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CASE REPORT

Spectrum of Multisystem Inflammatory Syndrome in Children (MIS-C)—a Report of Three Cases

Shruti Jain[1] · **Archana Kashyap**[1] · **Amitabh Singh**[1]

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Abstract

We report three cases of multisystem inflammatory syndrome in children (MIS-C) during July 2020 from a tertiary care hospital with different clinical presentations and course of management. This will guide in better management of children with MIS-C. All three patients, aged 1 to 12 years old, were critically ill. They presented with common features of MIS-C, such as fever, conjunctival congestion, gastrointestinal involvement, and skin manifestations. Clinical features were suggestive of shock, coagulopathy, and multiorgan involvement. Laboratory findings revealed raised inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and D-dimers (DD). All patients required intensive care with oxygen therapy, fluid resuscitation, inotropic agents, and broad-spectrum antibiotics. All patients received steroids, and two patients were given intravenous immunoglobulin. One patient died, and the remaining two patients were discharged. Our findings confirmed that COVID-19 may cause severe disease in children, and the presentation may vary, requiring early recognition and timely management.

Keywords COVID-19 · Multisystem inflammatory disease in children · Methyl prednisolone · Shock · Toxic shock syndrome

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 pandemic, which was declared in early 2020, has infected the world's population, including adults and children. MIS-C is a rare and serious complication of COVID-19, and management guidelines are evolving. We share our experience of management of these patients and outcome which will help in better management of such patients. Various clinical manifestations of the disease have been reported, which are not always consistent. The variations are even greater and atypical in children, which makes diagnosis more difficult. The condition generally has a milder course in children; however, manifestations in children can progress to severe disease and even death [1]. COVID-19 presents with typical fever and a flu-like illness, but it may also include findings in the gastrointestinal tract, skin, and central nervous system, along with cardiac involvement. Most patients have a favourable recovery, but others may experience multisystem inflammatory syndrome in children (MIS-C), making diagnosis and management difficult with a potentially grave outcome. MIS-C is a clinically severe illness that may require hospitalisation. There is no definitive diagnostic test for MIS-C, so clinical parameters and supportive laboratory investigations are the mainstay of diagnosis.

Knowledge of the COVID-19 course in the paediatric population has evolved over time, and the Kawasaki disease-like presentation of COVID-19-related MIS-C is being reported around the world. The condition may present in one of three ways: (1) as a COVID-19 acute infection, during which patients have an asymptomatic course or mild symptoms; (2) as a multisystem hyperinflammatory syndrome; or (3) as a hyperimmune phase during acute COVID-19, immediately after the viremia phase (adult type).

The multisystem hyperinflammatory syndrome associated with COVID-19 is categorised as a Kawasaki-like disease or

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✉ Amitabh Singh
doc.amitabh@gmail.com

[1] Department of Pediatrics, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi 110029, India

a febrile inflammatory state (FIS) and TSS-like presentation of MIS-C [2].

Case Presentation

Three critically ill children from a tertiary care hospital in New Delhi presented with a spectrum of MIS-C symptoms associated with COVID-19 infection.

Case 1

A 3-year 6-month-old female presented with febrile illness for 5 days (101–103°F) associated with conjunctival congestion and decreased appetite. There was no history of cough, cold, breathlessness, diarrhoea, vomiting, or altered sensorium. On arrival at the emergency department, the patient had tachycardia (HR 144), tachypnoea, skin rash, and hypotension. A diagnosis of a Kawasaki-like illness was made, and the child was started on intravenous immunoglobulin 2 gm/kg/day for 1 day with dobutamine support. The patient had raised inflammatory markers, and a nasopharyngeal swab was positive for COVID-19 reverse transcriptase polymerase chain reaction (RT-PCR) SARS COV2. Intravenous methylprednisolone pulse therapy 30 mg/kg/day for 3 days was added on clinical worsening. Recurrence of skin lesions was noticed on day 7 of hospitalisation, after having received oral prednisolone initially at 2 mg/kg/day for 1 week followed by tapering dose to 1 mg/kg in next 1 week. The patient responded gradually and was discharged, and there was no coronary involvement at the 4-week follow-up cardiac evaluation.

Case 2

A 1-year 6-month-old male presented after having a rash for 8 days, noticed first on the face but followed by generalised desquamation, accompanied by loose stools for 7 days (high purge rate) and fever (102°F) with altered sensorium for 2 days prior to admission. The patient was in shock, was hypoxic on room air (SpO2 88%), and had multiorgan involvement with gastrointestinal bleeding. A differential diagnosis of toxic shock syndrome (TSS)/bacterial sepsis was made, and broad-spectrum antibiotics were started. The patient had multiorgan dysfunction with hypotension, oliguria, and liver dysfunction. The patient tested positive for COVID-19 antigen on nasopharyngeal swab using reverse transcription polymerase chain reaction (RT-PCR). The patient received intravenous dexamethasone 0.15 mg/kg 2 doses in view of hypoxia. The patient required mechanical ventilation with vasopressor but died on day 5 of admission.

Case 3

An 11-year-old male presented with high-grade fever with generalised body aches, intermittent vomiting, and desquamated rash with conjunctivitis for 7 days. Initially in compensated shock, the patient required inotropic support but improved after intravenous immunoglobulin (IVIG) 2 mg/kg/day for 1 day and was continued on aspirin. The patient was started on oral prednisolone 2 mg/kg/day for 1 week, tapered, and stopped over the next 2 weeks. The patient was discharged and was positive for the COVID-19 IgG antibody. The patient had no coronary involvement at the 4-week follow-up.

Table 1 highlights the symptoms and signs of all three patients.

Table 2 highlights the laboratory workup of all three cases.

Discussion

The COVID-19 pandemic has affected people of all ages, including children. MIS-C is one of the spectrum of COVID-19 sequelae that may cause serious complications. MIS-C is defined as affecting children 0 to 19 years of age, and it produces a fever that lasts more than 3 days with at least two of the following comorbidities: rash, bilateral non-purulent conjunctivitis, mucocutaneous inflammation, hypotension or shock, features of myocardial dysfunction, pericarditis, valvulitis, coronary abnormalities (echocardiography findings, elevated troponin/NT-proBNP levels), coagulopathy (prolonged PT or PTT, elevated DD). Acute gastrointestinal problems (diarrhoea, vomiting, abdominal pain), elevated inflammation markers (ESR, C-reactive protein, procalcitonin) with no other obvious microbial cause of inflammation, and evidence of COVID-19 (RT-PCR, antigen, positive serology) or contact with patients with COVID-19 [2]. The pathophysiology of MIS-C is based on an abnormal immune response to the virus causing clinical features similar to Kawasaki disease and macrophage activation syndrome [3, 4]. Many children with MIS-C have a negative SARS-CoV-2 PCR test but are positive for COVID-19 serology [5–8]. Case 3 patient was PCR-negative with a positive COVID-19 serology. All three cases met the criteria for MIS-C. Case 1 had an acute febrile hyperimmune presentation similar to the adult condition. Case 2 had a TSS-like presentation, and case 3 had a Kawasaki-like presentation.

MIS-C, unlike Kawasaki disease, most commonly presents with cardiovascular symptoms (hypotension or depressed cardiac function) and impaired gastrointestinal

Table 1 Clinical presentation of three cases with MIS-C

Symptoms	Case 1	Case 2	Case 3
Fever (duration)	Yes (5 days)	Yes (7 days)	Yes (7 days)
Rash	Maculopapular	Erythema	Desquamation
Bilateral non-purulent conjunctivitis	Yes	Yes	Yes
Oral mucosal inflammation	Yes	No	Yes
Peripheral cutaneous inflammation signs (hands or feet)	Yes	Yes	Yes
Pale/mottled skin	Yes	Yes	No
Cold hands/feet	Yes	Yes	No
Prolonged capillary refill time	No	Yes	No
Chest pain	No	No	No
Diarrhoea	No	Yes	Yes
Vomiting	Yes	Yes	Yes
Bleeding from any site	No	Yes	No
Seizure	No	Yes	No
Hypoxia/oxygen requirement	No	Yes	No
Hypotension (age appropriate)	Yes	Yes	Yes
Urinary output < 2 mL/kg/h	No	Yes	No
Tachypnoea	Yes	Yes	No
Tachycardia	Yes	Yes	Yes

Table 2 Laboratory parameters of three cases with MIS-C

Parameters	Case 1	Case 2	Case 3
Hemoglobin (g/dL)	13.0	7.6	10.5
Platelets (per µL)	2,82,000	62,000	3,94,000
White blood cell count(per µL)	10,800	14,100	6,900
Neutrophils (per µL)	7,300	8,200	3,640
LYMPHOCYTES (per µL)	2,500	5,250	2,370
Prothrombin time/international normalised ratio	13/1.0	16/1.4	13.3/1.14
Activated partial thromboplastin time (seconds)	34/34	45/34	31.1/34
Urea/creatinine (mg/dL)	26/0.3	66/0.6	11/0.4
Sodium/potassium (mEq/L)	134/4.2	> 160/3.8	133/3.7
Serum glutamic oxaloacetic transaminase(SGOT)/serum glutamic pyruvic transaminase(SGPT) (U/L)	32/9	1053/445	24/16
Total bilirubin (mg/dL)	0.2	0.6	0.3
N-terminal pro–B-type natriuretic peptide (NT-proBNP)	134 pg/mL (< 300)	-	-
Troponin	Negative	-	Negative
COVID-19 reverse transcriptase polymerase chain reaction	Positive	Positive	Negative
SARS COV2 Ig G ELISA			Positive
Rapid malarial antigen test	Negative	Negative	Negative
Serum Widal	Negative	Negative	Negative
Dengue NS1 antigen	Negative	Negative	Negative
Urine routine and microbiology	No abnormality	No abnormality	No abnormality
Chest radiograph	Normal	Bilateral infiltrates	Normal
Blood culture	No growth	contaminants	No growth

function [5]. COVID-19 was initially thought to cause severe pneumonia progressing to acute respiratory distress syndrome (ARDS). MIS-C has now been shown to have variable presentations that resemble incomplete Kawasaki disease or TSS [3]. Myocardial dysregulation can be isolated or caused by a combination of factors like ischaemic

or hypoxic cardiomyopathy, acute viral myocardial injury, or systemic inflammation. It can even be caused infrequently by coronary artery ischaemia [9].

Clinical features similar to those in our cases have been reported across the world. All three of our cases had a fever that lasted 3 to 5 days, which is seen in 100% of reported cases. GI symptoms in the form of abdominal pain, diarrhoea, and vomiting have been reported in 60–100% of MIS-C patients and were seen in two of our cases [10–12]. Skin manifestations, which have been seen in 45–76% of reported paediatric COVID-19 cases in the form of vesicular eruptions, pseudo-chilblains, erythema multiforme-like lesions, palmar erythema, and erythematous rash were also observed in all three of our cases [13–16]. Eye involvement with non-purulent conjunctivitis has been reported in 30–81% of patients, and all our patients had eye involvement [5, 7, 8]. Mucosal involvement (seen in 27–76% of reported cases) was seen in only two of our cases with oral ulcerations, whereas respiratory involvement (reported in 21–65% of cases with features like tachypnoea, difficulty in respiration, and severe pulmonary involvement in the form of ARDS) was seen in only one of our cases. Case 2, which had the most severe presentation, demonstrated neurological involvement with seizures. In other studies, patients have reported neurological components such as headache, lethargy, encephalopathy, seizures, coma, meningoencephalitis, and brain stem and/or cerebellar signs [5, 17]. Other, less commonly reported symptoms in the paediatric population (up to 16%) are sore throat, muscle pain/myalgias, limb oedema (both hands and feet), and lymphadenopathy.

Common clinical findings of MIS-C are hypotension or shock (reported in 32–76% of patients) [5, 8, 11]. Our first case developed hypotension on day 2 of admission, whereas cases 2 and 3 demonstrated hypotension on day 1 of admission, which indicates the severity of the TSS- and Kawasaki-like disease elements of COVID-19-related MIS-C. Therefore, rapid identification and management are essential in cases of suspected TSS- or Kawasaki-like illness when COVID-19 is a possible underlying illness.

Laboratory results showed abnormal blood cell counts with lymphocytopenia, neutrophilia, or mild anaemia and thrombocytopenia [3, 5, 6, 8, 11]. We noted that cases 1 and 3 had normal haemograms, but case 2 showed moderate anaemia, neutrophilia, and thrombocytopenia. This anaemia could be due to underlying illness or bleeding because of disseminated intravascular coagulation (DIC).

The inflammatory profile showed all three cases to be CRP-positive, which has also has been observed in 90–100% of cases reported in other studies. The markers showed correlation with the severity of illness as well. In cases 1 and 3, for which almost all markers were tested, the values were confirmatory of the patients' clinical conditions. Interleukin 6 (IL-6), DD, and lactate dehydrogenase (LDH) were comparatively low in case 3 but were significantly high in cases 1 and 2. In patients suspected to have MIS-C, a high CRP value with neutrophilia, thrombocytopenia, and highly deranged kidney function or liver function tests should be evaluated with both serology and RT-PCR on a nasopharyngeal swab. Up to 60% of patients with a negative PCR have had a positive serology test, and 30–35% of patients with a negative PCR have had both serology and RT-PCR return positive [5–7, 11]. A large series from India has highlighted high incidence of hospitalised children with COVID-19 infection meeting MIS-C criteria [18].

As more evidence emerge, intravenous immunoglobulin and steroid are being used for critical multisystem inflammatory syndrome in children (MIS-C) with shock or multiorgan dysfunction or Kawasaki phenotype. Steroids are indicated in a child with MIS-C without shock.

The patient with the most severe presentation was case 2, and the initial presentation was multiorgan dysfunction along with immune dysregulation; hence, the management plan could have included antivirals like Remdesivir or immunomodulators like IVIG, which may have decreased the disease severity.

Multi country multi-site randomised controlled trials are required for better understanding of pathogenesis and management of MIS-C.

Conclusion

COVID-19 infection in children is mostly mild, although severe complications, such as MIS-C, have been reported. The diagnosis of this complication is primarily based on clinical signs and symptoms, along with supportive investigation. Early diagnosis will assist prompt initiation of management, which will result in better outcomes.

Author Contribution SJ, AK, and AS participated in conception of study, analysis, and interpretation of the data, drafting the article, or revising it critically for important intellectual content and all authors approved the final version.

Data Availability Reported data available for review.

Code Availability Not applicable.

Declarations

Ethics Approval Obtained from institute ethics committee IEC/VMMC/SJH/2020–08/CC-42.

Consent to Participate Obtained from legal guardian.

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Conflict of Interest The authors declare no competing interests.

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