinus Tachycardia | Sinus Tachycardia |
| 2D ECHO                  | WNL       | WNL       | Mild global hypokinesia | Biventricular dysfunction, mild pericardial effusion |
| Hospital stay, days      | 2         | 10        | 7         | 10        |

*SpO2 on RA oxygen saturation on room air, RT-PCR real-time polymerase chain reaction, Ab Antibody Hb hemoglobin, ESR erythrocyte sedimentation rate, LDH lactate dehydrogenase, INR international normalization ratio, Fever profile malaria, dengue, scrub typhus, and leptospira, WNL within normal limits, HRCT Chest high-resolution computed tomography of chest, ND not done, ECG electrocardiography, 2D ECHO two-dimensional echocardiography, ↑ increased, ↓ decreased, N normal, ND not done*
COVID-19 [18]. Based on these findings and pres-
11]. We used both methylprednisolone and IVIG in our
11]. RECOVERY trial concluded that the use of dexa-
methasone in adults with severe COVID-19 requiring
hospitalization, supplemental oxygen, or mechanical
ventilation, results in reduced 28 days mortality [15].
Additionally, due to immunomodulatory property and
better tolerability profile, human IVIG has been used
as a treatment option in severe cases, and patients with
MIS-C have been managed successfully with it [8, 10,
11].

In adults with hyperinflammation due to severe
COVID-19, coagulation disorders and thrombosis are
noticed probably as a result of endothelial damage [16].
Elevated levels of D-dimer, a marker of disseminated
intravascular coagulation, is associated with higher risk
of mortality [16, 17]. Use of thromboprophylaxis has
led to reduced risk of mortality in adults with severe
COVID-19 [18]. Based on these findings and pres-
ence of high levels of D-dimer in children with MIS-C,
anticoagulants have been tried in some of these chil-
dren and no adverse effects are reported, although the
advantage of anticoagulants in this age group remains
controversial [10]. Our patients had elevated levels
of D-dimer. Except patient with incidental diagnosis
of SCD, all other patients received LMWH with no
adverse effects, and none had thrombosis.

Conclusions
Findings of our series suggest that COVID-19 can trig-
ger hyperinflammatory state resulting in shock and
pulmonary involvement, in some of the patients. All
patients had raised inflammatory markers with biven-
tricular dysfunction in one of the patient. The patients
presented with distinct clinical features, with some
mimicking atypical KD, the underlying mechanism for
which still remain unclear. The physicians should be
suspicious of MIS-C in adolescents presenting with
fever, rash, and gastrointestinal symptoms. Personal-
ized treatment including hemodynamic and respiratory
support together with empirical antibiotics, fluids, ino-
tropes, thromboprophylaxis, and immunomodulatory
therapy was provided. Notwithstanding the require-
ment of MICU admission, the overall prognosis was
good.

Abbreviations
2D ECHO: Two-dimensional echocardiography; COVID-19: Coronavirus disease
2019; HRCT: High-resolution computed tomography; IgG: Immunoglobulin
G; KD: Kawasaki disease; MICU: Medicine intensive care unit; MIS: Multisys-
tem inflammatory syndrome; MIS-C: Multisystem inflammatory syndrome in
children; RT-PCR: Real-time polymerase chain reaction; SARS-CoV-2: Severe
acute respiratory syndrome coronavirus-2; SCD: Sickle cell disease; TSS: Toxic
shock syndrome.

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Authors’ contributions
RDB analyzed and interpreted the patient data and revised the final manu-
script. NMC analyzed and interpreted the patient data and supervised the
patient during hospital admission. BS participated in interpretation of the
interventional data of the patient. SB was a major contributor in writing the
manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

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