BENDING THE VALUE CURVE

What Are We Missing in Our Search for MIS-C?

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FEATURED CASE

A previously healthy 3-year-old boy presented with 6 days of fever and fatigue. Three days before, he saw his pediatrician and had negative rapid strep antigen and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction test results. Given persistent fever up to 40°C with decreased appetite and urine output, the patient presented to the emergency department. There was no reported rash, skin peeling, eye redness, redness of the oral mucosa, congestion, rhinorrhea, cough, shortness of breath, chest pain, abdominal pain, nausea, vomiting, or diarrhea. The patient had recently started preschool but had no known exposure to the coronavirus disease 2019 (COVID-19).

On arrival, the patient was febrile to 39.2°C, mildly tachycardic, and normotensive. On examination, he had clear conjunctivae, a normal oropharynx, and moist mucous membranes. No rash, extremity swelling, or lymphadenopathy was appreciated. He was breathing comfortably, and his lungs were clear to auscultation bilaterally. His abdomen was soft and nontender with mild left-sided flank tenderness. Given the patient's prolonged fever, multisystem inflammatory syndrome in children (MIS-C) was considered and an extensive laboratory evaluation was initiated, including all the laboratories suggested as potentially useful in the evaluation of MIS-C (Table 1). Laboratory results were notable for normal white blood cell and platelet counts and a metabolic panel with normal sodium and albumin. Inflammatory markers were elevated with a C-reactive protein (CRP) level of 14 mg/dL, an erythrocyte sedimentation rate (ESR) of 110 mm/hour, and mild elevations of ferritin, D-dimer, and fibrinogen levels. The patient's troponin level was within normal limits, and his B-type natriuretic peptide (BNP) level was mildly elevated. A urinalysis was notable for small protein, negative nitrite results, small leukocyte esterase, and 30 to 50 white blood cells per high-powered field. A blood culture, a urine culture, and serologies for SARS-CoV-2 were obtained.

On the basis of the patient's laboratory findings, there was concern for MIS-C versus incomplete Kawasaki disease and the patient was admitted to hospital medicine. Cardiology, rheumatology, and infectious disease departments were consulted. An echocardiogram obtained on the first day of admission was normal. The patient remained clinically stable and persistently febrile. Repeat laboratory tests were planned for the next day before initiating therapy because diagnostic uncertainty remained. On day 2 of admission, the patient's urine culture result became positive with Gram-negative rods, later speciating *Escherichia coli*. Ceftriaxone was initiated, and a renal ultrasound revealed left renal scarring. The patient clinically improved with resolution of fevers after 36 hours of treatment and was discharged from the hospital with a course of antibiotics and urology follow-up.

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TABLE 1 Potential Evaluations for Suspected MIS-C

SARS-CoV-2 PCR
SARS-CoV-2 serologies
Complete blood cell count with differential
Complete metabolic panel
Urinalysis
Urine protein and creatinine
CRP
ESR
Lactate dehydrogenase
Ferritin
Procalcitonin
D-dimer
Fibrinogen
Prothrombin time
Activated partial thromboplastin time
Troponin
BNP
Electrocardiogram

PCR, polymerase chain reaction.

A DIAGNOSIS DERAILED

In previous years, this clinical presentation likely would have led to a more focused evaluation for infectious causes, including pyelonephritis, given the lack of physical examination findings consistent with Kawasaki disease. However, the patient presented amid the COVID-19 pandemic, during which there was growing awareness of a new clinical entity. Anchored to the patient's persistent fever, the medical team initiated an extensive, costly, and ultimately unnecessary workup to avoid missing the diagnosis of MIS-C, a not yet well-described diagnosis with potentially severe morbidity. The team subsequently suffered from confirmation bias and diagnostic momentum, fitting abnormal laboratory values into the presumed MIS-C diagnosis rather than considering more likely alternative diagnoses. Specifically, the pyuria was attributed to the inflammatory sterile pyuria that is well described in Kawasaki disease but has not, to our knowledge, been described in MIS-C. The addition of mildly abnormal laboratory data that are not typically obtained in the evaluation of fever, such as BNP levels, led the team astray. The diagnosis of pyelonephritis and definitive treatment were delayed, extending the length of stay.

This was not an isolated event. Our institutional safety monitoring and divisional surveillance of diagnostic errors identified several other instances of both delayed diagnosis and overtesting related to our institutional approach to evaluating for MIS-C.[1]

A NEW CLINICAL ENTITY

With this case, we highlight some of the challenges and uncertainty with diagnosing and managing a new clinical entity. Pediatricians and other health care providers around the world are dealing with and learning about COVID-19. Most children infected with SARS-CoV-2 have mild symptoms and require only supportive care.[2] However, in late April 2020, clinicians in Europe and the United States began reporting clusters of children admitted with a Kawasaki-like hyperinflammatory process possibly related to SARS-CoV-2 infection.[3–5] On May 14, 2020, the Centers for Disease Control and Prevention (CDC) issued a national health advisory that included a case definition for MIS-C.[6]

Common manifestations of MIS-C include fever, gastrointestinal symptoms, cardiovascular symptoms, and dermatologic and/or mucocutaneous manifestations. Other clinical findings include lymphadenopathy, respiratory symptoms, musculoskeletal symptoms, neurologic symptoms, and shock.[7–15] These manifestations are nonspecific, creating diagnostic uncertainty and necessitating a broad differential diagnosis. Importantly, patients with MIS-C almost always have laboratory evidence of recent SARS-CoV-2 infection, with cases occurring 2 to 5 weeks after peak local incidence of COVID-19.[7,10,11,13–16] Notably, in the weeks leading up to this case, our local incidence of COVID-19 had been low, decreasing the likelihood of MIS-C.

Although the incidence of MIS-C remains unclear, it appears to be a rare complication of SARS-CoV-2 infection, occurring in <1% of infected patients.[10] Serious adverse events are not uncommon. Cardiovascular manifestations include left ventricular dysfunction, arrhythmia, and coronary artery aneurysms.[7,12,16–19] Although almost all children recover, a majority of admitted patients require intensive care and the reported mortality rate is 1% to 2%.[7,10,12,14,16] The impact of timely diagnosis and treatment on outcomes is unknown. The fear of missing this unfamiliar and potentially fatal syndrome must be balanced with the need to minimize low-value overtesting in patients with common presenting symptoms.

A STEPWISE APPROACH

The diagnostic evaluation for MIS-C is not straightforward. The CDC, the World Health Organization, and the Royal College of Pediatrics and Child Health offer similar but slightly different case definitions, which include fever, evidence of inflammation, lack of alternative diagnosis, and epidemiological link to SARS-CoV-2 infection.[6,20,21] Our institution's initial guideline recommended an extensive evaluation of patients with unexplained fever (Table 1).

Examining the laboratory data from reported MIS-C cases reveals nearly uniform elevation of inflammatory markers, such as CRP, ESR, and procalcitonin. Other laboratory findings commonly present are hyponatremia, hypoalbuminemia, neutrophilia, lymphopenia, and thrombocytopenia.[7–10,12,14–16] In one New York study with 99 patients, 99% of patients had a CRP level >5.0 mg/dL, with 87% having levels >10.0 mg/dL.[10] Using a modified Delphi approach, the American College of Rheumatology (ACR) devised a 2-tiered diagnostic approach for MIS-C. For children considered under investigation for MIS-C without life-threatening manifestations, a screening evaluation of inflammatory markers, complete blood cell count, and complete metabolic panel is recommended. Children with elevated CRP and/or ESR levels and at least one other suggestive laboratory feature should progress to a more extensive second-tier evaluation.[22] This tiered approach can be used to identify

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patients who do not warrant further evaluation for MIS-C, thus sparing a costly evaluation and limiting additional laboratory data with unclear diagnostic value.

After reflecting on this case and others, we reconsidered our approach to evaluating for MIS-C. After review of the literature and publicly available algorithms, we adopted a tiered diagnostic approach similar to that proposed by the ACR. The patient presented here demonstrated significant inflammation but did not have other laboratory findings suggestive of MIS-C and would not have progressed to the second tier of evaluation. This approach could have spared a significant amount of testing and avoided consults. In addition, this approach may have prompted providers to reconsider the cause of fever and arrive at a diagnosis of pyelonephritis sooner.

BALANCING VALUE IN A PANDEMIC

The challenges and stresses associated with a global pandemic causing a rare, severe syndrome in children are immense. As we learn more about SARS-CoV-2 infection and its complications, we can still strive to provide high value care to our patients. The continued focus on using only needed resources has been an important lesson in this pandemic. We recognized that our initial approach to evaluating for MIS-C was providing low-value care. In our desire to not miss MIS-C, we were performing costly evaluations that, at times, produced mildly abnormal, nonspecific results. This led to a cascade of consults and follow-up testing as well as a further focus on MIS-C as a potential diagnosis when other, more likely diagnoses existed. Incorporating available data on laboratory findings from reported cases allowed for a move to a less costly, tiered evaluation.

We also recognized that our approach did not emphasize the importance of considering other diagnoses. The CDC, the World Health Organization, and the ACR have stressed the importance of maintaining a broad differential diagnosis in the evaluation of MIS-C.[6,20,22] The strain related to the COVID-19 pandemic may increase the risk of diagnostic errors related to both cognitive and systems-based factors.[23] In this case, a number of well-described cognitive biases,[24] including anchoring bias, confirmation bias, and diagnostic momentum, resulted in a failure to consider the correct diagnosis despite urinalysis results and examination findings consistent with pyelonephritis. In addition, attention to local epidemiology remains critical. As incidence rates of SARS-CoV-2 ebb and flow, we must adjust our pretest probabilities of encountering MIS-C relative to other diagnoses. We hope that our updated approach increases the value of care both by reducing unnecessary testing and by helping us avoid a narrow focus on MIS-C. However, we must remain vigilant against diagnostic errors and continue to develop organizational mitigation strategies, such as mechanisms for diagnostic feedback and systematic event review, to identify opportunities for improvement. As we confront this pandemic together, the value of care we provide need not suffer.

REFERENCES

1. Marshall TL, Ipsaro AJ, Le M, et al. Increasing physician reporting of diagnostic learning opportunities. *Pediatrics*. 2021;147(1):e20192400
2. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr*. 2020;174(9): 882–889
3. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki Disease: novel virus and novel case. *Hosp Pediatr*. 2020;10(6):537–540
4. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020; 395(10237):1607–1608
5. 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*. 2020;395(10239):1771–1778
6. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). 2020. Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed November 9, 2020
7. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators; ; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in US children and adolescents. *N Engl J Med*. 2020; 383(4):334–346
8. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. *JAMA*. 2020;324(3):294–296
9. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. *J Pediatric Infect Dis Soc*. 2020;9(3): 393–398
10. Dufort EM, Koumans EH, Chow EJ, et al; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med*. 2020; 383(4):347–358
11. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*. 2020; 20(11):e276–e288
12. Kaushik S, Aydin SI, Derespina KR, et al. 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
13. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094
14. Whittaker E, Bamford A, Kenny J, et al; PIMS-TS Study Group and EUCLIDS and

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PERFORM Consortia. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259–269

15. Abrams JY, Godfred-Cato SE, Oster ME, 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

16. 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(11):e340–e346

17. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;142(5):429–436

18. Ramcharan T, Nolan O, Lai CY, et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. *Pediatr Cardiol*. 2020;41(7):1391–1401

19. Sperotto F, Friedman KG, Son MBF, et al. Cardiac manifestations in SARS-CoV-2 -associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. *Eur J Pediatr*. 2021;180(2):307–322

20. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. 2020. Available at: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed November 9, 2020

21. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. 2020. Available at: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf. Accessed November 9, 2020

22. Henderson LA, Canna SW, Friedman KG, 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(11):1791–1805

23. Gandhi TK, Singh H. Reducing the risk of diagnostic error in the COVID-19 era. *J Hosp Med*. 2020;15(6):363–366

24. Croskerry P. Achieving quality in clinical decision making: cognitive strategies and detection of bias. *Acad Emerg Med*. 2002;9(11):1184–1204

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