Case Report

Multisystem inflammatory syndrome in children post-COVID-19: A case report

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a complication associated with COVID-19. It is generally characterized by signs of inflammation, including fever and rashes. This is due to neutrophil hyperactivation and leads to a widespread release of inflammatory mediators, which can cause organ damage or even death in severe cases. These symptoms may mimic those of Kawasaki disease, toxic shock syndrome, hemophagocytic lymphohistiocytosis, etc. In this article, we describe one such case of MIS-C of a 21-month-old girl who presented with a high-grade fever of 38.1°C, which was not responsive to antibiotics. She went on to develop rashes on the next day, requiring more workup with detailed history and investigations. We will also discuss the similarities and differences of the mimicking diseases.

Key words: COVID-19, Kawasaki disease, Multisystem inflammatory syndrome in children

Acute episodes of COVID-19 in children are typically less severe; however, recent data have shown that there is a possibility of children experiencing severe consequences of COVID-19 infection. One such consequence was initially recognized in 2020 which was characterized by a widespread inflammatory response in the body. Multisystem inflammatory syndrome in children (MIS-C) is a serious illness that has been diagnosed in patients 21 years or younger. They present with persistent fever, laboratory evidence of inflammation, and multiorgan involvement. The condition is believed to originate from gastrointestinal sources of virus leaking across a permeable mucosal barrier into the circulation. In cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, neutrophils are responsible for recognizing and destroying the virus. However, when hyperactivated, neutrophils cause excessive inflammation, which leads to severe symptoms and complications in adults who have COVID-19. This condition in children is called MIS-C, which can lead to organ damage and even death in some cases [1]. Almost a third of patients diagnosed with MIS-C do not test positive for SARS-CoV-2 at the time of presentation. Lack of clear diagnostic criteria was leading to overtreatment of patients during periods of COVID-19 surge when many pregnant women tested positive for SARS-CoV-2. The criteria for diagnosing MIS during the neonatal period are controversial and evolving. Most case reports have relied on a positive immunoglobulin (Ig)G titer against SARS-CoV-2 spike protein or confirmed COVID-19 in the mother during the last few weeks of pregnancy. Children with MIS-C display signs of vascular injury, including increased C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, troponin, D-dimer, hepatic enzymes, and cardiac natriuretic peptide (BNP) [2]. Around 80% of children with MIS-C develop cardiac complications, including myocarditis, ventricular dysfunction, and coronary aneurysms, although mechanisms of cardiovascular injury are unclear [2].

Although there is still much that is unknown, ongoing research is shedding light on the underlying mechanisms that drive neutrophil activation in these conditions, paving the way for more effective treatments in the future. Clinical and laboratory features of MIS-C also mimic those of Kawasaki disease (KD) shock syndrome, toxic shock syndrome (TSS), etc. They also exhibit anemia, thrombocytopenia, and neutrophilia. According to recent studies, the majority of MIS-C patients require admission to the ICU, and 62% of patients with MIS-C require vasopressor support. To treat MIS-C, most patients are administered intravenous Ig (IVIg), which is a medication that helps to boost the immune system. Furthermore, almost half of the patients affected by MIS-C receive glucocorticosteroids [1].

Access this article online

Received - 23 October 2023
Initial Review - 10 November 2023
Accepted - 09 December 2023

DOI: 10.32677/ijcr.v10i1.4136

Quick Response code

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CASE REPORT

A girl of 21 months of age presented to the emergency department with a high-grade continuous fever of 38.1°C that started abruptly 6 days ago. The patient's condition was not responsive to the prescribed antibiotics outside. She did not have any signs of lethargy, irritability, or seizures. Her behavior, activity levels, appetite, and hydration were all normal. No associated symptoms, such as diarrhea, vomiting, cough, and shortness of breath, were noted. Necessary investigations such as COVID-19 polymerase chain reaction (PCR), complete blood count (CBC), urea, and electrolytes were performed, and she was admitted to the pediatric ward for uncontrolled high fever.

On the following day, she developed skin rashes and red eyes. The rash appeared to be a flat, small-to-medium annular plaques resembling dime-size circles, which were well-circumscribed, and a non-palpable lesion of around 1×2 cm with multiple generalized discrete macules of light pink color. It was predominantly found near the lips, nape of the neck, chest, and lower back. The lesions are blanchable and do not appear itchy. No signs of discharge or bleeding from the rash were there. The rest of the examination was unremarkable. The redness of the eyes was bilateral and associated with clear, watery discharge. She had swollen eyelids without any bulging of the eyes. There were no other associated symptoms, such as itching, pallor, and jaundice.

As part of her past medical history, she was infected with the COVID-19 virus 29 days ago. Her nutrition was up to standards with soft food, water, juices, milk, etc. She was developmentally normal and spoke a few short sentences such as "want food" and "want to play." She was able to run around the house and climb up the stairs. She was able to play simple games and was interactive with other children. Maternal history was normal, with no complications during the antepartum, intrapartum, and postpartum period. There were no known allergies. Her immunization was up to date according to the country's vaccination schedule. No reported side effects or allergic reactions at any given doses were reported. The systemic review of symptoms was insignificant.

At admission, the patient looked alert, oriented, conscious, and well-nourished without any acute distress. The hydration status was good. Her consciousness level was 15/15 on the Glasgow Coma Scale. Her respiratory rate was 28 breaths/min. Her pulse was 132 beats/min and regular. SpO_2 was 98% (FiO_2 0.21), and body temperature was 38.1°C. Her blood pressure was not taken. On examination, the eyes showed redness and had a discharge present. No signs of pallor, jaundice, or eye bulging were noted. There were signs of strawberry tongue and congested tonsils. Rashes were present on the neck, chest, lips, and back**.** Generalized lymphadenopathy was present.

Baseline investigations such as CBC, CRP, electrolytes and renal profile, liver function tests, and coagulation profile including D-dimer, troponin, and blood glucose levels were performed. CRP levels and D-dimer were elevated to 102.2 mg/L and >7 mg/L, respectively. Neutrophil was 61.80% (high). Hematocrit was 31% (low). The red blood cell distribution width was 14.80 (high). The platelet level was 99.00×10^3 (low). Lymphocyte was 28.10% (low).

Chest X-ray was performed, which revealed bilateral accentuated bronchovascular markings with pulmonary haziness suggesting bronchitis/bronchiolitis. Both cardiogenic and costophrenic angles were clear with normal cardiac size (Fig. 1). Blood cultures were repeated. Ferritin levels, COVID-19 PCR, and urine routine were performed. Because of the typical clinical presentation with laboratory findings, she was suspected to be a case of MIS-C.

Initial medical management was done with an acetaminophen suppository, IV ceftriaxone, and oral esomeprazole. Aspirin was started to reduce the risk of developing thrombosis. IV immunoglobulin was then given. The patient improved significantly with subsidence fever and gradual normalization of laboratory parameters. She was discharged after 6 days of admission. Parents were counseled about their daughter's condition and to stay compliant with the prescribed doses. They also were counseled to report to the hospital immediately in case of deterioration/no improvement post-treatment (signs of dehydration, persistent rashes, and fever lasting >24 h).

DISCUSSION

MIS-C is a rare complication of COVID-19 that affects children 2–6 weeks after infection [3,4]. It causes inflammation in various body parts, potentially leading to serious or even fatal outcomes. MIS-C has mimics such as KD, bacterial sepsis, and adenovirus, which must be ruled out before treatment.

KD is an acute febrile condition primarily affecting children under 5 years old, affecting blood vessels and leading to coronary artery complications. The CDC defines KD as a diagnosis involving a fever of 5 or more days, at least 4 clinical signs (oral mucosal changes, rash, bilateral conjunctival injection, cervical lymphadenopathy (at least 1.5 cm in diameter), and peripheral extremity changes) (Fig. 2) [5]. If these criteria are not met, and the patient has a fever or coronary artery disease, then the patient has atypical or incomplete KD. When a patient has a fever for 5 days or more and exhibits clinical signs and laboratory results (high CRP levels, ESR levels, alanine aminotransferase levels,

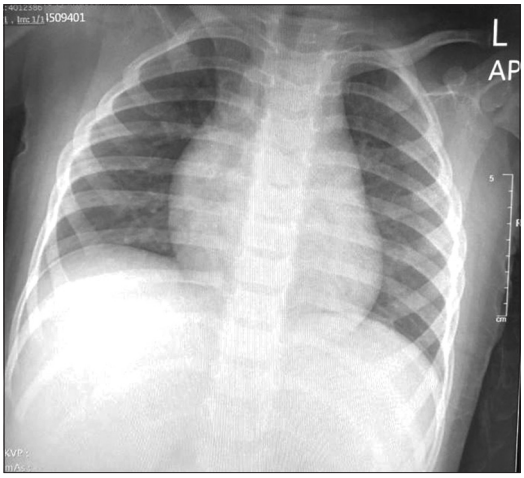

Figure 1: Chest X-ray in this child affected with multisystem inflammatory syndrome in children post-COVID

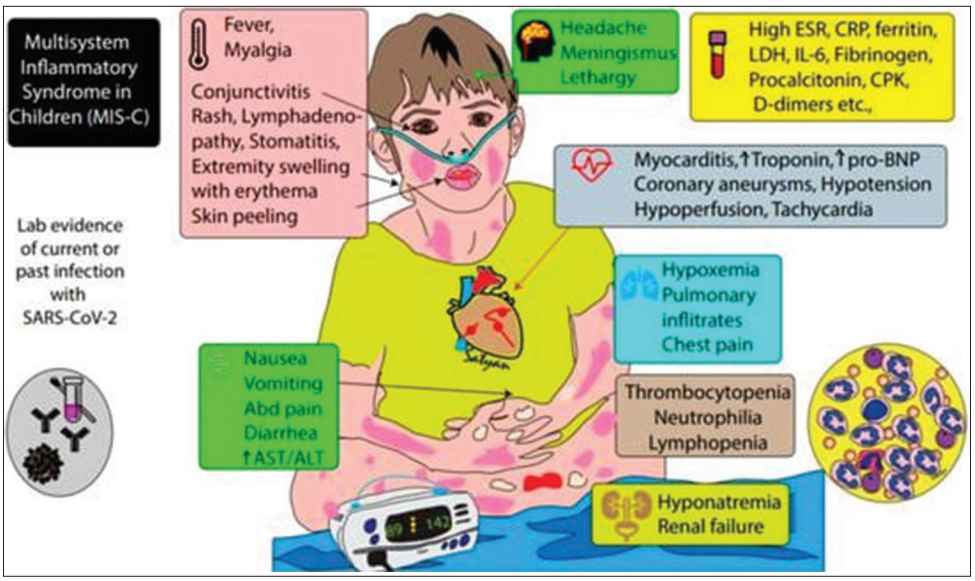

Figure 2: Infographic showing CDC criteria for the diagnosis of multisystem inflammatory syndrome in children. A combination of fever, evidence of inflammation, involvement of at least two organ systems, and prior evidence of SARS-CoV-2 infection is required to establish the diagnosis [5]

hypoalbuminemia, thrombocytosis, leukocytosis, anemia, and pyuria) that point to an illness or abnormalities in the ECHO, they are diagnosed with incomplete KD.

The management of KD involves a primary goal of preventing coronary artery disease. IV Ig and aspirin are the mainstay of treatment. Patients need to be treated within 10 days from the onset of fever to prevent any cardiac sequelae. Superantigen producers such as *Staphylococcus aureus* or Group A streptococcal (GAS) pyogenes can induce acute disease known as TSS, which results in hyperresponsiveness of inflammatory cells and cytokines. It frequently happens as a result of dialysis catheters, burns, surgical procedures, soft-tissue infections, and menstruation.

The CDC diagnoses TSS with fever, hypotension, rash, and multiorgan involvement. The rash is pale red, flat, and disappears under pressure. It may cause skin peeling, ulceration, or inflammation of mucous membranes (strawberry tongue). Patients may also experience confusion or mental state changes without neurological deficits.

The laboratory criteria for streptococcal TSS involve isolation of GAS from non-sterile sites, confirmation if obtained from an aseptic site, and treatment including fluid resuscitation, broad-spectrum antibiotics, removal of infection sources, IVIg, and vasopressors [6].

The clinical presentation of this specific case has many overlapping features such as the high fever, presence of rash all over the body, conjunctival injection, strawberry tongue, and cervical lymphadenopathy, which also fulfills the criteria of other differentials such as KD and TSS, thus becoming difficult to come up with the definitive diagnosis.

MIS-C is believed to be associated with an immune-mediated inflammatory process followed by a viral infection. This is supported by observation of clinical cases occurring in the peak phase of COVID-19 illness. However, the underlying mechanisms responsible for the development of this syndrome remain unknown.

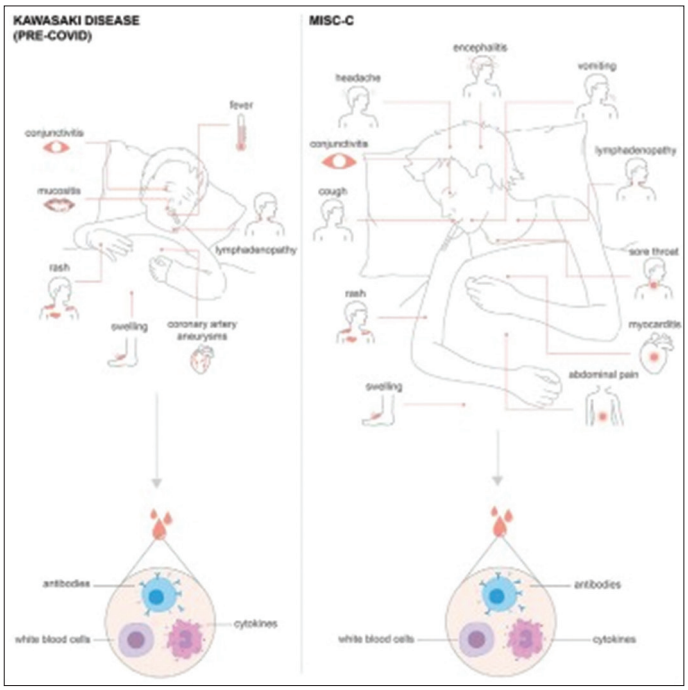

Figure 3: A systems immunology approach describes how multisystem inflammatory syndrome in children (MIS-C) is distinct from Kawasaki disease as well as the cytokine storm associated with severe COVID-19 in terms of its molecular and immune profiles [7]

The characteristic principle of differentiating MISC from the rest is to have a previous SARS-COVID-19 infection in the past 2–6 weeks. The next ruling out factor comes in the laboratory values where in MIS-C, there is evidence of lymphocytopenia and thrombocytopenia, which is in contrast with KD (Fig. 3) [7]. Although TSS also shows thrombocytopenia, there are signs of end-organ failure such as renal impairment (elevated creatinine and BUN), liver involvement (LFTs elevated), and elevated CPKs which is absent in MIS-C [8,9] (Table 1). Hence, we can conclude the diagnosis of this patient to be MIS-C.

Table 1: A comparison between MIS-C, Kawasaki Diseases and Toxic Shock Syndrome [8]

	Kawasaki Disease	Toxic Shock Syndrome	Multi-system Inflammation Syndrome in Children
Presenting symptoms	Fever for 5+days plus 4/5:Conjunctivitis, rash, adenopathy, strawberry tongue, hand/foot swelling	Fever, rash, hypotension, weakness, confusion	Persistent fever>24hrs, GI symptoms, rash, conjunctivitis
Average age	1-4 years old	Any age (<2 years old and menstrual women highest risk)	~8 years old (range 2-17)
Rash	YesPolymorphous; trunk, extremities, perineal; may have skin peeling	YesDiffuse, red, macular, involves toes/palms, mucosal involvement	YesLess common to have mucosal involvement
GI symptoms	Less common	Common(diffuse diarrhea)	Very common(abdominal pain, vomiting, diarrhea)
Labs	Leukocytosis, thrombocytosis, elevated CRP & ESR, abnormal LFTs	Anemia, thrombocytopenia, elevated BUN, creatinine, LFTs, CPK	Lymphocytopenia, Thrombocytopenia, Elevated CRP & ESR, elevated cardiac markers (troponin, BNP)
Echocardiogram	Coronary artery abnormalities	Normal or hyperdynamic	Decreased left ventricular function, coronary artery abnormalities
Treatment	IVIG, Aspirin	Shock resuscitation, antibiotics +/- surgical debridement	Generally supportive, anticoagulation, steroids, IL-1/IL-6 antagonists

CONCLUSION

Although COVID-19 episodes in children are typically less severe, recent statistics have shown that they may be affected by MIS-C, which is a life-threatening complication of COVID-19. Early diagnosis and treatment are of paramount importance to manage this widespread inflammatory response.

ACKNOWLEDGMENT

We would like to thank our university RAK Medical and Health Sciences University for providing us with the opportunity to perform this study. We would also like to thank our supervisor Dr. Subhranshu Kar, for her valuable guidance and supervision throughout this study.

AUTHOR CONTRIBUTIONS

Conceived and designed the review: Aisha Iram Mohsin; *Performed the literature search:* Aisha Iram Mohsin, Mariam Mehwish Mohsin, Saima Javed *Writing and editing of the manuscript*: Aisha Iram Mohsin, Mariam Mehwish Mohsin, Saima Javed; *Read and approved the final manuscript*: Aisha Iram Mohsin, Mariam Mehwish Mohsin, Saima Javed.

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Funding: Nil; Conflicts of interest: Nil.

How to cite this article: Mohsin MM, Mohsin AI, Javaid S, Kar SS, Jhancy M, Wahab LA. Multisystem inflammatory syndrome in children post-covid-19: A case report. Indian J Case Reports. 2024; 10(1):4-7.