Published in final edited form as:

Pediatr Infect Dis J. 2021 April 01; 40(4): e159–e161. doi:10.1097/INF.0000000000003050.

Mistaken MIS-C: A Case Series of Bacterial Enteritis Mimicking MIS-C

Zephyr D. Dworsky, MD[1,2,*], **Jordan E. Roberts, MD**[3,4,*], **Mary Beth F. Son, MD**[3,4], **Adriana H. Tremoulet, MD, MAS**[1,2], **Jane W. Newburger, MD, MPH**[3,5], **Jane C. Burns, MD**[1,2]

[1]Department of Pediatrics, University of California San Diego School of Medicine, La Jolla, CA, USA

[2]Rady Children's Hospital San Diego, San Diego, CA, USA

[3]Department of Pediatrics, Harvard Medical School, Boston, MA, USA

[4]Division of Immunology, Boston Children's Hospital, Boston, MA, USA

[5]Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) following SARS-CoV-2 infection is characterized by fever, elevated inflammatory markers, and multisystem organ involvement. Presentations are variable, but often include gastrointestinal symptoms. We describe five children with fever and gastrointestinal symptoms initially concerning for MIS-C who were ultimately diagnosed with bacterial enteritis, highlighting the diagnostic challenges presented by the SARS-CoV-2 pandemic.

Keywords

Multisystem Inflammatory Syndrome in Children (MIS-C); SARS-CoV-2; COVID-19; bacterial enteritis

Introduction:

Several months into the SARS-CoV-2 pandemic, physicians described a new clinical entity characterized by severe inflammation in the setting of recent SARS-CoV-2 infection.[1,2] Shortly thereafter, the Centers for Disease Control and Prevention (CDC) released a case definition for the Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19, which included fever, laboratory evidence of inflammation, and multisystem organ involvement.[3] Further case series showed that while patients with MIS-C have a wide spectrum of presentations, common symptoms include gastrointestinal symptoms (abdominal pain, vomiting, and diarrhea), cardiovascular involvement, and mucocutaneous

Corresponding Author: Zephyr D Dworsky, 3020 Children's Way MC 5064, San Diego, CA 92123, USA, zdworsky@health.ucsd.edu, (p): 858-966-5841, (f): 858-966-6728.

*Contributed equally

There are no conflicts of interest for any authors.

features, with significantly elevated inflammatory markers, including C-reactive protein (CRP) and ferritin.[4,5] No single diagnostic test is diagnostic for MIS-C; rather, it is a clinical diagnosis with supportive laboratory features and evidence of exposure to SARS-CoV-2. Thus, healthcare providers must maintain a high index of suspicion when caring for patients with fever and elevated inflammatory markers, while remembering that other disease entities can mimic MIS-C. We present a series of five pediatric cases who presented to hospitals in San Diego, California and Boston, Massachusetts, with fever, gastrointestinal symptoms, and elevated inflammatory markers, concerning for MIS-C.

Case Descriptions:

Initial Presentations:

All five patients presented with fever, abdominal pain, and diarrhea (Table 1). In all patients, the diarrhea was initially non-bloody, becoming blood-tinged on the day of admission in two of the cases. All appeared dehydrated and had tachycardia at presentation, raising concern for possible cardiac involvement. Case 1 also had red, cracked lips on initial exam, but none of the other patients had any clinical features of Kawasaki disease, including rash, conjunctival injection or strawberry tongue. None of our patients had known sick contacts or animal exposures with the exception of Case 1, who had a pet turtle at home that he had not touched and Case 3, who had a puppy with a concurrent diarrheal illness.

Both parents of Case 2 had acute SARS-CoV-2 infections within two weeks of this presentation, Case 3 had a documented SARS-CoV-2 infection four months prior to this presentation, and the mother of Case 4 had a documented SARS-CoV-2 infection three months prior to this presentation. These three patients had SARS-CoV-2 antibodies, but none of our patients were SARS-CoV-2 PCR positive (Table 1).

As these patients presented during surges of MIS-C in their respective cities and vigilance for MIS-C cases was high, the constellation of signs and symptoms triggered additional laboratory evaluation, which further increased the suspicion for MIS-C. All of our patients were found to have elevated inflammatory markers, specifically elevated CRP, ferritin, and D-dimer (Table 1). Neutrophilia was also present in all patients. Two had significantly elevated immature neutrophil counts, although bands were only reported in three of our patients. Four patients had lymphopenia, though none had an absolute count less than 1000 cells/mm^3.

Hospital Courses:

Given the concern for MIS-C, all patients were admitted to the hospital for further evaluation and management. In all five, tachycardia resolved with fluid resuscitation and their echocardiograms were normal. With this additional information, the decision was made to observe three of the patients (Cases 2, 3, and 4) without immunomodulatory treatment, all of whom quickly improved. Shortly thereafter, their stool studies returned positive for Salmonella species in Cases 2 and 4, and Campylobacter species in Case 3. None of these patients were treated for their bacterial enteritis given their clinical improvement and negative blood cultures.

After admission, Case 1, who had red, cracked lips in addition to his gastrointestinal symptoms, was treated with intravenous immunoglobulin (IVIG) and steroids. His symptoms improved within a matter of hours of admission and his echocardiogram was normal. After a multidisciplinary discussion, steroids were stopped the morning after admission. He continued to improve clinically, and his stool studies returned positive for Salmonella species and blood cultures remained negative. He was treated with a seven-day course of azithromycin.

Case 5 had a history of liver hamartoma and was admitted on day five of fever with elevated inflammatory markers, leukocytosis, and anemia. There was no history of SARS-CoV-2 exposure and her echocardiogram was normal, so MIS-C treatment was deferred in favor of additional evaluation for infection and malignancy. Abdominal ultrasound and MRI were normal. Due to continued fevers without a source, a second echocardiogram was performed on hospital day 5, which was also normal. She remained febrile and her white blood cell count increased to 43,000 cells/μL, which raised concerns for malignancy. She underwent bone marrow biopsy, which was unrevealing. Stool studies subsequently returned positive for Salmonella species. Due to persistent fever and inflammation, she was treated with azithromycin.

Discussion:

We describe five children presenting with fever, gastrointestinal symptoms, and hyperinflammation mimicking MIS-C, who were ultimately found to have bacterial enteritis. Our cases highlight several diagnostic challenges presented by children with febrile illnesses during the COVID-19 pandemic.

Fever and gastrointestinal symptoms are some of the most common features of MIS-C[4,5,]. However, these symptoms are nonspecific and have multiple other etiologies, most notably acute bacterial or viral gastroenteritis. A distinguishing feature of MIS-C is that multiple organ systems are affected. All of our patients had tachycardia on presentation, which raised concern for cardiac dysfunction and triggered additional evaluation for MIS-C. However, tachycardia resolved after fluid resuscitation in all five cases, which was more consistent with dehydration. None had elevated cardiac enzymes, which has been noted in most MIS-C patients with myocardial dysfunction.[6] Thus, none of our patients ultimately had true multisystem organ involvement needed to fulfill the CDC case definition. However, as children with MIS-C may develop additional organ system involvement over the course of admission, it is prudent to maintain a high index of suspicion.

Only one of our patients had clear recent SARS-CoV-2 exposure. However, the lack of other sick contacts in patients who had been sequestered at home and the low community prevalence of other common viral illnesses as a result of social distancing raised concern for MIS-C over infectious etiologies. The presence of SARS-CoV-2 antibodies in three of our patients also heightened suspicion for MIS-C. However, it remains unclear how antibody testing should be interpreted. Large series of MIS-C patients have reported antibody positivity in the majority of diagnosed cases, but not universally[4,5,7]. Further, commercially available antibody assays may not detect all subunits of the spike protein or nucleocapsid

protein;[8] anti-spike antibodies have been shown to occur more in children than adults, and at higher titers in children with MIS-C than acute COVID-19[7,9]. Further research is needed to better understand the time course and specificity of the antibody response in MIS-C so that more comprehensive diagnostic panels can be developed.

Further complicating the utility of SARS-CoV-2 antibody testing is the rising prevalence of infection in the community. As the SARS-CoV-2 pandemic continues and prevalence rates of the antibody rise, a positive antibody test does not guarantee a diagnosis of MIS-C. MIS-C is now described as occurring 2–6 weeks post-SARS-CoV-2 infection, and the CDC case definition includes SARS-CoV-2 exposure within the past 4 weeks.[4] This was true for only one patient in our series; however, at the time many of these patients presented, the timing of MIS-C presentation following SARS-CoV-2 infection was unclear.

All five patients had neutrophilia and variably elevated inflammatory markers and D-dimer. Two of the three patients in whom it was reported also had elevated immature neutrophils. While these laboratory value abnormalities have been associated with MIS-C in many series, elevation of these markers is nonspecific and overlaps with other infectious and inflammatory diseases. Prior to the emergence of MIS-C, obtaining laboratory values such as ferritin and D-dimer in otherwise healthy febrile children presenting for initial evaluation was uncommon. Therefore, expected laboratory values in comparison groups of children with more common febrile illnesses such as viral syndromes and bacterial enteritis are unknown. Only one of the five patients had ferritin greater than 200 ng/mL, which may help distinguish MIS-C from infectious etiologies of fever.[10] More research is needed to establish the most specific laboratory features of MIS-C.

Despite the increasing prevalence of SARS-CoV-2 in the United States, MIS-C is still a rare manifestation. Due to the nonspecific features of the current MIS-C case definition, many children initially appear to meet MIS-C criteria, and non-SARS-CoV-2 infections are common in children evaluated for MIS-C.[10] However, severe illness and death have occurred in MIS-C, and thus a delay in diagnosis may have significant consequences. Therefore, vigilance in considering MIS-C must be balanced with prompt evaluation for more common childhood febrile illnesses, including bacterial sources.

Acknowledgments

Conflicts of Interest and Sources of Funding: This work was funded in part with support from the Patient Centered Outcomes Research Institute (PCORI; CER-160234473) to Dr. Jane C Burns and Dr. Adriana H Tremoulet, from the NIH Grant 5T32AI007512-34 to Dr. Jordan E Roberts, from the Samara Jan Turkel Clinical Center to Dr. Mary Beth F Son, and the McCance Family Foundation to Dr. Jane W Newburger.

References:

1. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet Lond Engl. 2020;395(10237):1607–1608. doi:10.1016/S0140-6736(20)31094-1
2. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet Lond Engl. 2020;395(10239):1771–1778. doi:10.1016/S0140-6736(20)31103-X

3. CDCHAN-00432, May 14, 2020. Multisystem Inflammatory Syndrome in Children(MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed November 28, 2020.

4. Whittaker E, Bamford A, Kenny J, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. 2020;324(3):259–269. doi:10.1001/jama.2020.10369 [PubMed: 32511692]

5. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal Symptoms as a Major Presentation Component of a Novel Multisystem Inflammatory Syndrome in Children That Is Related to Coronavirus Disease 2019: A Single Center Experience of 44 Cases. Gastroenterology. 2020;159(4):1571–1574.e2. doi:10.1053/j.gastro.2020.05.079

6. 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. Published online August 15, 2020. doi:10.1007/s00431-020-03766-6

7. Weisberg SP, Connors TJ, Zhu Y, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol. Published online November 5, 2020. doi:10.1038/s41590-020-00826-9

8. Rikhtegaran Tehrani Z, Saadat S, Saleh E, et al. Performance of nucleocapsid and spike-based SARS-CoV-2 serologic assays. PLoS One. 2020;15(11):e0237828. Published 2020 Nov 2. doi:10.1371/journal.pone.0237828

9. Rostad CA, Chahroudi A, Mantus G, et al. Quantitative SARS-CoV-2 Serology in Children With Multisystem Inflammatory Syndrome (MIS-C). Pediatrics. 2020;146(6). doi:10.1542/peds.2020-018242

10. Campbell JI, Roberts JE, Dubois M, Naureckas Li C, Sandora TJ, Lamb GS. NON-SARS-CoV-2 INFECTIONS AMONG PATIENTS EVALUATED FOR MIS-C ASSOCIATED WITH COVID-19. Pediatr Infect Dis J. Published online November 3, 2020. doi:10.1097/INF.0000000000002977

Table 1.

Patient Characteristics and Laboratory Findings.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Demographics					
Sex	Male	Male	Female	Male	Female
Patient age	4 years	7 years	4 years	2 years	9 months
Race	Hispanic	Hispanic	Hispanic	Not Reported	Non-Hispanic
Ethnicity	White	White	White	Not Reported	Asian
Presenting Symptoms					
# Days of Fever at Presentation	3	4	3	10	5
Abdominal Pain	yes	yes	yes	yes	yes
Vomiting	no	no	yes	no	no
Diarrhea	yes	yes	yes	yes	yes
Admission Laboratory Values					
WBC (x 10^3/μL)	5.9	8.1	5.1	15.1	28.2
Hgb (g/dL)	12.4	13.1	12.2	12.1	10.1
Platelets (x 10^3/μL)	207	252	170	322	475
Absolute Neutrophil Count (cells/mm^3)	4720	6561	3470	13330	13240
Band %	46	32	12	Not Done	Not Done
Absolute Lymphocyte Count (cells/mm^3)	1062	1134	1300	1100	10860
Albumin (g/dL)	4.2	3.9	4.5	4.1	3.4
CRP (mg/dL)	18.1	6.5	15.8	7.6	23.5
ESR (mm/hr)	22	22	32	22	106
Ferritin (ng/mL)	176	276	101	95.6	189.3
D-dimer (μg/mL)	1.74	0.99	2.8	1.95	19.58
Fibrinogen (mg/dL)	407	527	459	157	Not Done
BNP (pg/mL)	<10	<10	<10	14	12
Troponin (ng/mL)	<0.01	<0.01	0.01	<0.01	Not Done
SARS-CoV-2 RT-PCR	Negative	Negative	Negative	Negative	Negative
SARS-CoV-2 Antibody	Negative *	Positive *	Positive *	Positive **	Negative **

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Stool Studies	Salmonella species	Salmonella species	Campylobacter species	Salmonella species	Salmonella species
Echocardiogram	Normal	Normal	Normal	Normal	Normal

*Abbott Architect SARS-CoV-2 Anti-Nucleocapsid IgG

**Roche Diagnostics Elecsys Anti-SARS-CoV-2 Immunoassay