Multisystem Inflammatory Syndrome in Child after Covid-19

Abstract

MIS-C is a disorder that causes inflammation of several organ systems, involving the brain, lungs, heart, kidneys, GIT, skin, and eyes, among pediatric patients with COVID-19. Here, we investigated a male child aged 6 years presented by high grade fever (39-40 C) for five days, not responding to oral antipyretic, with swollen hands and feet started 2 days after fever, Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea). In addition, he had difficulty of breathing, erythematous rash on the back appeared on the third day. The case was admitted to pediatric intensive care unit (PICU) and received IV IG once and corticosteroids 60 mg/kg/d for 3 days. Blood test showed elevated inflammatory markers, increased liver enzymes, hypoalbuminemia, thrombocytopenia, and coagulopathy. Finally, he recovered well after IV IG and corticosteroids and discharged well on corticosteroids with gradual withdrawal within 1 month.

Keyword: MIS-C, SARS-CoV-2, Acute COVID-19

Introduction

"Severe acute respiratory syndrome (SARS-CoV-2), that is known to result in the fast transmission of coronavirus virus disease 2019 (COVID-19), has caused widespread morbidity and death. Although the virus affects all ages, it was believed that children fared better during the COVID-19 outbreak, since this age group comprised only 1% to 5% of diseased cases and seldom acquired severe disease" [1].

The majority of COVID-19 children present with a variety of manifestations which are neither severe nor specific enough to warrant testing. A disorder called multisystem inflammatory syndrome in children (MIS-C) is one of the uncommon but possibly fatal COVID-19 consequences.

“MIS-C is a disease that causes inflammation of several organ systems, including the brain, lungs, heart, kidneys, GIT, skin, and eyes, in COVID-19 children patients” [2, 3].

“Uncertainty surrounds the worldwide prevalence of MIS-C, however it seems to be low. The United Kingdom reported the initial instances, which were preceded by Canada, Europe, South Africa, and the United States” [4].

“Most studies indicate a 2–6-week latency between infection with COVID-19 and the onset of MIS-C. Up to 70% of MIS-C occur in persons who were healthy, with asthma and obesity as the greatest prevalent underlying health problems. Although Kawasaki illness (KD) and MIS-C have several manifestations in common, their epidemiologies are distinct. The median age of confirmed MIS-C patients is 7 to 11 years, while 80–90% of KD children patients are less than 5 years old” [5, 6].

“Males are highly susceptible to MIS-C (over 59%) and KD (over 60%). 25–62% of MIS-C cases are black, 15–25% are white, 30–40% are Hispanic, and as many as 28% are Asian, according to various studies. In contrast, KD affects babies and Asian young children more often, with a frequency of 30 per 100,000 for individuals of Asian or Pacific Islander heritage, while the lowest prevalence is observed among Caucasians (12 per 100,000)” [7].

“The consequences of MIS-C may be serious, involving distributive shock or cardiogenic shock accompanied by a lack of vasomotor tone. In a comprehensive review about 917 cases, 11 individuals (1.9%) died. The majority of individuals with heart condition (involving arrhythmias or reduced ventricular function) average restoration. 20–45% of patients at the hospital discharge time might still with moderately lower ejection fraction” [8, 9].

Clinicians have had difficulty distinguishing MIS-C from other hyperinflammatory disorders, like KD and toxic shock syndrome. MIS-C cases are often elder than KD cases (average age eight to nine years vs. two to three years respectively) and have higher troponin. Abdominal discomfort and heart dysfunction may assist in distinguishing between toxic shock syndrome and KD [1].

Here, we presented a case of child who presented with MIS-C symptoms and managed by a conservative management.

Case presentation

A male child aged 6 years presented by high grade fever (39-40 C) for five days, not responding to oral antipyretic, with swollen hands and feet started 2 days after fever, Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea). In addition, he had difficulty of breathing, erythematous rash on the back appeared on the third day.

Case was subjected full laboratory testing Complete blood count (CBC) with differential erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Ferritin, Liver function tests and kidney function tests, urine analysis, and coagulation tests.

In fifth day, the patient developed dyspnea, and the swelling increased in both hands and feet and started also in the face and eyes, conjunctival injection, cracked lips and strawberry tongue. The abdomen distended and his ability to walk decreased.

Initial therapy consists of resuscitation and ultrasound-guided evaluation for cardiac versus vasodilatory shock.

The case was admitted to PICU and received IV IG once and corticosteroids 60 mg/kg/d for 3 days.

Blood test showed higher levels of inflammatory markers, increased liver enzymes, hypoalbuminemia, thrombocytopenia, and coagulopathy.

Table 1: Laboratory findings

Hb	9.5 (g/dl)
WBCs	5(10^3/UL)
Neutrophil counts	66%
Lymphocyte	21%
Basophile	1%
Platelets	210(10^3/UL)
RBCS	5.3(10^6/UL)
MCV	77 (fl)
MCH	25.3 (pg)
MCHC	32.8 (g/dl)
CRP	96 (mg/l)
ESR	45 (mm/hr)
Iron	8.7(ug/dl)
Ferritin	196(ng/ml)
Albumin	2.5(g/dl)
Alkaline phosphates	387(IU/l)
AST	200(IU/l)
ALT	100(IU/l)
Creatinine	0.1(mg/d)
Urea	18 (mg/dL)
Prothrombin	15 (seconds)
INR	1.4
D-dimer	4 (mg/L)

Other pathogens testing: Other viral and bacterial pathogen testing involves [10]:

- Blood culture
- Throat culture
- Nasopharyngeal aspirate or throat swab for respiratory viral panel
- Urine culture
- Stool culture
- Cytomegalovirus serology and PCR
- Epstein-Barr virus serology and PCR
- Adenovirus PCR.
- Enterovirus PCR

By echocardiography children had depressed LV function and abnormal strain patterns. Image studies showed pleural effusion, pericardial effusion, and mild ascites.

Table 2: CDC and WHO case definitions of MIS-C

CDC case definition
All four conditions must be fulfilled:
1. Age <21 years
2. Clinical manifestations associated with MIS-C include the following:
▪ **Fever:** • Documented fever >38.0°C (100.4°F) for ≥24 hours ▪ **or** • Report of subjective fever lasting ≥24 hours
▪ Laboratory indications of inflammation • Not limited to, but include any of the following: o Elevated CRP o Elevated ESR o Elevated fibrinogen o Elevated procalcitonin o Elevated ferritin o Elevated D-dimer o Elevated IL-6 o Elevated LDH o Neutrophilia o Hypoalbuminemia o Lymphocytopenia

- Multisystem participation
  - **2 or more** organ systems included:
    - Cardiovascular (i.e., shock, increased troponin, increased BNP, arrhythmia, abnormal echocardiogram)
    - Neurologic (i.e., seizure, aseptic meningitis, stroke)
    - Respiratory (i.e., pneumonia, ARDS, pulmonary embolism)
    - Gastrointestinal (i.e., abdominal pain, diarrhea, vomiting, increased liver enzymes, GI bleeding, ileus)
    - Renal (i.e., kidney failure, AKI)
    - Hematologic (i.e., coagulopathy)
    - Dermatologic (i.e., erythroderma, other rashes, mucositis)

- Critical disease necessitating hospitalization

3. No other possible diagnoses

4. Recent or current infection or exposure to SARS-CoV-2

- **Any** of the following:
  - Positive SARS-CoV-2 RT-PCR
  - Positive antigen test
  - Positive serology
  - COVID-19 infection within four weeks of the beginning of manifestations

WHO case definition
All six conditions must be fulfilled:
1. Age 0 to 19 years
2. Fever for three days or longer
3. At least 2 of the following are clinical indicators of multisystem involvement:
▪ Bilateral non-purulent conjunctivitis, rash, or mucocutaneous inflammation manifestations (oral, feet, or hands)
▪ Shock or hypotension
▪ Heart dysfunction, valvulitis, pericarditis, or coronary anomalies (involving elevated troponin/BNP or echocardiographic findings)
▪ Proof of coagulopathy (increased D-dimer; extended PT or PTT)
▪ Acute GI manifestations (diarrhea, abdominal pain, or vomiting)
4. Increased inflammation markers (e.g., CRP, ESR, or procalcitonin)
5. No other apparent microbiological source of inflammation, such as bacterial sepsis or staphylococcal/streptococcal toxic shock syndromes
6. Proof of SARS-CoV-2 infection
▪ **Any** of the following: • Positive antigen test • Positive serology • Positive SARS-CoV-2 RT-PCR • Contact with a person infected with COVID-19

CDC: Centers for Disease Control and Prevention; **WHO:** World Health Organization; **MIS-C:** multisystem inflammatory.

This table covers the MIS-C case definitions of the CDC and WHO. Patients who fit these criteria plus complete or partial KD criteria should be deemed to have MIS-C and reported as such. In addition, MIS-C should be evaluated in any case of pediatric fatality associated with SARS-CoV-2.

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; IL-6: interleukin 6; BNP: brain natriuretic peptide; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: reverse transcription polymerase chain reaction; COVID-19: coronavirus disease 2019; PT: prothrombin time; PTT: partial prothrombin time.

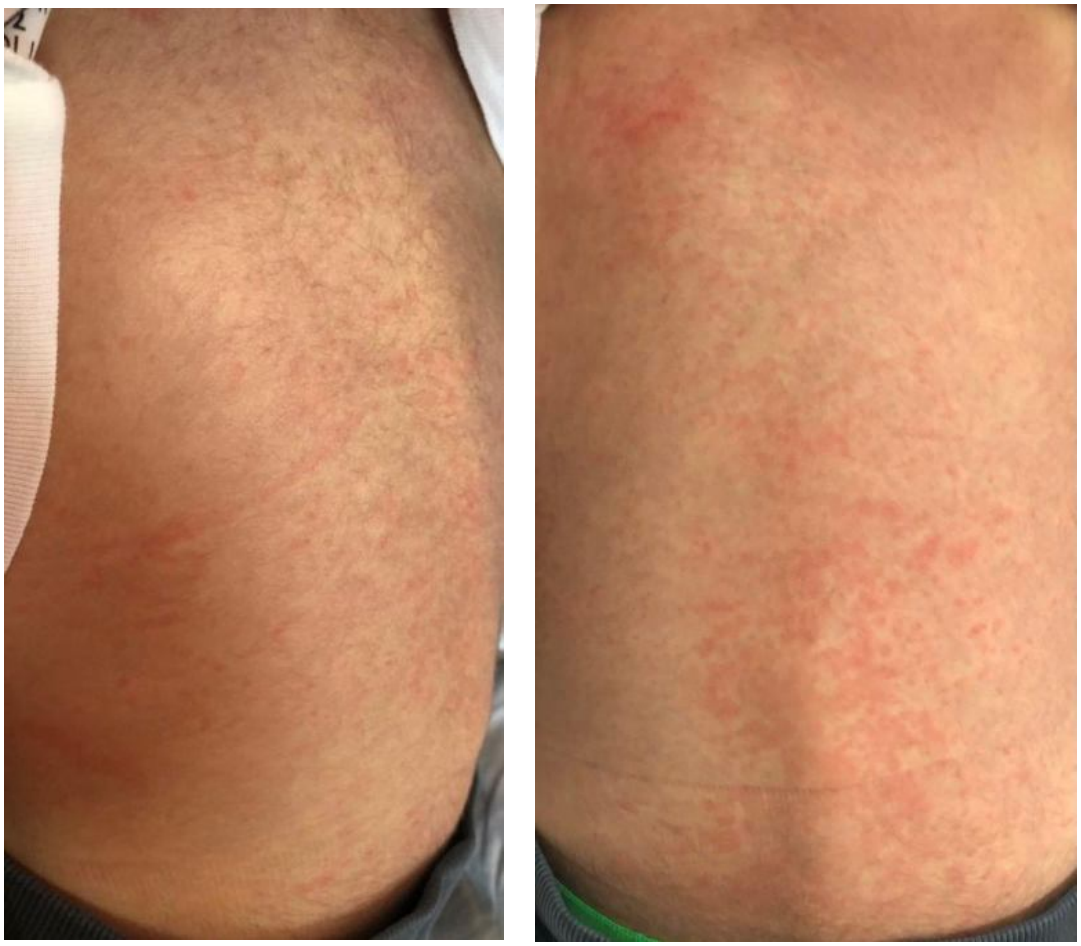

Figure 1 **Multisystem Inflammatory Syndrome in Child After Covid-19**

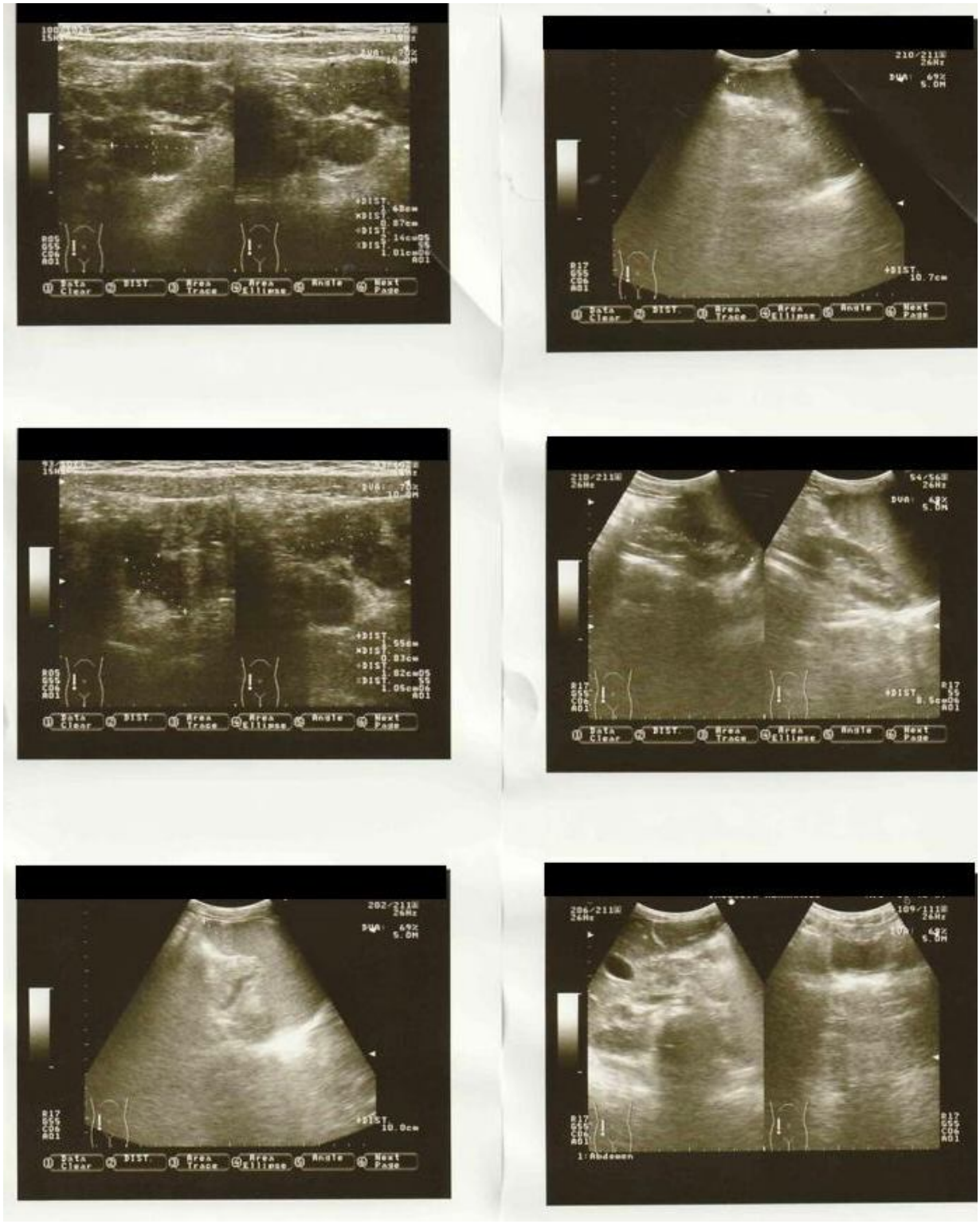

Figure 2: echocardiography images

Differentiation between MIS-C and acute COVID-19

MIS-C and severe COVID-19 clinical characteristics coincide. Yet, distinct characteristics and organs and systems participation patterns might aid distinguish between them [7, 11, 12]:

- The majority of MIS-C happened in healthy cases, while the majority of severe acute COVID-19 happened in cases with health issues.
- In the weeks before the development of febrile/inflammatory manifestations, MIS-C children might have a known or suspected history of SARS-CoV-2.
- Different patterns of organ system involvement exist [7, 11]:
    - In severe acute COVID-19, significant pulmonary involvement (e.g., pneumonia, ARDS) is a major characteristic. Although respiratory manifestations are prevalent in MIS-C, they are frequent the result of shock and/or heart dysfunction.
    - Shock and myocardial dysfunction have higher prevalent in MIS-C than severe COVID-19.
    - In MIS-C, gastrointestinal manifestations (especially abdominal pain) are more prevalent.
    - Mucocutaneous manifestations are prevalent in MIS-C but uncommon in severe acute COVID-19.
- In MIS-C, inflammatory markers (CRP, D-dimer, and ferritin) are often higher relative to severe acute COVID-19. Furthermore, thrombocytopenia and lymphopenia have higher prevalent in MIS-C [7].
- Individuals with MIS-C had greater SARS-CoV-2 antibody titers than acute COVID-19 cases [13].

Table 3: Differentiating between MIS-C and KD

MIS-C	KD
– More often impacts older children and adolescents (>7 years) – GI manifestations are very prevalent – More prevalent shock and myocardial dysfunction	– More often impacts younger children and infants (<5 years) – GI manifestations not prevalent – Less prevalent shock and myocardial dysfunction

– Inflammation markers [CRP (12–22 times typical values), D-dimer (10–20 times typical values), ferritin (1–3 times typical values)] more significantly increased – Absolute counts of lymphocytes and platelets are low	– Inflammation markers (CRP, D-dimer, ferritin) not very increased – Thrombocytosis and leukocytosis occur often

MIS-C: Multisystem Inflammatory Syndrome in Children; **KD:** Kawasaki disease; **GI:** gastrointestinal; **CRP:** C reactive protein. Finally, he recovered well after IV IG and corticosteroids and discharged well on corticosteroids with gradual withdrawal within 1 month..

Discussion

The condition has been termed MIS-C; also referred to as pediatric multisystem inflammatory syndrome (PMIS), Temporal association between PMIS and SARS-CoV-2 (PIMS-TS, pediatric hyperinflammatory shock, or pediatric hyperinflammatory syndrome). It seems to be a rather uncommon consequence of COVID-19 in children, occurring in less than 1 percent of children with proven SARS-CoV-2 infection.

Regarding our study, case presented by high grade fever (39-40 C) for five days, not responding to oral antipyretic, with swollen hands and feet started 2 days after fever, GI manifestations (abdominal pain, diarrhea, vomiting). In addition, he had difficulty of breathing, erythematous rash on the back appeared on the third day.

The manifestation of MIS-C varies and may resemble a number of different illnesses, including KD. The variances between MIS-C and KD are shown in Table 2. MIS-C cases may exhibit GI manifestations (abdominal pain, diarrhea and vomiting in 60–100% of cases), neurocognitive manifestations (headache, lethargy, and reduced mental state in 29–58% of cases), respiratory manifestations (21–65%), myalgias (8–10%) and sore throat (10–16%) [11, 14-17].

Severe instances may manifest with cardiogenic shock (66%), myocardial dysfunction (55%), cardiogenic shock (66%), cytokine storm, and multisystemic organ failure, that may coincide with KD, secondary hemophagocytic lymphohistiocytosis, septic shock, and toxic shock syndrome [18, 19].

In a global study of 183 children diagnosed with MIS-C, fever in every instance. Shock was seen in 43.2% with high prevalent in elder children (mean nine years vs seven years). Similar findings were found in a meta-analysis, with 100% of cases presenting with fever, 73.3% coming with abdominal pain or diarrhea, and 68.3% with vomiting. Most cases will have fever for at least three days, with a median period of four to six days [17].

Our findings showed that blood test showed high levels of inflammatory markers, increased liver enzymes, hypoalbuminemia, thrombocytopenia, and coagulopathy [20].

Inflammatory laboratory indicators seem to correspond with disease severity. In one study, children with shock had higher CRP levels (mean 32.1 vs 17.6 mg/dL), greater neutrophil counts (16 versus 10.8 x 10^9/L), lower lymphocyte counts (0.7 against 1.3 x 10^9/L), and lower serum albumin levels (2.2 versus 2.7 g/dL). Additionally, more children with shock showed increased cardiac markers [15].

In MIS-C, cardiac involvement is prevalent. In numerous large case series, 30 to 40% of children showed reduced LV function, and 8 to 24% had CA anomalies [7].

Tests for electrolytes, CBC, renal and hepatic function, ESR, and CRP should be performed on children who seem healthy but are at risk for MIS-C. If testing reveals ESR 40 mm/h or CRP 5 mg/dL in conjunction and one of the next laboratory defects (absolute lymphocytes 1.5, platelets 150,000, neutrophilia, sodium 135 mmol/L, or hypoalbuminemia), then comprehensive tests as mentioned above is advised. To minimize recurring blood draws in this group, it is advisable to get more blood tubes for this further tests if MIS-C is detected but the individual seems otherwise healthy [21].

92% of cases have at least four of the anomalies listed below: increased ESR (75–80%), increased CRP (90–100%), increased D-dimer (67–100%), neutrophilia (68–90%), lymphocytopenia (80–95%), increased ferritin (55–76%), anemia (48–95%), hypoalbuminemia (48–95%), thrombocytopenia (31–80%), or elevated liver enzymes (62–70%). In a large-scale investigation, individuals who presented with shock had elevated inflammatory markers and decreased platelets.

Cardiovascular involvement is typical, with elevated troponin (50–93%) and BNP/pro-BNP (73–95%). Acute kidney damage may happen to 8–52% of patients, and laboratory assessment might indicate increased hypertriglyceridemia (70%) or lactate dehydrogenase (10–60%), if these laboratory tests are performed [20, 22, 23].

In a previous study comparing 28 children with MIS-C to 20 children with classic KD, LV systolic and diastolic performance were poorer in MIS-C, although CA involvement was low frequent in classic KD [24].

Regarding management of MIS-C; The American College of Rheumatology has released MIS-C clinical recommendations. They involved a large degree of agreement for the use of high-dose IVIG (2 g/kg according to ideal body weight), glucocorticoids, or both as first-line therapies. IVIG may be administered at a rate of 1 g/kg per day for two days to individuals with cardiac dysfunction, who may need strict monitoring and diuretics. Patients with extremely raised B-type natriuretic peptides, inexplicable tachycardia, or a deteriorating look, but who do not yet have shock or other organ-threatening diseases, may receive 1 to 2 mg/kg of methylprednisolone or another steroid daily as first-line treatment. If cases do not react to corticosteroids plus IVIG, 10–30 mg/kg/day of corticosteroids should be administered [21].

Conclusion

MIS-C is a COVID-19 consequence, that generates a multi-inflammatory syndrome capable of affecting practically every organ system. Frequent symptoms involve fever, GI, neurologic, and dermatologic manifestations.

Major cases will have increased inflammatory markers, and their echocardiograms might be abnormal. Cases will typically need to be admitted to an ICU.

Therapy consists of IVIG, anticoagulation, and perhaps corticosteroids. Aspirin is advised in cases of thrombocytosis.

Consent

As per international standard or university standard, parental(s) written consent has been collected and preserved by the author(s).

Ethical Approval:
As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Conflict of interest: none

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Kim MM, Murthy S, Goldman RD. Post-COVID-19 multisystem inflammatory syndrome in children. Can Fam Physician. 2021;67:594-6.

2. Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection - United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1450-6.

3. Abrams JY, Godfred-Cato SE, Oster ME, Chow EJ, Koumans EH, Bryant B, et al. Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2: A Systematic Review. J Pediatr. 2020;226:45-54.e1.

4. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. Jama. 2020;324:294-6.

5. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020;383:334-46.

6. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated

with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Health. 2020;4:669-77.

7. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. Jama. 2021;325:1074-87.

8. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection. Pediatr Infect Dis J. 2020;39:e340-e6.

9. Capone CA, Subramony A, Sweberg T, Schneider J, Shah S, Rubin L, et al. Characteristics, Cardiac Involvement, and Outcomes of Multisystem Inflammatory Syndrome of Childhood Associated with severe acute respiratory syndrome coronavirus 2 Infection. J Pediatr. 2020;224:141-5.

10. Paediatrics R, Healteh C. Guidance—Paediatric Multisystem Inflammatory syndrome Temporally Associated with COVID-19. 2020.

11. 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. MMWR Morb Mortal Wkly Rep. 2020;69:1074-80.

12. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. Bmj. 2020;370:m3249.

13. Rostad CA, Chahroudi A, Mantus G, Lapp SA, Teherani M, Macoy L, et al. Quantitative SARS-CoV-2 Serology in Children With Multisystem Inflammatory Syndrome (MIS-C). Pediatrics. 2020;146.

14. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med. 2020;383:347-58.

15. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. Jama. 2020;324:259-69.

16. Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, et al. Acute Cardiovascular Manifestations in 286 Children With Multisystem Inflammatory Syndrome Associated With COVID-19 Infection in Europe. Circulation. 2021;143:21-32.

17. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020;26:100527.

18. Bridwell R, Long B, Gottlieb M. Neurologic complications of COVID-19. Am J Emerg Med. 2020;38:1549.e3-.e7.

19. Hennon TR, Penque MD, Abdul-Aziz R, Alibrahim OS, McGreevy MB, Prout AJ, et al. COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) guidelines; a Western New York approach. Prog Pediatr Cardiol. 2020:101232.

20. Bautista-Rodriguez C, Sanchez-de-Toledo J, Clark BC, Herberg J, Bajolle F, Randanne PC, et al. Multisystem Inflammatory Syndrome in Children: An International Survey. Pediatrics. 2021;147.

21. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. Arthritis Rheumatol. 2020;72:1791-805.

22. Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA, Duarte-Neto AN, Soares Gomes-Gouvêa M, Viu Degaspare N, et al. SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. Lancet Child Adolesc Health. 2020;4:790-4.

23. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180:307-22.

24. Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With COVID-19 in the United States. J Am Coll Cardiol. 2020;76:1947-61.