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

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Abbreviations: ACR, American College of Rheumatology; BNP, B-type natriuretic peptide; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ED, emergency department; ESR, erythrocyte sedimentation rate; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization

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Featured Case

A previously healthy 3-year-old boy presented with six days of fever and fatigue. Three days prior, he saw his pediatrician and had negative rapid strep antigen and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR tests. Given persistent fever up to 40°C with decreased appetite and urine output, he 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 he was febrile to 39.2°C, mildly tachycardic, and normotensive. On exam, 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 his prolonged fever, multisystem inflammatory syndrome in children (MIS-C) was considered and an extensive laboratory evaluation was initiated, including all the labs suggested as potentially useful in the evaluation of MIS-C (Table 1). Labs were notable for normal white blood cell and platelet counts and a metabolic panel with normal sodium and albumin. Inflammatory markers were elevated with C-reactive protein (CRP) of 14 mg/dL, erythrocyte sedimentation rate (ESR) of 110 mm/hour, and mild elevations of ferritin, D-dimer, and fibrinogen. A troponin was within normal limits and B-type natriuretic peptide (BNP) was mildly elevated. A urinalysis was notable for small protein, negative nitrite, small leukocyte

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esterase, and 30-50 white blood cells per high powered field. Blood culture, urine culture, and serologies for SARS-CoV-2 were obtained.

Based on his 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 were consulted. An echocardiogram obtained on the first day of admission was normal. He remained clinically stable and persistently febrile. Repeat labs were planned for the following day prior to initiating therapy as diagnostic uncertainty remained. On day two of admission, the patient's urine culture became positive with gram negative rods, later speciating *Escherichia coli*. Ceftriaxone was initiated and a renal ultrasound demonstrated left renal scarring. The patient clinically improved with resolution of fevers after 36 hours of treatment and was discharged home with a course of antibiotics and urology follow-up.

A Diagnosis Derailed

In prior years, this clinical presentation likely would have led to a more focused evaluation for infectious causes, including pyelonephritis, given the lack of physical exam findings consistent with Kawasaki disease. However, the patient presented in the midst of the COVID-19 pandemic with 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 lab values into the presumed MIS-C diagnosis rather than considering more likely

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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, 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 over-testing related to our institutional approach to evaluating for MIS-C.[1]

A New Clinical Entity

This case highlights some of the challenges and uncertainty with diagnosing and managing a new clinical entity. Pediatricians and other healthcare 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]

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Common manifestations of MIS-C include fever, gastrointestinal symptoms, cardiovascular symptoms, and dermatologic/mucocutaneous manifestations. Other clinical findings include lymphadenopathy, respiratory symptoms, musculoskeletal symptoms, neurologic symptoms, and shock.[7-15] These manifestations are non-specific, creating diagnostic uncertainty and necessitating a broad differential diagnosis. Importantly, MIS-C patients almost always have laboratory evidence of recent SARS-CoV-2 infection, with cases occurring 2-5 weeks following 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 very low, decreasing the likelihood of MIS-C.

While 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 1-2%.[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 over-testing in patients with common presenting symptoms.

A Stepwise Approach

The diagnostic evaluation for MIS-C is not straightforward. The CDC, World Health Organization (WHO), and Royal College of Paediatrics and Child Health offer similar, but slightly different, case definitions that include fever, evidence of inflammation, lack of

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alternative diagnosis, and epidemiologic 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 like 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 >5.0 mg/dL, with 87% >10.0 mg/dL.[10] Using a modified Delphi approach, the American College of Rheumatology (ACR) devised a two-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 and at least one other suggestive laboratory feature should progress to a more extensive second tier evaluation.[22] This tiered approach can identify 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. Upon 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

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significant amount of testing and avoided consults. In addition, this 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, non-specific 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, WHO, and 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 exam findings consistent with pyelonephritis. In addition,

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attention to local epidemiology remains critical. As incidence rates of SARS-CoV-2 ebb and flow, we must adjust our pre-test 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 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.

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Table 1. Prior Recommended Evaluation for Suspected MIS-C

SARS-CoV-2 PCR	C-reactive Protein	Fibrinogen
SARS-CoV-2 Serologies	Erythrocyte Sedimentation Rate	Prothrombin Time
Complete Blood Cell Count with Differential	Lactate Dehydrogenase	Activated Partial Thromboplastin Time
Complete Metabolic Panel	Ferritin	Troponin
Urinalysis	Procalcitonin	B-type Natriuretic Peptide
Urine Protein and Creatinine	D-Dimer	Electrocardiogram

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