International Journal of Contemporary Pediatrics
Pendyala I et al. Int J Contemp Pediatr. 2023 Apr;10(4):599-603
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20230747

Case Report

An interesting manifestation of COVID-19 in children: case report and review on multisystem inflammatory syndrome in pediatric patients

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Received: 19 February 2023
Revised: 16 March 2023
Accepted: 17 March 2023

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 or PIMS-TS (pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection) has been presenting itself in children in connection to the SARS-CoV-2 infection. Along with a brief review of global data on MIS-C, we present two case reports of critically ill pediatric patients (aged 16 and 14 years), presenting with features of MIS-C from May 2020 to March 2021, to a tertiary-care hospital in Telangana, India. The patients with MIS-C were healthy prior to testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Clinical presentations were similar, with fever, abdominal pain, gastrointestinal complaints, or maculopapular rash. The diagnostic parameters revealed elevated levels of C-reactive protein, D-dimer, and NtProBNP. Other infectious aetiologies were ruled out. Both patients required ionotropic support, and intravenous immunoglobulin (IVIG), and were also given empiric antibiotics. Both were hemodynamically stable upon discharge. As knowledge of the various COVID-19 manifestations in children increases, reporting is essential to better-educating healthcare professionals in clarifying and streamlining the variety of symptoms connected to MIS-C and assessing the associated risk factors that predispose the pediatric population to develop severe disease.

Keywords: MIS-C, COVID-19, PIMS-TS

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C), also known as pediatric inflammatory multisystem syndrome (PIMS) or PIMS-TS, is a clinical syndrome in children and adolescents that was first identified in April 2020. MIS-C is associated with recent COVID-19 infection and shares common features with toxic shock syndrome and Kawasaki disease (KD), including symptoms such as rash, renal involvement, and coronary artery dilation.[1-4]

Children with COVID-19 can be asymptomatic or have mild symptoms, including fever, cough, rhinorrhea, sore throat, headache, diarrhea, vomiting, myalgia, fatigue, tachypnea, tachycardia, and rash. Anosmia or ageusia may not be common in children but are strong predictors of a positive SARS-CoV-2 test. Severe and critical cases are less common in children, but some may develop neurological manifestations or complications such as acute disseminated encephalomyelitis, respiratory failure, myocarditis, shock, ocular manifestations, acute renal failure, multi-organ system failure, intussusception, diabetic ketoacidosis, or MIS-C. MIS-C is a rare but serious condition that can occur weeks after a SARS-CoV-2 infection and presents with gastrointestinal, dermatologic/mucocutaneous, and cardiac symptoms, as well as elevated diagnostic markers.[6-10]

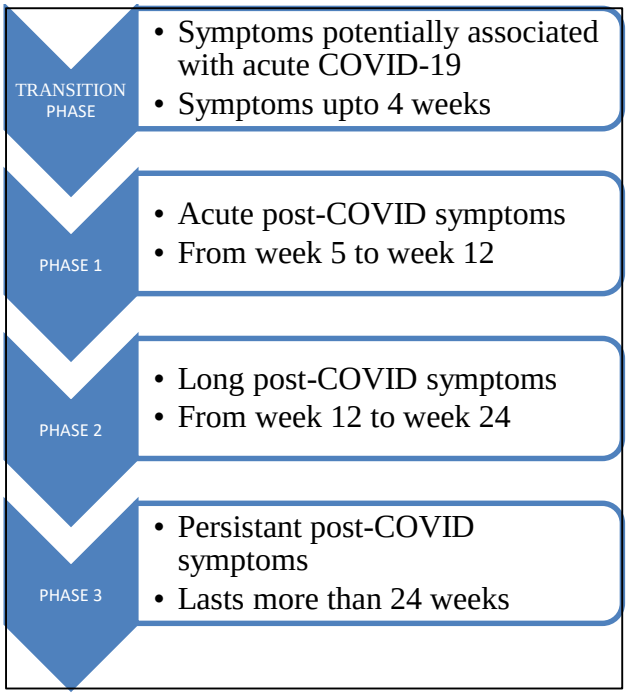

Figure 1: Phases of post-COVID-19 infection.[5]

The world health organization (WHO) has defined a set of clinical criteria to identify children and adolescents between the ages of 0 and 19 who have a suspected case of MIS-C associated with COVID-19. To meet the criteria, patients must have a fever lasting for three or more days and two or more of the following symptoms: rash or bilateral conjunctivitis, mucocutaneous inflammation of the mouth, hands, or feet, hypotension or shock, features of myocardial dysfunction, pericarditis, valvulitis, or coronary artery abnormalities, coagulopathy, acute gastrointestinal symptoms, and elevated levels of nonspecific indicators of inflammation. Additionally, there should be no obvious alternate microbial cause of inflammation and evidence of COVID-19 (positive RT-PCR test result, detectable antigen, or antibody) or likely exposure to the virus.[11]

Weisberg et al suggest that MIS-C may be caused by a lower level of persistent SARS-CoV-2 infection in different sites leading to a multisystem inflammatory response. The presence of SARS-CoV-2 in arterial and venous endothelial cells and arterial smooth muscle cells has been reported. Diorio et al report the finding of extensive burr cells in the peripheral blood smears of patients with MIS-C, which may be caused by activated macrophages inducing nitrosative stress. Persistent immune inflammatory responses are facilitated by the immune responses that fail to control an ongoing infection. Patients with MIS-C are treated with aspirin, corticosteroids, and immunoglobulin therapy and have achieved recovery states.[12-16]

As per global data, 5-month-old boy presented with fever, irritability, lip ulceration, and perineal cellulitis, with laboratory findings of nonregenerative anemia, leukopenia, and severe neutropenia. He was diagnosed with MIS-C secondary to COVID-19 and treated with filgrastim, antibiotics, and immunoglobulin therapy. Other cases reported symptoms of acute abdominal pain, initially diagnosed as appendicitis, but later found to have MIS-C. One case reported a potential neurological complication with MIS-C, wherein a 7-month-old male child developed seizures and was diagnosed with MIS-C based on raised CRP levels and positive IgG antibody results. All patients received treatment and showed improvement.[17-20]

MIS-C in comparison with KD

KD is an acute febrile illness that primarily affects children under the age of 5, first described in Japan in 1967. MIS-C, on the other hand, is a distinct disease from KD, although it shares some symptoms like persistent fever, gastrointestinal symptoms, myocardial dysfunction, and rash. While MIS-C can cause mild and transient coronary artery dilation, KD can cause severe dilation and aneurysm formations. The incidence of KD is highest among children of Asian descent, while MIS-C tends to occur in older children around 9 years of age. Immunophenotyping studies suggest that MIS-C is an immunopathogenic illness that is distinct from KD. Recent CDC findings have classified pediatric patients with COVID-19 symptoms into different classes, with Class 1 showing very little overlap with patients with KD.[20-24]

These classes' presentations in comparison to Kawasaki are elucidated as follows:

Table 1: Features of three groups of children (non-overlapping classes 1, 2 and 3) reported to CDC as MIS-C and their comparison to KD, as elucidated by Rowley et al.[20]

Class	Median age (Years)	SARS-COV-2 PCR antibody	Abdominal pain	Shock	ARDS
Class 1 (Classic MIS-C)	9	0.5%	80%	76%	7%
Class 2 (Acute COVID-19)	10	84%	49%	28%	10%
Class 3 (Other conditions including KD)	6	2%	54%	0%	1.5%
KD	1.6	N/A	Infrequent	Rare	Very rare

CASE REPORT

Patient 1

A 16-year-old female patient weighing 70 kg and measuring 170 cm in height was admitted with moderate-grade fever, cough, and breathlessness gradually progressing in nature. She had tested positive for COVID-19 two weeks before admission. The initial clinical examination showed a pulse rate of 140/min, a temperature of 98°F, blood pressure of 80/60 mmHg, and a respiratory rate of 22/min. Investigations showed low platelet count, hemoglobin, and TLC. The CT scan of the chest was performed which showed a score of CORAD-3, with a severity score of 4/25. The 2D Echo yielded results of global LV hypokinesia, with EF (ejection fraction)-25-30%. The patient was treated with several medications to control the cardiac manifestations. The differential diagnosis included COVID-19 pneumonia-related conditions, MIS-C, Dengue, or CMV infection. The patient received IVIg therapy along with methylprednisolone due to viral-induced cytopenia and high CRP. The patient's test results showed high Procalcitonin of 60, D-Dimer of 880, CRP of 252, and NTProBNP of 25,905. The patient's ferritin value and CRP remained high on Day 3.

The patient was started on drugs to control cardiac manifestations, and IVIg therapy and methylprednisolone were initiated for cytopenia induced by viral infection. Remdesivir was given for treating the existing COVID-19 infection. The patient was also given inotropes and empirical antibiotics. Bone marrow studies showed normocellular marrow with post-viral neutropenia. The patient responded well to filgrastim and steroids, and the TLC normalized at the time of discharge. After one month and three days, the patient was readmitted to the hospital with a fever, and bone marrow assessment showed agranulocytosis. The patient was given IV antibiotics and filgrastim, GCSF, and TPO agonist.

Table 2: Progress chart of patient 1.

Days	1	4	5	6	7	8	9	10	11	12
Hb (gm%)	10.2	10	10	9.4	9.5	9.2	10.2	10.2	10.5	10.6
PCV	29.5	30.5	30.8	29.6	29.8	28	30	31	33	33
TLC (cells/cumm)	1,830	1,500	1,120	1,200	1,100	1,300	1,800	1,900	3,200	6,200
Platelets (lacs/cumm)	332	355	395	335	300	280	310	3.36	3.21	3.75
Neutrophils					3.4%	5%	7%	33%	47%	64%
ANC						65	96			

Patient 2

The patient is a 14-year-old female child who presented to the hospital with high-grade fever, chills, headache, weakness/malaise, generalized body pains, and vomiting. The patient also exhibited rash on palms, arms, and soles, redness of eyes, and pain in the abdomen. The patient received the second dose of COVID-19 vaccination 10 days ago, and also had a history of COVID-19 infection one month ago. Other symptoms include TMJ tenderness and excessive hair fall. The patient's family history revealed a sibling with a history of recurrent loose stools and three siblings affected by complete blindness by 17 years of age on the maternal grandfather's side.

The patient's temperature spiked on day 1 post-admission with a maculopapular rash and constipation. The patient's left eye showed scleritis. The test for Dengue and Malaria was negative. The possibility of rickettsial fever was also ruled out. Among the diagnostic parameters tested, the ANA was negative, SARs-Cov-2-Antibody titer at 3.74, CRP-133, ESR-40, HSTroPI-0.9, and CPK-57. Other diagnostic parameters were tested, including HSTroPI, CPK, USG abdomen, 2D Echo, and RA factor, all of which were within normal limits. Since the patient showed signs of MISC/Kawasaki/Enteric fever, it was planned to start steroids and IVIg along with empiric ceftriaxone and azithromycin.

On day 2, noradrenaline was initiated in view of hypotension. On day 3, the maculopapular rash disappeared, and the labs were suggestive of an autoimmune phenomenon or MISC. The 2DEcho revealed normal LV systolic function, along with small pericardial effusion (3 mm), with signs of subclinical myocardial dysfunction, and pericarditis. The patient was started on low dose of Aspirin along with the IVIg therapy and started to wean off (tapering) of noradrenaline in view of stabilizing blood pressure. The NTProBNP was found to be 2350 (very high), suggestive of cardiac dysfunction. On day 3, The maculopapular rash disappeared and CRP reduced to 80.6, procalcitonin was 2.75, LDH-218, D-dimer-197, fibrinogen-424, IL-6-36, ferritin-239, ProBNP-2360, and TLC-9000. The labs were suggestive of an autoimmune phenomenon or MISC.

The patient showed improvement on day 5 with reduced symptoms and CRP levels. A 2D echo showed normalized cardiac function. IV steroids were replaced with oral prednisolone on Day 6 due to further reduction in CRP levels. A transthoracic echocardiography on day 6 showed normal cardiac anatomy and function with a small posterior pericardial effusion. The patient was discharged with a tapering dose regimen of prednisolone, pantoprazole, multivitamins, and low-dose aspirin to be continued for 2 weeks.

DISCUSSION

The CDC declared MIS-C a reportable illness on May 14, 2020, and provided a case definition that includes patients under 21 years of age with fever, laboratory evidence of inflammation, severe illness requiring hospitalization, involvement of two or more organ systems, and positive testing for SARS-CoV-2 indicating current or recent infection or COVID-19 exposure. The case definition also specifies that no other alternative plausible diagnoses should exist.[25]

MIS-C and KD are two distinct inflammatory diseases that can affect children. KD usually affects children under the age of 5, while MIS-C typically affects older children and adolescents. KD usually occurs a few weeks after a viral or bacterial infection, while MIS-C often occurs several weeks after a COVID-19 infection or exposure. While both diseases share some clinical features such as fever, rash, and gastrointestinal symptoms, MIS-C is more severe and presents with cardiovascular, respiratory, and neurological symptoms. In KD, there is a marked elevation of acute-phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, in MIS-C, there are more pronounced elevations of inflammatory markers such as ferritin, D-dimer, and interleukin-6 (IL-6). MIS-C is distinct from KD in terms of age of onset, timing, and triggers, clinical presentation, and laboratory findings."[26]

Another study notes that while there are some similarities between the two conditions, MIS-C tends to be more severe and presents with additional symptoms such as cardiac dysfunction, shock, and hyperinflammation.[27] A review by Burns et al provides an overview of KD, including its clinical presentation, laboratory findings, and treatment. The authors note that while KD typically affects young children and presents with fever, rash, and mucocutaneous changes, MIS-C is a distinct condition that is characterized by more severe cardiovascular and respiratory symptoms.[28]

Both of our patients diagnosed as MIS-C were consistent with this definition of MIS-C. The patients with MIS-C were healthy prior to testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Clinical presentations were similar as well, with fever, abdominal pain, gastrointestinal complaints, or maculopapular rash. The diagnostic parameters revealed elevated levels of C-reactive protein, D-dimer, and NtProBNP. Other infectious etiologies were ruled out. The presentations of these patients might have intersected with those of KD and toxic shock syndrome, and hence needed to be examined in order to justify the existence of a viral infection-related inflammatory syndrome in these patients. Both patients required ionotropic support, and IVIG, and were also given empiric antibiotics. Both were hemodynamically stable upon discharge.

CONCLUSION

The two pediatric patients who were previously healthy individuals with SARS-CoV-2 infection, developed MIS-C, progressively developing serious illness with multisystem involvement. The presentation of MIS-C linked to SARS-CoV-2 deserves additional investigation. As understanding various COVID-19 manifestations in children grows, reporting is critical to better inform healthcare professionals in elucidating and streamlining the array of symptoms associated with MIS-C, and therefore assessing the associated risk factors that predispose the pediatric population to develop severe disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Pendyala S, Maqsood M, Kaza VK. An interesting manifestation of COVID-19 in children: case report and review on multisystem inflammatory syndrome in pediatric patients. Int J Contemp Pediatr 2023;10:599-603.