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A Case of Multisystem Inflammatory Syndrome in Children Following SARS-CoV-2 Infection in a Rural Emergency Department

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ABSTRACT
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), also known as COVID-19, has rapidly spread across the globe resulting in a worldwide pandemic. This disease has such varying presentation within the population. Although rare, multisystem inflammatory syndrome in children (MIS-C) is a potentially fatal complication of SARS-CoV2 infection and can be easily missed in the early stages. Because emergency department (ED) providers are often the initial treating providers, knowledge of the clinical manifestations and treatment of MIS-C is essential. The purpose of this article is to present a case of MIS-C in a rural ED, describe the subtle signs of disease, and educate clinicians on this rare and potentially deadly disease. **Key words:** COVID-19, MIS-C, multisystem inflammatory syndrome in children, pediatric emergency medicine

IN LATE 2019, a novel coronavirus was discovered and attributed to multiple pneumonia cases in the city of Wuhan, China (Nakra, Blumberg, Herrera-Guerra, & Lakshminrusimha, 2020; Son & Friedman, 2020). Since its identification, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), also known as coronavirus disease-2019 (COVID-19), has quickly spread across the globe resulting in a worldwide pandemic (Nakra et al., 2020). Oddly enough, initial reports indicated that children were unequally affected by COVID-19 infection, with the majority demonstrating little to no symptoms (Dufort et al., 2020; Nakra et al., 2020).

However, in April 2020, reports emerged from Europe describing a hyperinflammatory process possibly related to SARS-CoV2 in previously healthy children with features similar to Kawasaki disease (KD) and toxic shock syndrome (TSS) (Dufort et al., 2020; Feldstein et al., 2020; Godfred-Cato et al., 2020; Levin, 2020). On May 14, 2020, the Centers for

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Box 1. CDC case definition of multisystem inflammatory syndrome in children

An individual <21 years presenting with:
1. Subjective or objective fever ≥38.0 °C for ≥24 hr
2. Laboratory evidence of inflammation[a]
3. Severe illness requiring hospitalization *and*
4. Multisystem (≥2) organ system involvement[b]
5. Current or recent positive SARS-CoV-2 infection by RT-PCR serology or antigen test *or* COVID-19 exposure within 4 weeks prior to onset of symptoms
6. No alternative diagnosis

Note. COVID-19 = coronavirus disease-2019; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. Adapted from CDC (2020a).
[a]Including but not limited to elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lithium dodecyl sulfate, interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin.
[b](i.e., renal, cardiac, respiratory, hematologic, gastrointestinal, dermatologic, or neurological).

Disease Control and Prevention (CDC, 2020a) released a national health advisory, which established reporting guidelines and a case definition of multisystem inflammatory syndrome in children (MIS-C; Levin, 2020) (see Box 1).

EPIDEMIOLOGY

Since MIS-C is an emerging syndrome, the incidence remains unclear. However, in the majority of children, COVID-19 infection is typically mild with MIS-C being a rare complication (Son & Friedman, 2020). As of October 1, 2020, a total of 1,027 patients meeting the case definition of MIS-C have been reported to the CDC (CDC, 2020b). One study estimated the incidence of MIS-C as 2 per 100,000 (Dufort et al., 2020).

Unlike KD, the majority of MIS-C cases have been reported in older children and adolescents (Son & Friedman, 2020). Black and Hispanic children seem to be disproportionally affected, accounting for 73.6% of reported cases (Godfred-Cato et al., 2020; Son & Friedman, 2020). Most patients were admitted to the intensive care unit (ICU) with a median length of stay of 5 days (Godfred-Cato et al., 2020). Interestingly, research has consistently demonstrated an approximate 1-month lag between the peak of COVID-19 cases in communities and the rising incidence of MIS-C (Nakra et al., 2020; Son & Friedman, 2020).

PATHOPHYSIOLOGY

The pathogenesis of MIS-C is presently under active investigation (Feldstein et al., 2020; Son & Friedman, 2020). Although not well understood, the pathophysiology of MIS-C is believed to be related to an abnormal immune response to COVID-19 infection, similar to the pathogenesis of KD, secondary hemophagocytic lymphohistiocytosis (SHLH), and macrophage activation syndrome (MAS) (Nakra et al., 2020; Son & Friedman, 2020). Given the timeline of rising MIS-C cases in relation to peak COVID-19 cases within communities, a postinfectious hyperinflammatory process is suspected. Furthermore, the majority of reported MIS-C cases have had negative SARS-CoV-2 polymerase chain reaction (PCR) testing and positive serologic testing (Nakra et al., 2020; Son & Friedman, 2020). This further validates the hypothesis that MIS-C is the result of postinfectious immune dysregulation (Son & Friedman, 2020).

CLINICAL CASE PRESENTATION

Chief Complaint

Fever and rash.

History of Present Illness

The patient was a 7-year-old boy who presented to a rural emergency department (ED) fastrack with a 1-day history of fever, intermittent rash, and fatigue. The patient's mother reported that he developed a rash the previous night, which she treated with

diphenhydramine. She reported that patient was "restless" throughout the night. However, the rash had resolved the next morning, so she sent him to school. The patient's mother reported that the school contacted her later that day stating that he had a fever of 100.5 °F and that "he didn't look like he felt well." The patient's mother also reported decreased appetite and oral intake. She denied any associated nausea, vomiting, or diarrhea. His mother also stated that she and patient's father had both tested positive for COVID-19 approximately 1 month prior.

Review of Systems

The patient reported fever, fatigue, nasal congestion, and rhinorrhea. He denied sore throat, chest pain, shortness of breath, dizziness, or loss of taste or smell. He also reported an intermittent rash.

Medical and Surgical History

The patient's mother reported a history of *Helicobacter pylori* infection as a toddler. She denied any previous hospitalizations or surgeries. The patient had no known drug allergies and denied taking any prescription medications. His immunizations were up to date.

Family and Social History

The patient's parents and grandparents were treated for COVID-19 infection approximately 1 month prior.

Physical Examination

Vital signs: Temperature 101.5 °F; pulse 125 bpm; blood pressure 120/72 mmHg; respiratory rate 26 breaths/min; SaO_2 98% on room air.

General: Mildly ill appearing child. Well-groomed. Active and attentive.

Skin: Pink, warm, and dry. Very faint well-circumscribed, urticarial rash noted to anterior aspect of the left knee.

HEENT (heads, eyes, ears, nose, throat): PERRLA (pupils equal, round, and reactive to light and accommodation). Conjunctiva clear and without injection bilaterally. Nose patent and clear without rhinorrhea. tympanic membranes (TMs) pearly gray without bulging or loss of landmarks. Mucous membranes moist. Uvula midline. Pharynx without erythema, postnasal drip, tonsillar hypertrophy, or exudate. Neck supple. No lymphadenopathy.

Thorax/lungs: Respirations regular and unlabored. Lungs clear to auscultation bilaterally. No accessory muscle use, retractions, or nasal flaring noted.

Cardiovascular: Mild tachycardia. No murmurs, rubs, or gallops.

Gastrointestinal: Abdomen soft and nontender to palpation.

Neurological: Alert. Answered questions appropriately. Steady gait.

Labs

A complete blood cell count (CBC) with differential, comprehensive metabolic panel (CMP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urinalysis, mononucleosis (mono) spot, and point-of-care (POC) RNA PCR COVID-19 test were ordered. Pertinent results included a white blood cell count of $4 \times 10{,}000/\mu l$, platelets $225 \times 10{,}000/\mu l$, hemoglobin 9.7 g/dl, sodium 134 mmol/L, creatinine 0.4 mg/dl, blood urea nitrogen (BUN) 10 mg/dl, CRP 5.0 mg/dl, ESR 48 mm/hr, negative mono spot, and negative POC RNA PCR COVID-19.

Initial Management

The child had a nontoxic appearance; however, given fever, rash, and recent SARS-CoV-2 in the home, workup was initiated to evaluate for MIS-C. The rash was faint, but photographs the mother had taken revealed a left knee with what appeared to be urticarial rash. The case was discussed with the on-call pediatrician. Based on the physical examination and laboratory findings, the on-call pediatrician felt that the patient did not meet the CDC diagnostic criteria for MIS-C. He was afebrile on reassessment and had tolerated

two popsicles without difficulty. The mother was counseled on reasons to return, and next day follow-up was scheduled with his pediatrician.

Treatment Course and Outcome

The patient was evaluated by his pediatrician in clinic the next day due to persistent fever and intermittent rash. He had also developed some diarrhea. Mild scleral injection and a blanching, erythematous rash that had spread to his trunk, hands, feet, and face were also noted on examination. The patient was still tolerating fluids and having normal urine output, so he was discharged home. However, overnight his condition deteriorated, and he was admitted to the pediatric floor of a rural community hospital for further workup and management of dehydration. Repeat laboratory reports were significant for sodium 131 mmol/L, BUN 46 mg/dl, creatinine 1.6 mg/dl, and CRP 19.1 mg/dl. Despite fluid resuscitation, the patient demonstrated persistent hyponatremia and elevated BUN and creatinine. Overnight, he developed worsening rash, periorbital edema, conjunctival injection, and hypotension. Therefore, the patient was transferred to a tertiary children's hospital for further evaluation by pediatric subspecialists.

At the accepting facility, the patient's laboratory findings revealed hyponatremia, hypokalemia, and elevated ferritin, CRP, D-dimer, fibrinogen, B-type natriuretic peptide (BNP), and troponin. Although his initial electrocardiogram (EKG) and echocardiogram (ECHO) were both within normal limits, repeat ECHO demonstrated a decreased ejection fraction of 50%–55% and mild left atrial dilation concerning for diastolic dysfunction. In addition, the patient's COVID-19 antibodies were positive. This combined with persistent fever, elevated inflammatory markers, and multiorgan dysfunction met the diagnostic criteria for MIS-C (CDC, 2020a). The patient received intravenous immunoglobulin (IVIG), methylprednisolone, aspirin, and famotidine. Following a complicated hospital course, he was discharged home after a week-long hospitalization. He remains symptom free and is being monitored by a pediatric cardiologist and rheumatologist for the next year.

DISCUSSION

This case demonstrates that patients with MIS-C can rapidly progress to critical condition. Although MIS-C is a rare complication of COVID-19 infection, prompt recognition and evaluation are essential. In this case, CDC criteria were reviewed and followed. Because the rash had faded, it was felt that this child did not qualify for two-organ system involvement. Retrospectively, the child also had elevated liver functions and recent rash, which would meet diagnostic criteria for MIS-C. With a new emerging illness with varying presentation, the authors hope this case will help educate clinicians. Based on this case presentation, do not discount the benign appearance of a rash and realize that a recent rash in this setting should meet the criteria of organ system involvement.

APPROACH TO THE PATIENT IN THE ED

Health History and Physical Examination

Initial evaluation of patients under investigation for MIS-C should include assessment of vital signs, perfusion, and oxygenation (American Academy of Pediatrics [AAP], 2020). Unless the patient is unstable, a thorough health history should be obtained. This may reveal clues that lead to a diagnosis of MIS-C and help guide medical management. The clinician should inquire about a history of documented or suspected SARS-CoV-2 infection in the past 1–2 months, including exposures, travel, and pets (Children's Hospital of Philadelphia [CHOP], 2020; Wolfe, Nassar, Divya, Krilov, & Noor, 2020).

The clinician should also ask about the onset of symptoms and length of illness. One study found that the average time span from symptom onset to hospital admission was 4 days (Dufort et al., 2020).

The health history should also focus on ascertaining the presence of fever associated with multiorgan dysfunction including cardiac, gastrointestinal, dermatological, hematological, renal, respiratory, and neurological manifestations (AAP, 2020; CHOP, 2020). Assessment of the patient's hydration status and urine output should also be obtained (CHOP, 2020).

Although there is a wide variety of signs and symptoms, the majority of reported cases of MIS-C had similar clinical presentations (see Table 1) (Son & Friedman, 2020; Whittaker et al., 2020). A persistent fever without an identifiable source is the clinician's first clue (AAP, 2020). Most patients present with a 3 to 5-day history of fever, although shorter durations have been reported (Son & Friedman, 2020).

In addition to fever, other common presenting symptoms include gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain. Several children have presented with symptoms similar to acute appendicitis. (Nakra et al., 2020). Respiratory symptoms such as cough are uncommon unless related to severe shock. Many patients with MIS-C often report neurocognitive symptoms such as headache, lethargy, and confusion (Son & Friedman, 2020).

Symptoms similar to KD are also common. During the physical examination, patients with suspected MIS-C should be assessed for the presence of mucous membrane changes, conjunctivitis, rash, red/swollen hands and feet, and lymphadenopathy (AAP, 2020; Son & Friedman, 2020). The rash associated with MIS-C is typically polymorphic, maculopapular, and/or petechial. It is not vesicular. Erythroderma may also be present (CHOP, 2020).

As previously mentioned, these patients should be assessed for signs and symptoms of hemodynamic instability as a result of acute heart failure and shock. The clinician should monitor for the development of shortness of breath, hypotension, tachypnea, tachycardia, and poor perfusion (AAP, 2020; CHOP, 2020)

Diagnostic Workup

Children under investigation for MIS-C may require a variety of diagnostic tests (American College of Rheumatology, 2020). Figure 1 outlines the initial assessment and evaluation of these patients in the ED. According to the American College of Rheumatology (ACR) (2020), other infectious and noninfectious etiologies that could explain the patient's presentation should first be evaluated and ruled out.

Initial screening for MIS-C may include CBC, CMP, ESR, CRP, urinalysis, and SARS-CoV-2 PCR and/or serologies (AAP, 2020;

Table 1. Signs and symptoms of multisystem inflammatory syndrome in children

Body system	Physical examination findings
General	Fever (median 4–6 days), epidemiologic connection to COVID-19
Eyes	Conjunctivitis
Mucous membranes	Erythema and cracking of lips, strawberry tongue, and/or pharyngitis
Neck	Lymphadenopathy
Chest	Shortness of breath, hypotension, tachypnea, tachycardia, poor perfusion
Gastrointestinal	Vomiting, diarrhea, abdominal pain
Neurologic	Headache, irritability, lethargy, altered mental status, meningismus, cranial nerve palsies
Integumentary	Rash (polymorphic, maculopapular, or petechial; *not* vesicular)
Extremities	Erythema/edema of hands and feet

Note. Adapted from CHOP (2020).

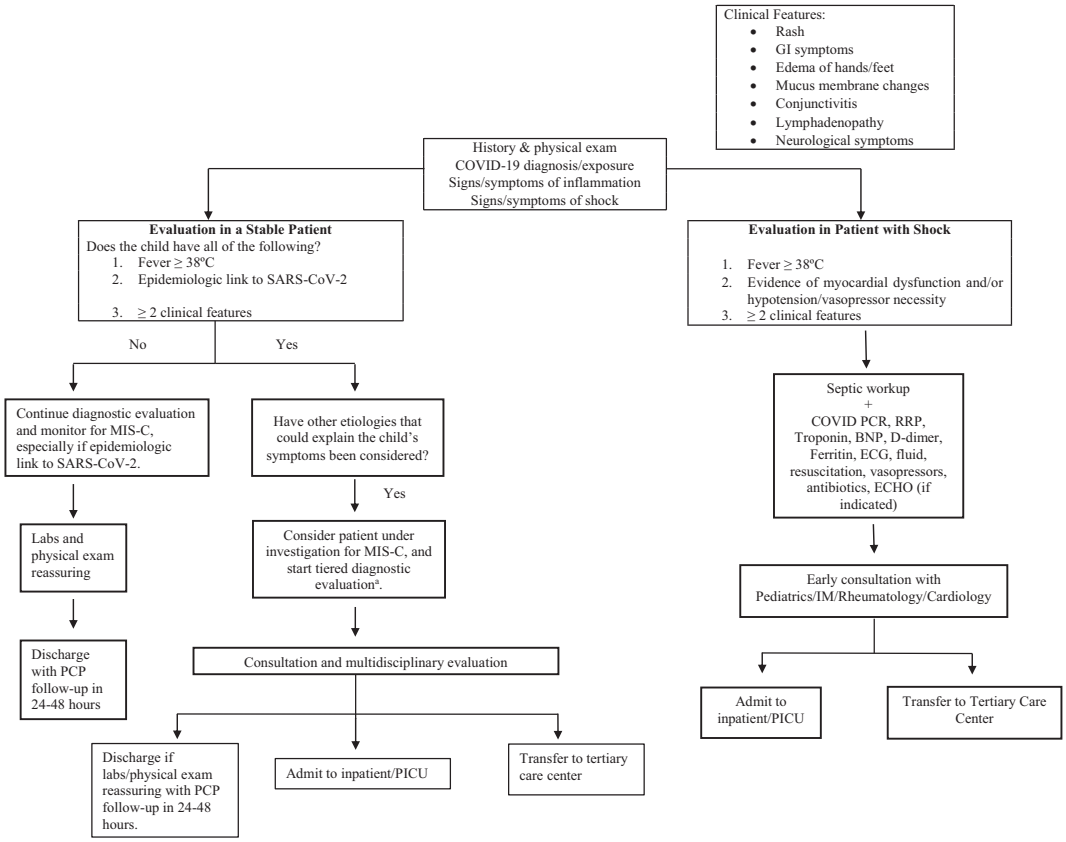

Figure 1. Diagnostic pathway for multisystem inflammatory syndrome in children in the emergency department. From CHOP (2020) and ACR (2020).

ACR, 2020; CHOP, 2020). Children with MIS-C demonstrate marked elevation in inflammatory markers (Whittaker et al., 2020). In addition, other notable laboratory abnormalities include lymphocytopenia, neutrophilia, mild anemia, thrombocytopenia, hyponatremia, and hypoalbuminemia (ACR, 2020; Son & Friedman, 2020). If present, further evaluation is warranted including but not limited to BNP, troponin, procalcitonin, ferritin, prothrombin time, partial thromboplastin time, D-dimer, lactate dehydrogenase, cytokine panel, triglycerides, EKG, and ECHO (ACR, 2020).

Common ECHO findings include decreased left ventricular function and coronary artery abnormalities, including dilation and aneurysm (Nakra et al., 2020; Son & Friedman, 2020). In addition, patients with suspected MIS-C may require further diagnostic studies and imaging such as chest x-ray, abdominal imaging, and lumbar puncture (ACR, 2020). (see Figure 2)

Diagnosis

Diagnosis of MIS-C is based on the case definition established by the CDC (see Box 1). However, as more cases are reported and information becomes available, this definition is likely to evolve (Son & Friedman, 2020). Therefore, prompt consultation with pediatric specialists and subspecialists is essential (AAP, 2020).

Differential Diagnosis

Due to the vague case definition and lack of confirmatory laboratory testing, it is often

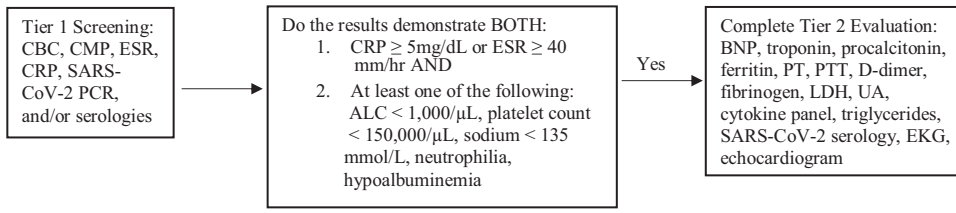

Figure 2. Multisystem inflammatory syndrome in children tiered diagnostic approach. From ACR (2020).

difficult to distinguish MIS-C from other infectious and inflammatory conditions (Godfred-Cato, 2020, Son & Friedman, 2020). The differential diagnoses of MIS-C include bacterial sepsis, TSS, KD, staphylococcal scaled skin syndrome, rickettsial illnesses, appendicitis, SHLH, MAS, and other viral illnesses (CHOP, 2020; Son & Friedman, 2020). Other more minor differential diagnoses are viral respiratory infections and strep pharyngitis (Nakra et al., 2020).

Treatment

The goal of treatment in patients MIS-C is to decrease systemic inflammation and repair organ damage, which results in decreased mortality and the risk of long-term complications (Nakra et al., 2020). Because MIS-C results in multiorgan dysfunction, treatment should be based on a multidisciplinary approach including many pediatric specialists and subspecialists such as cardiology, infectious disease, immunology, hematology, rheumatology, and critical care (AAP, 2020).

Treatment is dependent upon the patient's individual presentation, but interventions often include IVIG, steroid therapy, biologics, empiric antibiotics, and prophylactic antithrombotic therapy (AAP, 2020; Son & Friedman, 2020).

Disposition

Appropriate disposition is contingent upon the patient's condition and severity of illness (Son & Friedman, 2020). The majority of children under investigation for MIS-C should be admitted to a tertiary care setting with pediatric ICU capabilities (AAP, 2020, Nakra et al., 2020). ED providers should initiate early consultation with pediatric subspecialists. However, this should not delay transfer (AAP, 2020).

Outpatient management may be considered in children who are well-appearing with stable vital signs and a short duration of fever. Close follow-up must be ensured, and these patients should be reevaluated every 24 hours (ACR, 2020; Nakra et al., 2020).

CONCLUSION

MIS-C is an emerging, life-threatening hyperinflammatory syndrome that results in multiorgan dysfunction in previously health children (Feldstein et al., 2020). A case definition has been established by the CDC, but further research is needed to establish the exact incidence, predisposing factors, pathogenesis, and optimal management (Nakra et al., 2020).

Based on the case presentation, not every pediatric patient with a rash should have such an extensive workup. ED provider knowledge of MIS-C criteria for further evaluation is crucial. A thorough health history including documented or suspected COVID-19 infection or exposure within the preceding month may be beneficial in establishing an accurate diagnosis. ED providers are often the first clinicians to care for these patients and can help identify this illness to ensure proper treatment by pediatric subspecialists.

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