Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The Journal for Nurse Practitioners 17 (2021) 941–945

Contents lists available at ScienceDirect

The Journal for Nurse Practitioners

journal homepage: www.npjournal.org

Multisystem Inflammatory Syndrome in Children

Barbara Holstein

Keywords:
children
immune response
inflammatory
MIS-C

A B S T R A C T

Multisystem inflammatory syndrome in children (MIS-C), which was first documented in the United Kingdom and later recognized in other countries, is a postinfectious immune response to coronavirus disease 2019 (COVID-19). Its clinical manifestation resembles that of other inflammatory processes. Differentiation can be accomplished through epidemiology, a positive temporal relationship to COVID-19, and multiorgan involvement. Health care providers should maintain a high level of suspicion for MIS-C during the COVID-19 pandemic. A consistent picture of this immune response is emerging and diagnostic and treatment approaches are evolving. Advances continue to be made in the knowledge attainment regarding MIS-C clinical presentation and management.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that causes coronavirus disease 2019 (COVID-19), emerged in December 2019 in Wuhan, China, and was declared a pandemic by the World Health Organization (WHO) in March 2020. The pandemic has persisted worldwide to the present time. Respiratory illness from the virus has been devastating in adults. In contrast, children, generally have experienced mild symptoms or no symptoms at all from COVID-19, although severe illness, similar to that in adults, has developed.

An inflammatory immune response that targets children emerged during the pandemic and has been temporally linked to COVID-19. In April 2020, Riphagren et al[1] reported a unique hyperinflammatory shock that occurred in a cluster of 8 children in the United Kingdom (UK).[1] Subsequent reports arose elsewhere in the UK and then in other countries including the United States.[2-6] This novel inflammatory process has been named multisystem inflammatory syndrome in children (MIS-C).[3-8] It has been compared to Kawasaki disease (KD) and toxic shock syndrome (TSS).[2,5] However, MIS-C has demonstrated, over time, that it has its own characteristic presentation.[8] As in KD, there is no pathognomonic findings or diagnostic test.[5]

Epidemiology and Pathophysiology

The pathogenesis of MIS-C is not well understood. Based on its similarities to well-defined syndromes such as KD and TSS, MIS-C is hypothesized to be an immune dysregulation after a COVID-19 infection. This dysregulation seems to trigger macrophage activation that stimulates T-helper cells. Cytokine release then occurs, as well as neutrophil, monocyte, and macrophage stimulation. This sequence leads to B-cell and plasma cell activation. An immune response ensues with the production of antibodies.[9] Elevated levels of circulating cytokines, immune-cell hyperactivation, and secondary organ dysfunction comprise a life-threatening systemic inflammatory syndrome known as a cytokine storm.[10]

The epidemiology of MIS-C has a distinct age and race incidence, in which Black and Hispanic children representation is disproportionately high. In 2 large case series, patients had the following distribution: Black (25%-45%), Hispanic (30%-40%), White (15%-25%), and Asian (3%-28%).[3,5] A link to COVID-19 is provided by locations that are highly impacted by the virus and also have clusters of MIS-C.[9] In the US, to date, 3,185 cases have been documented, in which the median age has been 9 years old. Of the affected children, 99% tested positive for COVID-19, and 1% had an epidemiologic link. There have been 36 associated deaths.[11]

MIS-C or KD?

MIS-C shares many clinical characteristics with KD, an acute febrile illness in infants and children with the potential for coronary complications. Shared characteristics include high fever, exanthema, conjunctivitis, and cardiovascular involvement.[12] Approximately 40%-50% of MIS-C cases meet the definition of KD or partial KD.[3,5,6,13] Definitions for both inflammatory responses can be accessed from the Center for Disease Control and Prevention (CDC) and the WHO websites (Table 1).[14] Notable distinctions between KD and MIS-C are found in their epidemiology, laboratory markers, imaging, and clinical findings, which can assist in differentiation. From an epidemiologic perspective, KD is prevalent in Asian children,[12] and, as mentioned, MIS-C largely affects Blacks and Hispanics.

Clinical findings specific to MIS-C are a positive polymerase chain reaction (PCR) or serology test for COVID-19 and multiorgan involvement.[2] Gastrointestinal symptoms (particularly acute

https://doi.org/10.1016/j.nurpra.2021.05.008
1555-4155/

Table 1
Case Definitions

The Centers for Disease Control and Prevention (CDC) Definition—Multisystem Inflammatory Syndrome in Children
- An individual aged <21 years presenting with fever,[a] laboratory evidence of inflammation,[b] and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurologic); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks before the onset of symptoms.

The World Health Organization Definition—Multisystem Inflammatory Syndrome in Children

Children and adolescents 0-19 years of age with fever ≥ 3 days AND 2 of the following:
- Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet).
- Hypotension or shock.
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiography findings or elevated Troponin/NT-pro-BNP),
- Evidence of coagulopathy (by PT, PTT, elevated D-dimers).
- Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain). AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND

Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19.

CDC Definition-Kawasaki Disease:

For epidemiologic surveillance, CDC defines a case of Kawasaki disease as illness in a patient with fever of ≥ 5 days' duration (or fever until the date of administration of intravenous immunoglobulin if it is given before the fifth day of fever), and the presence of at least 4 of the following 5 clinical signs:
- Rash
- Cervical lymphadenopathy (at least 1.5 cm in diameter)
- Bilateral conjunctival injection
- Oral mucosal changes
- Peripheral extremity changes

Patients whose illness does not meet the above Kawasaki disease case definition but who have fever and coronary artery abnormalities are classified as having atypical or incomplete Kawasaki disease.

COVID-19 = coronavirus disease 2019; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; PT = prothrombin time; PTT = partial thromboplastin time; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

From: Centers for Disease Control and Prevention. Kawasaki case definition. https://www.cdc.gov/kawasaki/case-definition.html

World Health Organization Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

Centers for Disease Control and Prevention. Multisystem inflammatory Syndrome in Children (MIS-C) associated with coronavirus disease 2019 (COVID-19) Control https://emergency.cdc.gov/han/2020/han00432.asp

[a] Fever ≥ 38.0°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours.

[b] Including, but not limited to, 1 or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin.[14]

abdominal pain), myocardial dysfunction, and shock are seen in MIS-C more frequently than in KD.[3-6,8] In a study of 58 children with MIS-C by Whittaker et al,[6] inflammation was perceived to be more intense compared with that usually seen in KD. In health centers across the US, 186 children with MIS-C had organ systems affected as follows: gastrointestinal in 92%, cardiovascular in 80%, hematologic in 76%, mucocutaneous in 74%, and respiratory in 70%.[5]

Diagnostic and Management Considerations

Health providers should hold a high degree of suspicion for MIS-C when evaluating a child with fever and inflammatory symptoms and who tests positive for COVID-19 by PCR or serology testing or has had a known epidemiologic link to the virus.[15] Other infectious or noninfectious etiologies for the clinical presentation should also be considered. Differential diagnoses for MIS-C include KD, TSS, bacterial sepsis, appendicitis, and other viral infections. Recommendations for distinguishing MIS-C from KD are found in Table 2. Bacterial sepsis and TSS can be definitively diagnosed though microbiologic testing. In the presence of fever, vomiting, and abdominal pain, abdominal imaging may be needed to differentiate appendicitis from MIS-C. Viral infections, such as enteroviruses, Epstein-Barr virus, adenovirus, and cytomegalovirus, could potentially present with multisystem involvement, but these infections can be ruled out through serology or PCR testing.[14] Early recognition of MIS-C is essential, because these children are at risk for coronary aneurysms, circulatory shock, and cardiovascular complications.[16]

Presenting symptoms of MIS-C can include fever, myalgia, lymphadenopathy, changes in perfusion, tachycardia, or hypotension, all of which are indicators of inflammation.[8] The latter 3 can also be indicative of shock. Cardiopulmonary symptoms that could manifest include chest pain and respiratory distress. A rash may present as reticular, purpuric, erosive, morbilliform, or blisters. Other potential mucocutaneous symptoms are acral swelling, peeling and swollen lips, strawberry tongue, and conjunctivitis. Diarrhea, vomiting, nausea, or abdominal pain are common gastrointestinal symptoms. Headache, altered mental status, seizures, meningismus, and focal deficits are possible neurologic symptoms.[1-6,8,9,13,15]

Clinicians should be alert for possible multisystem involvement represented by these symptoms. Clinical findings that are typically found in MIS-C include shock, myocardial dysfunction, neurologic deficits, acute respiratory failure requiring noninvasive or invasive ventilation, and criteria met for complete KD, thrombosis, or acute kidney injury.[8,14]

Laboratory investigations and imaging can assess for evidence of inflammation and cardiac, renal, and hepatic function.[14] Common findings in MIS-C that are addressed through these assessments include:

- elevated inflammatory markers—C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, fibrinogen, D-dimer, procalcitonin, and interleukin 6;
- abnormal blood cell counts—neutrophilia, thrombocytopenia, lymphocytopenia, and mild anemia, and
- elevated cardiac markers—troponin and B-type natriuretic peptide (BNP).[1-8,13-16]

Miscellaneous laboratory results that may be elevated, abnormal, or low include lactase dehydrogenase (LDH), liver function tests (LFTs), albumin, and blood and urine cultures.[8,14]

Table 2
Comparison of Multisystem Inflammatory Syndrome in Children and Kawasaki Disease Characteristics

Variable	Multisystem Inflammatory Syndrome	Kawasaki Disease
Alanine aminotransferase	↑	Normal or ↑
White blood cell differentiation	Neutrophilia, lymphopenia	Neutrophilia
Platelet count	↓	↑
PT/PTT	↑↑	Normal
Fibrinogen	↑ , Normal, or ↑	Normal ↑
Troponin	↑	Normal or
B-type natriuretic peptide	↑	↑ or Normal
Ferritin	↑	↑ or Normal
Circulatory shock	+	−
Ventricular dysfunction	+	+/−
Coronary artery/dilations/aneurysms	+	+
Hypotension	+/−	−
Gastrointestinal symptoms	++	Rare
Desquamation	+	+
Mucous membrane involvement	+/−	+
Respiratory distress	+	Rare
Rash	+	+
Altered mental status	+	−

+ = generally present; ++ = almost always present; − = generally absent; +/− = may be present or absent; ↑ = increased; ↑↑ = highly increased; ↓ = decreased; PT/PTT, prothrombin time and partial thromboplastin time.
From Nakra et al.[9]

Whittaker et al[6] noted a correlation between inflammatory markers and illness severity. Children in their study demonstrated a greater likelihood of developing shock when there was a high CRP, lower lymphocyte count, and higher neutrophil count compared with those with lower values.

An echocardiogram is essential. It augments cardiac marker findings in the assessment of cardiac function or injury and is a key component in detecting coronary artery abnormalities, such as dilation or aneurysm, depressed left ventricle (LV) function, mitral valve regurgitation, or pericardial effusion.[1-8,13-16]

Initial laboratory tests include a complete blood count (CBC), a complete metabolic panel, an ESR, a CRP, as well as testing for COVID-19 through PCR or serology.[16] In preliminary laboratory findings, elevated inflammatory markers, and at least 1 of the following: neutrophilia, lymphopenia, hyponatremia, thrombocytopenia, or hypoalbuminemia warrants hospital admission for further evaluation.[16]

If hospital admission is determined as necessary, additional assessment includes an echocardiogram, an electrocardiogram (ECG), and additional laboratory testing for inflammation including ferritin, D-dimer, troponin, and pro-BNP. The latter 2 tests can further assist in identifying cardiac involvement. An elevated BNP, in particular, may help determine whether there is LV dysfunction. ECGs are recommended a minimum of every 48 hours and echocardiograms a minimum of every 7 to 14 days, initially, then every 4 to 6 weeks.[16]

Once a diagnosis for MIS-C has been determined, the goals of treatment are stabilization and prevention of long-term sequelae.[14] The best management approach is yet to be determined, but treatment guidelines have been recommended by the CDC, the American College of Rheumatology, and the American Academy of Pediatrics (AAP), all of which have relied greatly on treatment approaches that have been used in published case series.[7,14,15]

Initial treatment for MIS-C can be appropriate in an outpatient setting for children who appear well, have reassuring physical examinations with stable vital signs, and for whom there is ensured close clinical follow-up.[14,16] Treatment measures are usually directed toward underlying inflammation. It is strongly recommended that other concerning clinical findings be managed by appropriate pediatric specialist in a multidisciplinary team. Such a team can include pediatric infectious disease, cardiology, rheumatology, immunology, intensivists, and hematology. Neurology and gastroenterology consultation may also be appropriate.[8,16,17]

Some children may need to be immediately treated for shock, while treatment in others can be deferred, as in the case of minimal elevation of cardiac markers, minimal inflammation, and normal results on an ECG and echocardiogram. The need for treatment in the latter group can then be assessed through serial laboratory and imaging evaluations.[8,17] Of the 58 children in the study by Whittaker et al,[6] 22% recovered with supportive care only and pharmacotherapy was not needed.

Patients with MIS-C who meet KD or atypical KD criteria require immunomodulation therapy. Intravenous immune globulin (IVIG) is the first-line treatment. Son and Friedman[17] recommend that if a child remains persistently febrile with elevated inflammatory markers (particularly ferritin) and they are clinically worsening, IVIG should be administered.

Children considered to have mild MIS-C may not need IVIG, unless they meet criteria for KD or there is a change in clinical status or laboratory/imaging test results. In mild MIS-C, there is usually minimal respiratory support needed, no vasoactive requirements, and minimal organ injury.[8] Children who have cardiac involvement, shock, or exhibit any other severe manifestation requiring intensive care can receive IVIG without meeting KD criteria.[17] These children are considered to have moderate to severe MIS-C and typically require invasive or noninvasive ventilatory support, may have L.V. dysfunction, and usually have moderate to severe organ injury.[8] The dose of IVIG for these patients is 2 g/kg/d administered in a single infusion over 8 to 12 hours. For patients without KD, the dose is 1 g/kg/d over 8 to 12 hours.[8,15,16,17]

Glucocorticoids (eg, methylprednisolone) can be added to IVIG for refractory shock or other severe manifestation and can also serve as a second-line treatment (2 mg/kg/d) for illness that is refractory to IVIG (unrelenting fevers or significant end-organ involvement).[16] In serial case reports, in which 70% to 80% of patients were treated with IVIG and 50% to 60% received a glucocorticoid, illness improved in most patients in both groups.[2,3,5,8,18] To prevent rebound inflammation, a 2- to 3-week taper of oral steroids (eg, prednisone or prednisolone) is required for patients who received intravenous steroids. Patients who do not respond to IVIG or steroids should receive anakinra (2-10 mg/kg/d), which is an

interleukin 1 receptor antagonist that has proven very safe in the pediatric population for inflammatory illness.[15-17] Anakinra and glucocorticoids are therapeutics used for cytokine storm.[10]

Cardiac involvement that occurs in MIS-C can include LV dysfunction and coronary artery aneurysm. Serial echocardiograms can guide the management of these findings. In significant LV dysfunction, inotropic medications and intravenous diuretics may be required, including milrinone, dopamine, and dobutamine.[17]

Development of thrombotic complications, such as a thrombosis, can occur in MIS-C, due to marked elevations in D-dimer, fibrinogen levels, and severe LV dysfunction.[17] Low-dose aspirin (aspirin, 3-5 mg/kg/d) is recommended for patients with thrombocytosis as well as KD or coronary artery aneurysm [8,16,17] The AAP recommends that all MIS-C patients receive low-dose aspirin therapy.[15] Prophylactic treatment with a histamine-2 blocker or a proton pump inhibitor should be initiated concurrently with aspirin to prevent associated gastritis. Similar prophylactic treatment is recommended during steroid administration.[8] Anticoagulation with enoxaparin or low-molecular-weight heparin can be considered for moderate to severe LV dysfunction (ejection fraction < 35%).[8,17] Enoxaparin and heparin therapy are best managed by a cardiologist or hematologist.

Until cultures exclude bacterial infection, all patients should receive broad-spectrum antibiotics empirically.[7,8,15,17] The protocol for these antibiotics varies by institution. Son and Friedman[17] recommend concomitant ceftriaxone and vancomycin, whereas Godfred-Cato et al[2] prefer linezolid and ceftriaxone. Hennon et al[19] suggest adding metronidazole when there are gastrointestinal symptoms.

Patients younger than 21 years treated for suspected MIS-C should be reported to a local, state, or territorial health department. Clinicians can do so through the submission of a case report or medical records for review.[7]

Case Report 1

An 8-year-old African American boy presented to the emergency department (ED) with 2 days of fever and mild periumbilical pain without peritoneal signs. His mother reported testing positive for COVID-19 4 weeks earlier (asymptomatic). A significant stool burden was seen on an abdominal x-ray image. The boy was discharged with a diagnosis of mild gastritis, early gastroenteritis, and constipation.

The child returned to the ED the next day with persistent abdominal pain and a subjective high fever. He was tachycardic and exhibited periumbilical tenderness. An ultrasound due to suspicion for appendicitis was inconclusive. Laboratory results indicated mild thrombocytopenia and an elevated CRP (15.8 mg/dL). Further observation and a repeat abdominal ultrasound showed no evidence of appendicitis. Meanwhile, a nasopharyngeal swab for COVID-19 that had been done earlier returned as negative. He was admitted to the hospital overnight for serial abdominal examinations and received a normal saline bolus and antipyretics for persistent tachycardia and fever (>39°C). Due to elevated CRP and a 4-day history of fever, further laboratory tests included were obtained: respiratory virus panel (RVP) (negative), blood and urine cultures, repeat CRP (24.7 mg/dL), D-dimer (2.7 μg/mL), BNP (624 pg/mL), LDH (687 U/L), coagulation studies (fibrinogen, 623 mg/dL), troponin level (normal), and serologies (COVID-19). Urine was positive for hematuria, so a culture was obtained. A chest x-ray was negative. Empiric ceftriaxone was started pending culture results.

Twelve hours after admission, high fever, tachycardia, and abdominal pain continued. There were still no characteristic symptoms of MIS-C such as mucocutaneous changes, conjunctivitis, diarrhea, or vomiting. Abdominal magnetic resonance imaging definitively ruled out appendicitis. An echocardiogram showed significant ectasia of the left anterior descending coronary artery and reduced peak global longitudinal strain (a sensitive marker for cardiac dysfunction). Because the echocardiogram finding was consistent with KD (due to ectasia), IVIG and high-dose aspirin were administered.

Shortly after pharmacologic treatment, the child became hypotensive and was transferred to the pediatric intensive care unit (PICU), where he rapidly decompensated due to cardiogenic shock (ejection fraction < 30%) and subsequent respiratory failure associated with pulmonary edema and acute kidney injury. He was intubated, and mechanical ventilation and inotropic support were initiated. Low-molecular-weight heparin was started due to elevated BNP and a potential for thrombosis, IVIG was repeated, and ASA was continued. Methylprednisolone and anakinra were administered due to concern for a possible cytokine storm upon further diminishing in cardiac function. A second nasopharyngeal swab and serology for COVID-19 returned positive. A diagnosis of MIS-C was established. Remdesivir, an antiviral, was given due to concurrent COVID-19.

An echocardiogram 20 hours after anakinra and methylprednisolone showed an increased ejection fraction (60%) and improvement in myocardial strain. Thirty-six hours after administration of remdesivir and anakinra, improvement continued, with fever consistently abating and respiratory status allowing for mechanical ventilation weaning. Four days after admission, new laboratory results showed CRP (26.1 mg/dL), ferritin, (904 ng/mL), LDH (939 U/L), troponin (668 ng/mL), BNP (9500 pg/mL), D-dimer (4.4 μg/mL), and fibrinogen (769 mg/dL).

The patient was successfully extubated 66 hours after administration of remdesivir and anakinra. No further cardiopulmonary complications arose. A final echocardiogram showed diffuse ectasia and normal biventricular size, wall thickness, and systolic function. The child was discharged after receiving 2 weeks of anakinra and 10 days of remdesivir. Discharge medications included aspirin, famotidine, enalapril, tapered prednisolone, and enoxaparin. Follow-up with hematology was arranged.[20]

Summary: This child had elevated inflammatory markers, involvement of 5 organ systems, and a positive PCR for COVID-19. Emergency-use remdesivir is defined as “when there is suspected COVID-19 in hospitalized children > 3.5 kg.”[21] A 4-day illness and hospitalization raised suspicion for a hyperinflammatory process. Hence, steroids and anakinra were given to prevent a cytokine storm.[10] CDC and WHO criteria were met for MIS-C. CDC criteria was met for atypical KD. Either high-dose aspirin (80-100 mg/kg) or low-dose aspirin (3-5 mg/kg) and IVIG are first-line treatments for KD.[12]

Case Report 2

A 9-year-old African American, previously healthy boy, presented to the ED with altered mental status, a 4-day history of fever, conjunctivitis, shortness of breath, diarrhea, vomiting, and facial swelling. The child was admitted to the pediatric intensive care unit, where he was intubated and placed on bilevel inspiratory positive airway pressure, after becoming hypoxic and progressing to respiratory failure. An echocardiogram showed borderline low systolic function with a shortened ejection fraction (29%-30%) so milrinone and dopamine were administered. Laboratory results indicated neutrophilia (16.04 K/uL), leukocytosis (white blood cells, 100/μl), hypoalbuminemia (3.4 g/dL), CRP (284.4 mg/L), fibrinogen (495 mg/dL), D-dimer (4.29 μg/mL), ferritin (2,574 ng/mL) troponin (1.456 ng/mL), BNP (383 pg/mL), RVP (neg), and PCR for COVID-19 (positive). A chest x-ray showed bilateral infiltrates, and the ECG showed nonspecific T wave changes and a low voltage QRS. Cerebrospinal fluid was consistent with meningitis (100/μL white cells and 52% lymphocytes). Blood cultures were pending.

Broad-spectrum antibiotics were given (intravenous linezolid and ceftriaxone) in addition to methylprednisolone and enoxaparin. Hospitalization was complicated by kidney function impairment with a high serum creatine (2.08), which resolved with fluids.

The child became afebrile on day 3 with negative blood cultures. He recovered after an intensive care unit course of 6 days. He was discharged to home with appropriate follow-up to screen for long-term complications.[22]

Summary: This child had elevated inflammatory markers, involvement of 4 organ systems, and a positive PCR for concurrent COVID-19. CDC and WHO criteria were met for MIS-C. Emergency-use remdesivir could have been considered due to the positive PCR for COVID-19.[20] Enoxaparin was given to prevent thrombosis due to a shortened ejection fraction (29%-30%).[17]

Case Report 3

A 5-year-old girl, after 10 days of fever, presented to the ED with hyperemic macules on her hands and feet, which were reported as developing 4 days after fever onset. Conjunctival hyperemia, oral fissures, and strawberry tongue were also found on examination. In addition, there was peeling of her hands and feet associated with palmoplantar hyperemia. A 2-cm, right-sided, nonsuppurative cervical lymph node was noted (unknown onset). The child reported nausea, diffuse abdominal pain, and headache.

Because KD criteria were met, IVIG and aspirin were administered immediately. She was admitted to the hospital. An echocardiogram showed dilation of the right coronary artery and normal diameter of the left coronary artery. Initial laboratory/imaging included COVID-19 serology (positive), ESR (33 mm/hr), leukocytes (7.5/μl), platelets (182/μl), and chest x-ray, blood, and urine cultures (negative). Additional laboratory tests were done after 36 hours of IVIG: BNP (174 pg/mL), troponin (0.003 ng/mL), D-dimer (780 μg/mL), fibrinogen (260 mg/dL), ferritin, (295.8 ng/mL), and LDH (403 U/L).

Within 48 hours of presentation, abdominal pain subsided, fever abated, lymphadenopathy was diminishing (1.5 cm), and planter scaling and oral lesions were resolving. The child was discharged on aspirin with a scheduled follow-up.[23]

Summary: This child had 3 organ systems involved, laboratory results showing hyperinflammation and positive serology for COVID-19 indicating past infection, so remdesivir is not recommended.[20] WHO and CDC criteria were met for MIS-C. CDC criteria were met for KD.

Conclusion

Follow-up care is essential for MIS-C and could include cardiology for further echocardiograms, rheumatology for steroid tapering, or hematology for management of ongoing anticoagulation.[10] MIS-C has an uncertain prognosis. Most children survive it, but the disease course can be quite severe and require intensive care. Significant sequelae, including death, can occur. A further understanding of the pathogenesis of MIS-C could advance prevention, diagnostic, and management approaches. Long-term outcomes could be impacted as more knowledge is gained.

References

1. Riphagren S, Gomez X, Gonzalez-Martinez C, Wilkinson C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* 2020;395:1607-1608. https://doi.org/10.1016/S0140-6736(20)31094-1.
2. Godfred-Cato S, Bryant B, Leung J, Oster M. COVID-19-associated multisystem inflammatory syndrome United States—March-July 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69:1074-1080. https://doi.org/10.15585/mmwr.mm6932e2.
3. Dufort E, Koumans E, Chow E, Rosenthal E. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med.* 2020;383:347-358. https://doi.org/10.1056/NEJMoa2021756.
4. Chiotos K, Bassiri H, Behren E, Blatz A, Chang J. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. *J Pediatric Infect Dis Soc.* 2020;9(3):393-398. https://doi.org/10.1093/jpids/piaa069.
5. Feldstein L, Rose S, Horwitz J, Collins M, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med.* 2020;383(4):334-346. https://doi.org/10.1056/NEJMoa2021680.
6. Whittaker E, Bamford A, Kenny J, Kaforou M. Clinical characteristics of 58 children with a pediatric inflammatory multisystem temporally associated with SARS-CoV-2. *JAMA.* 2020;324:259-269. https://doi.org/10.1001/jama.2020.10369.
7. Centers for Disease Control and Prevention. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C); Accessed April 13, 2021, https://www.cdc.gov/mis-c/hcp/index.html.
8. Jonat B, Gorelik M, Boneparth A, Gleneslaw S. Multisystem inflammatory syndrome in children associated with coronavirus disease 2019 in a children's hospital in New York City: patient characteristics and an institutional protocol for evaluation, management, and follow-up. *Pediatr Crit Care Med.* 2021;22(3):e178-e191. https://doi.org/10.1097/PCC.0000000000002598.
9. Nakra N, Blumberg D, Herrara-Guerra A, Lakshminrusimh S. The emergence of clusters of cases in locations that have been heavily impacted by COVID 19, such as Italy, the U.K, and New York City, is highly suggestive of a link to infection with SARS-CoV-2. *Children (Basel).* 2020;7(7):69. https://doi.org/10.3390/children7070069.
10. Fajgenbaum DC, June CH. Cytokine storm. *N Engl J Med.* 2020;383:2255-2273. https://doi.org/10.1056/NEJMra2026131.
11. Centers for Disease Control and Prevention. Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States; Accessed April 13, 2021, https://www.cdc.gov/mis-c/cases/index.html.
12. McCrindle B, Rowley A, Newburger J, Burns J. Diagnosis, treatment, and long-term management of Kawasaki disease: a **s**cientific **s**tatement for health professionals from the American Heart Association. *Circulation.* 2017;135:e927-e999. https://doi.org/10.1161/CIR.0000000000000484.
13. Verdoni L, Mazza A, Gervason A, Martelli L. Kawasaki-like disease at the Italian epicentre of the Sars-CoV-2 epidemic: an observational study. *Lancet.* 2020;395:1771-1778. https://doi.org/10.1016/S0140-6736(20).31103-X.
14. Son M, Friedman K. COVID-19: multisystem inflammatory syndrome in children (MIS-C) clinical features, evaluation, and diagnosis. *Up to Date*; Accessed March 26, 2021, https://www.uptodate.com/contents/covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-clinical-features-evaluation-and-diagnosis.
15. American Academy of Pediatrics. Multisystem Inflammatory Syndrome in Children (MIS-C): Interim Guidance. May 14, 2020; Accessed March 24, 2021, https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/.
16. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology: clinical guidance for pediatric patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in COVID-19. Version 2. *Arthritis Rheumatol.* 2020;73:e13-e29. https://doi.org/10.1002/art.41616.
17. Son M, Friedman K. COVID-19: multisystem inflammatory syndrome in children (MIS-C) management and outcome. *Up to Date*. Accessed March 26, 2021, https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-management-and-outcome.
18. Kaushik S, Aydin S, Derespina K, Bansal P. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. *J Pediatr.* 2020;224:24-29. https://doi.org/10.1016/j.peds.2020.06.045.
19. Hennon T, Penque M, Abdul-Aziz R, Alibrahim O. COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) guidelines; a Western New York approach. *Progr Pediatr Cardiol*; Published online May 23, 2020, https://doi.org/10.1016/j.ppedcard.2020.101232.
20. Mahajan N, Chang H, Leeman R, Manalo R. Case of multisystem inflammatory syndrome in children presenting as fever and abdominal pain. *BMJ Case Rep.* 2020;13, e237306. https://doi.org/10.1136/bcr-2020-237306.
21. Lexicomp. Remdesivir: Pediatric drug information. *Up to Date*. Accessed April 11, 2021, https://www.uptodate.com/contents/remdesivir-pediatric-drug-information.
22. Kest H, Kaushik A, DeBruin W, et al. Multisystem inflammatory syndrome in children (MIS-C) associated with 2019 novel coronavirus (SARS-CoV-2) infection. *Case Rep Pediatr.* 2020;224:24-29. https://doi.org/10.1155/2020/8875987.
23. Carraro M, Rodrigues B, Rodrigues V. Case report: multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 with coronary involvement. *Arch Med Res.* 2020;4:760-765. https://doi.org/10.26502/acbr.50170141.

Barbara Holstein, MSN, FNP (retired), is a volunteer provider at Hope Clinic, Midvale, UT, and can be contacted at barbholstein9@gmail.com.

In compliance with standard ethical guidelines, the author reports no relationships with business or industry that would pose a conflict of interest.