COVID-19 Pandemic in the Disguise of Multi System Inflammatory Syndrome in Children: A Case Series

Anahita Sanaei Dashti

Shiraz University of Medical Sciences

Kamyar Ebrahimi

Shiraz University of Medical Sciences

Reza Shahriarirad

Shiraz University of Medical Sciences

Shabnam Hajjani Ghotbabadi (✉ sh_h86@yahoo.com)

Shiraz University of Medical Sciences <https://orcid.org/0000-0003-2029-4619>

Shiva Aminnia

Shiraz University of Medical Sciences <https://orcid.org/0000-0003-4238-3532>

Case report

Keywords: Kawasaki Disease, Systemic Inflammatory Response Syndrome*, COVID-19, Pandemics*, Coronavirus Infections* / complications

Posted Date: January 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-139961/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Although nearly a year has passed since the emerge of the SARS-CoV-2 virus, with it, a serious and novel pediatric condition called children's multisystem inflammatory syndrome (MIS-C) has subsequently emerged. In order to achieve a better understanding and management of the disease, documentation and reporting of atypical cases is justified, particularly with the growing number of children with inflammatory syndrome with clinical features simulating MIS during the ongoing COVID-19 pandemic. Based on similar reports from numerous countries with temporal relation to COVID-19 infection in the community, it is essential for general pediatricians to be on alert for such atypical presentations and early referral to tertiary care should be considered as appropriate. Here we four cases of Multisystem Inflammatory Syndrome (MIS) during the COVID-19 pandemic. Early diagnosis and treatment of patients meeting full or partial criteria for MIS are critical to preventing end-organ damage and other long-term complications, especially during times of public crisis and global health emergencies, such as the novel coronavirus pandemic.

Background

Initial reports identified children as less vulnerable to coronavirus disease 2019 (COVID-19) than adults in the severe acute respiratory coronavirus 2 (SARS-CoV-2) pandemic. However, a serious and novel pediatric condition called children's multisystem inflammatory syndrome (MIS-C) has subsequently emerged. MIS-C patient reports identified varying clinical signs and symptoms at initial assessment, but most cases included shock characteristics, cardiac dysfunction, gastrointestinal symptoms, significantly elevated markers of inflammation and cardiac damage, and serologically positive SARS-CoV-2 test results. (1) Since the case description is unspecific and there is no confirmatory laboratory testing, it may be hard to differentiate MIS-C from other clinical overlapping conditions such as extreme acute COVID-19 and Kawasaki disease. (1, 2). Here we present four cases of COVID-19 with features of MIS-C.

Case Presentation

Case 1

The patient is a 3-year-old boy, with no history of past medical diseases and a history of SARS-CoV-2 related symptoms in parents, who presented with a 5-day history of fever which did not respond to empirical antibiotic therapy (cephalexin, co-amoxiclav). The patient then received a dose of penicillin (1,200,000 unit) due to the continuation of fever, hours before developing generalized skin rashes including extremities, abdomen, and face. These findings then resulted in the hospitalization of the patient for 2 days where the patient received ceftriaxone as a treatment for his symptoms. The patient's parents then transferred the patient to our center, due to the continuation of the symptoms.

In our primary evaluations, which was the fifth day after initiation of the symptoms, the patient had stable vital signs except for a fever (39.9°C) and was fully awake and oriented (GCS=15). In his physical exam,

the patient had a generalized erythematous multiform rash, mucositis in his mouth (figure 1), and scaling in the perianal area. Notable laboratory findings on initial admission (2 days before admission in our center) were microcytic anemia alongside a decreased platelet count in the complete blood count (CBC) and an active inflammatory process in the patient's body due to increased erythrocyte sedimentation rate (ESR) and qualitative C-reactive protein (CRP). Abnormal Urine analysis and Low levels of creatinine and sodium also suggested some inflammation in kidneys (Table 1). High SARS-CoV-2 immunoglobulin-G (IgG) level (28.14 AU/ml >10 AU/ml) was also detected on the second hospitalization day.

Laboratory findings on admission in our center were a shift to the left in leukocytes, microcytic anemia, and an improved platelet count in CBC. The patient had also increased bleeding times, inflammation in kidneys, and high inflammatory factors. glucose-6-phosphate dehydrogenase (G6PD) enzyme level was also sufficient. A high-resolution computed tomography (HRCT) of the patient's chest was also done which did not show any abnormalities. Also, the patient had a high SARS-CoV-2 Immunoglobulin-G (IgG) level (28.14 AU/ml >10 AU/ml) and a positive nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) test. Therefore the patient was considered a case of COVID-19 disease.

Echocardiography was done for the patient which revealed myocarditis, mitral valve regurgitation, tricuspid valve regurgitation, and left ventricular diastolic dysfunction which led to administration of captopril, Lasix, and Aldactone. Due to the findings in his echocardiogram, the troponin I level was requested which showed a rise in the troponin I level (0.528 ng/mL).

Based on the abovementioned findings, which were fever for 5 days, generalized erythematous multiform rashes, changes in the lips and oral cavity, and high ESR and CRP levels, the patient did not fulfill the criteria for Kawasaki disease (KD); However, the patient was suspected of Multisystem Inflammatory syndrome in children (MIS-C) by the definition of World Health Organization (WHO) and was in need for treatment.

The patient received 3 doses of methylprednisolone 30mg/Kg as individual pulses and 2gr/Kg Intravenous Immunoglobulin (IVIG) for the treatment of Multisystem Inflammatory Syndrome in the hospital course. He also received enoxaparin sodium 0.5mg/Kg SC Q12hr to reduce the risk of any thrombosis during his disease. He was then put on aspirin 3-5mg/kg (antithrombotic dose) and prednisolon 1mg/kg/day for 5days then then decreased to 0.5mg/kg/day for 5 days and then discontinued.

In his hospital course, the abdomen and pelvic sonography result showed no abnormalities and peripheral blood smear (PBS) was unremarkable. After receiving treatments, the patient's symptoms started to disappear, and his laboratory data showed improved results. The patient was then discharged from hospital after about a week due to the improvement of his symptoms and his laboratory data. The patient was discharged with oral Aldactone.

The patient's post-hospitalization course was uneventful, and his follow-up echocardiography (2 weeks after the initial echocardiography) showed normal results with no sign of dysfunctions and/or

regurgitations that were seen before.

Table 1
Clinical and Paraclinical Features of 4 Children with Multisystem Inflammatory Syndrome in Children (MIS-C)

Clinical features	Patient 1	Patient 2	Patient 3	Patient 4
Age	3 y/o	4y/o	2y/o	2.5y/o
Gender	Male	Male	female	Male
Presenting Symptoms				
Fever	+	+	+	+
Myalgia	-	+	-	-
Rash	+	-	-	+
Conjunctivitis	+	-	+	+
Mucositis/Strawberry Tongue	+	-	+	+
Lymphadenopathy	-	+	-	-
Extremity Edema	-	-	-	-
Perianal Scaling	+	-	-	-
Headache	-	+	-	-
Altered Mental Status/Irritability	-	-	-	-
Respiratory Failure	-	-	-	-
Shock	-	-	-	-
Key Initial Findings				
C-Reactive Protein (mg/L)	>150			143
(Ref: 0-6 mg/L)				
Erythrocyte Sedimentation Rate (mm/hr)	58			46
(Ref: 0-20 Male, 0-30 Female, mm/hr)				
Procalcitonin (ng/mL)	1.91			.
(Ref: 0.0-0.1 ng/mL)				
Ferritin (ng/mL)	499.4			.
(Ref: 22.8-275.6 Male, 4.6-204.0 Female ng/mL)				
Platelets (×10 ³ /μL)	131			185

(Ref: 150-450 ×10 ³ /mL)				
White Blood Cell Count (×10 ³ /μL)	9.0		7.3	
(Ref: 4-10 ×10 ³ /μL)				
Troponin (ng/mL)	0.528		.	
(Ref: 0.0-0.3 ng/mL)				
Fever Duration (Total Days)	10			
Troponin (ng/mL)				
Maximum		.	.	
(Ref: 0.0–0.3 ng/mL)				
Echocardiogram				
Initial		Tubular dilation of LCA, Mild MR	Normal	.
Final or most recent	Normal	Normal	Normal	.
Initial chest radiograph findings	Normal	.	.	.
Anti-SARS-CoV-2 Immunoglobulin G	+	.	.	+
Chest HRCT Scan	-	.	.	.
Known SARS-CoV-2 Exposure	+	+	+	-
Outcome	Discharged	Discharged	Discharged	Discharged

Case 2

The patient is a 4-year-old boy, with no past medical history of chronic diseases and a history of SARS-CoV-2 related symptoms in parents (fever and loss of smell about 1 month before the patient's admission), who presented with a history of fever 1 week before admission in our center which had not responded to empirical treatments (Azithromycin, Acetaminophen, and Diclofenac suppository). The patient then visited an associated center 4 days after his first visit which led to his hospitalization since his symptoms were not subsided. IVIG was started for the patient from the previous center and was transferred to our center for further evaluation and treatment. However, the patient's symptoms were subsided when he was admitted to our center.

In our primary evaluations, which was 4 days after initiation of the symptoms, the patient had mild conjunctivitis and no rash. Notable laboratory findings on admission in our center were increased ESR and CRP, increased leukocyte count, decreased red blood cell count and hemoglobin, and decreased albumin. Nasopharyngeal SARS-CoV-2 PCR was negative. Echocardiography was done for the patient which revealed a tubular dilation of left coronary artery, a mild mitral regurgitation, no coronary artery involvement, and a minimal pericardial effusion. Based on findings such as a history of exposure to COVID-19 infected patient and high (positive) SARS-CoV-2 IgG level, the patient was considered a case of COVID-19 disease.

Based on the findings mentioned above, which were fever for 5 days, myalgia, lymphadenopathy in the neck, and high ESR and CRP levels, the patient did not fulfill the criteria for Kawasaki disease (KD); However, the patient was suspected of Multisystem Inflammatory syndrome in children (MIS-C) by the definition of WHO and was in need for treatment.

The patient received methyl prednisolone 1mg/Kg/dose, IVIG 2gr/Kg, and aspirin for the treatment of his Multisystem Inflammatory Syndrome. He was then put on aspirin 3-5mg/kg (antithrombotic dose) and prednisolone 1mg/kg/day for 5 days then the dose decreased to 0.5mg/kg/day for 5 days and then discontinued.

After receiving treatments, the patient's symptoms started to disappear, and his laboratory data showed improvement. The patient was then discharged after 5 days due to the improvement of his symptoms and his lab data since they showed response to the treatment. Finally, the patient was discharged with oral aspirin. The patient's post-hospitalization course was uneventful, and his follow-up exam showed no abnormalities or problems.

Case 3

The patient is a 2-year-old girl, with no past medical history of chronic diseases and a history of exposure to SARS-CoV-2 (COVID-19) (Some of her relatives' nasopharyngeal SARS-CoV-2 PCR were positive), who presented with a 2-week history of fever and pharyngitis which did not respond to empirical treatments (Co-amoxiclav, Acetaminophen, and Pediatric cough & cold syrup). The patient then visited an associated center after her first visit which led to her hospitalization with the impression of Kawasaki disease (KD). The patient received treatments for KD in that center and then she developed redness and ecchymosis of the eyes, suggestive of conjunctivitis, and swelling of the lips. The patient then was transferred to our center for further evaluation and treatment. In our primary evaluations, which was 3 days after initial hospitalization, the patient had conjunctivitis and an erythematous multiform rash with edema on both palms and soles. Notable initial laboratory findings were low red blood cell count and hemoglobin, low platelet count, increased inflammatory markers (ESR, CRP), hypocalcemia, hyponatremia, hypoalbuminemia, hypoproteinemia, high levels of lactate dehydrogenase (LDH) and D-dimer, and slightly elevated liver enzymes.

Echocardiography was done for the patient which revealed normal heart function with no coronary artery involvement. Based on findings such as a history of exposure to COVID-19 infected patients and high (positive) SARS-CoV-2 IgG level, the patient was considered to be a case of COVID-19 disease.

Based on the findings mentioned above, which were fever for more than 10 days, pharyngitis, lip swelling and changes, conjunctivitis, and high ESR and CRP levels, the patient did not fulfill the criteria for Kawasaki disease (KD); However, the patient was suspected of Multisystem Inflammatory syndrome in children (MIS-C) by the definition of WHO and was in need for treatment.

The patient received methyl prednisolone 1mg/Kg/dose, IVIG 2gr/Kg, and aspirin for the treatment of Multisystem Inflammatory Syndrome. After receiving treatments, the patient's symptoms started to disappear, and improvements in laboratory data were observed. Then, the patient was discharged home from our center after 5 days due to the improvement of his symptoms and lab data. The patient was discharged with oral aspirin. After discharge, the patient had no further complications and his follow-up exam showed no abnormalities or problems.

Case 4

The patient is a 2.5-year-old boy, with no past medical history of chronic diseases and no history of COVID-19 exposure, who presented with a history of 4-day fever, diarrhea, and erythematous polymorphous rash on extremities and body. The patient's parents then brought him to the hospital due to the development of periorbital rash and conjunctivitis.

In our primary evaluations, which was 4 days after his initial symptoms, the patient had stable vital signs except for a low-grade fever (38°C) and was fully awake and oriented (GCS=15). In his physical exam, the patient had a generalized erythematous multiform rash, oral changes (mucositis), periorbital edema, and conjunctivitis (figure 2).

Laboratory findings on admission were normal CBC, slightly increased prothrombin time (PT) (15.4 sec.) and partial prothrombin time (PTT) (40.7 sec.), high fibrinogen level, increased Alkaline phosphatase level (353 Unit/L), hypoalbuminemia, increased inflammatory markers (ESR and CRP), and a high level of LDH (Table 1).

Based on findings such as high (positive) SARS-CoV-2 IgG level (39.8 AU/mL, ref:<10 AU/mL), and negative PCR for SARS-CoV-2, the patient was considered a case of COVID-19 disease. Also, based on the abovementioned findings, which were fever for more than 4 days, generalized erythematous multiform rashes, changes in the lips and oral cavity, conjunctivitis, and high ESR and CRP levels, the patient did not fulfill the criteria for KD; However, the patient was suspected for Multisystem Inflammatory syndrome in children (MIS-C) by the definition of WHO and was in need for treatment. It is notable that, the periorbital erythm seen in figure 2, is very unusual and not typical for patients suspicious of KD.

The patient initially received ceftriaxone as empirical therapy for his fever, and then methyl prednisolone 1mg/Kg/dose, IVIG 2gr/Kg, and aspirin for the treatment of MIS-C. After receiving treatments, the patient's symptoms started to disappear, and his laboratory data showed improvement. The patient was then discharged after 5 days with oral aspirin. The patient's post-hospitalization course was without complications, and his follow-up exam showed no remaining abnormalities or problems.

Discussion And Conclusions

Herein we reported four cases of MIS-C which were also diagnosed with COVID-19 disease. KD is an acute vasculitis of childhood, with 50% of cases occurring in those under two years of age and 80% in those under five years of age, and is the leading cause of acquired heart disease in children in developed countries(3). Despite that KD affects children from all races, it is most frequent in the Asian populations(4). Our study presents three cases of MIS-C which were also positive for COVID-19. Taking into consideration these presentations and features is advised especially during the times of public crisis and emergencies.

Lately, reports from North America and Europe have described clusters of children and adolescents requiring admission to intensive care units due to MIS accompanied by some characteristics similar to those of KD and toxic shock syndrome. Case reports and small case series have described a presentation of acute illness accompanied by a hyperinflammatory syndrome, leading to multiorgan failure and shock (5-7). Laboratory features of these patients included neutrophilia and high CRP levels which were also similar to our patients' findings, and other case reports' results (8, 9). Furthermore, in our study, the patient was located in a COVID-19 hotspot area (10) with a recent history of attending public places; hence, it could have been possible that she has developed a previous asymptomatic infection, as the positive IgG for SARS-CoV-2 in our patient is in favor of this theory.

In this regard, the COVID-19 which was declared a pandemic and global emergency by WHO on 11th March 2020 has seized the attention of medical staff, governments, and people and affected other disease management and diagnosis approaches. There is a growing global concern that a SARS-CoV-2 related inflammatory syndrome is emerging in children. Multiple infectious triggers such as adenovirus and novel coronavirus have been inconclusively associated with KD (11, 12). Also, KD has been associated with Epstein- Barr virus (EBV), rotavirus, and specific bacteria (13, 14). In this regard, WHO has also developed a preliminary case definition and case report form for MIS in children and adolescents for approaching these diseases (15).

A leading hypothesis is that MIS may be related to COVID-19 based on initial laboratory testing showing positive serology in a majority of patients. Children have been treated with anti-inflammatory treatment, including parenteral immunoglobulin and steroids.

The relationship between COVID-19 and MIS is still unknown, however, a possible explanation may be in PCR negative- antibody-positive cases, previous infection by the coronavirus could possibly trigger an immune response simulating MIS (16). Furthermore, COVID-19 during the active infective phase has been

linked to excessive cytokine and inflammation storm similar to MIS. Similar reports from the USA regarding MIS in pediatrics with features similar to our patients such as rashes, high CRP and troponin levels, and negative PCR for COVID-19 have been published (7, 17). Rauf et al also reported a similar case of MIS presenting as atypical KD in India with negative PCR for COVID-19 (9).

Based on similar reports from numerous countries with temporal relation to COVID-19 infection in the community, it is essential for general pediatricians to be on alert for such atypical presentations and early referral to tertiary care should be considered as appropriate. Furthermore, If MIS is suspected, pediatricians should immediately refer patients to a specialist in pediatric infectious disease, rheumatology, and/or critical care, as indicated. Early diagnosis and treatment of patients meeting full or partial criteria for MIS is critical in preventing end-organ damage and other long-term complications.

List Of Abbreviations

CBC: *Complete Blood Count*, COVID-19: *coronavirus disease 2019*, CRP: *C-Reactive Protein*, ESR: *Erythrocyte Sedimentation Rate*, G6PD: *Glucose-6-phosphate dehydrogenase*, HRCT: *High-Resolution Computed Tomography*, IgG: *Immunoglobulin-G*, KD: *Kawasaki disease*, LDH: *lactate dehydrogenase*, MIS: *Multisystem Inflammatory Syndrome*, PCR: *polymerase chain reaction*, PT: *prothrombin time*, PTT: *partial prothrombin time*, SARS-CoV-2: *severe acute respiratory coronavirus 2*, WHO: *World Health Organization*

Declarations

1. Ethics approval and consent to participate

Medical Ethics Committee of Shiraz University of Medical Sciences approved this study.

2. Consent for publication

Consent was obtained from the patients' parents regarding the publication of this case report.

3. Availability of data and materials

All available information regarding this case series has been reported in the manuscript. Please contact the corresponding author in case of any further information.

4. Competing interests

The authors declare that they have no competing interests.

5. Funding

No financial support was received for these case reports.

6. Authors' contributions

Anahita Sanaei Dashti; Study design, Data gathering, Critically revising

Shabnam Hajiani Ghotbabadi; Study design, Data gathering, Critically revising, Correspondance

Kamyar Ebrahimi; Data gathering, Drafting the work

Reza Shahriarirad; Data gathering, Drafting the work

Shiva Aminnia; Data gathering, Drafting the work

All authors read and approved the final manuscript.

7. Acknowledgments

Not applicable

References

1. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19–associated multisystem inflammatory syndrome in children—United States, March–July 2020. *Morbidity and Mortality Weekly Report*. 2020;69(32):1074.
2. Covid C, COVID C, COVID C, Bialek S, Gierke R, Hughes M, et al. Coronavirus Disease 2019 in Children—United States, February 12–April 2, 2020. *Morbidity and Mortality Weekly Report*. 2020;69(14):422.
3. Rowley AH, Shulman ST. The epidemiology and pathogenesis of Kawasaki disease. *Frontiers in pediatrics*. 2018;6:374.
4. Holman RC, Christensen KY, Belay ED, Steiner CA, Effler PV, Miyamura J, et al. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. *Hawaii Med J*. 2010;69(8):194-7.
5. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *The Lancet*. 2020;395(10237):1607-8.
6. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe COVID-19 in children and young adults in the Washington, DC metropolitan region. *The Journal of Pediatrics*. 2020.
7. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki disease: novel virus and novel case. *Hospital Pediatrics*. 2020;10(6):537-40.

8. Health. RCoPaC. Guidance- COVID-19 paediatric multisystem inflammatory syndrome. [Available from: <https://www.rcpch.ac.uk/resources/guidance-paediatricmultisystem-inflammatory-syndrome-temporally-associatedcovid-19>.
9. Rauf A, Vijayan A, John ST, Krishnan R, Latheef A. Multisystem inflammatory syndrome with features of atypical Kawasaki disease during COVID-19 pandemic. *The Indian Journal of Pediatrics*. 2020:1-3.
10. Shahriarirad R, Khodamoradi Z, Erfani A, Hosseinpour H, Ranjbar K, Emami Y, et al. Epidemiological and clinical features of 2019 novel coronavirus diseases (COVID-19) in the South of Iran. *BMC infectious diseases*. 2020;20(1):1-12.
11. Jaggi P, Kajon AE, Mejias A, Ramilo O, Leber A. Human adenovirus infection in Kawasaki disease: a confounding bystander? *Clinical infectious diseases*. 2013;56(1):58-64.
12. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. *The Journal of infectious diseases*. 2005;191(4):499-502.
13. Maggio MC, Fabiano C, Corsello G. Kawasaki disease triggered by EBV virus in a child with Familial Mediterranean Fever. *Italian Journal of Pediatrics*. 2019;45(1):129.
14. Son MB, Sundel RP. Kawasaki disease. *Textbook of pediatric rheumatology*. 2016:467.
15. Organization WH. Multisystem inflammatory syndrome in children and adolescents with COVID-19: scientific brief, 15 May 2020. World Health Organization; 2020.
16. Shahriarirad R, Sarkari B. COVID-19: clinical or laboratory diagnosis? A matter of debate. *Tropical Doctor*. 2020.
17. #13 NYCHA. Pediatric multi-system inflammatory syndrome potentially associated with COVID. [Available from: www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf?referringSource=articleShare.

Figures

A

B

Figure 1

(a) Erythematous multiform rash on the abdomen, upper extremities, and face. (b) Mucositis in the mouth including fissures on the buccal cavity.

Figure 2

Periorbital edema and conjunctivitis (a) on the patient's face, and Erythematous polymorphous rash (b) on the patient's extremities and abdomen.