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Delayed Development of Coronary Artery Dilitation in Suspected Severe Acute Respiratory Syndrome Coronavirus 2 Multisystem Inflammatory Syndrome: More Research Needed

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Background: Although significant disease burden in the severe acute respiratory syndrome coronavirus 2 pandemic has been relatively uncommon in children, worldwide cases of a postinfectious multisystem inflammatory syndrome in children and possible atypical Kawasaki-like disease attributing to severe acute respiratory syndrome coronavirus 2 infection have arisen. Original thinking for coronavirus disease-19 disease was that an overwhelming proinflammatory response drove disease pathogenesis. Emerging reports suggest that a robust immune suppression may be more relevant and predominant. Recently reported data on children with multisystem inflammatory syndrome in children have demonstrated a heterogeneity of immune phenotypes among these patients, with concern for a strong initial proinflammatory state; however, data are lacking to support this. Likewise, understanding development of certain clinical findings to changes in the immune system is lacking.

Case Summary: We report a 12-year-old multiracial male with negative coronavirus disease-19 nasopharyngeal RNA polymerase chain reaction testing but positive severe acute respiratory syndrome coronavirus 2 serology, subsequent development of vasodilatory shock with myocardial depression, and subsequent delayed development of coronary artery dilatation after resolution of myocardial depression. Unlike previous reported cases of multisystem inflammatory syndrome in children, he exhibited profound lymphopenia without specific inflammatory cytokines elevations, whereas nonspecific markers (ferritin and C-reactive protein) were increased. He subsequently was discharged on day 12 of hospitalization with complete recovery.

Conclusion: Our representative case of a patient with coronavirus disease-19-associated multisystem inflammatory syndrome in children without robust hyperinflammation and a delayed finding of coronary artery dilatation compared with reported case series highlights the need for further mechanistic understanding of coronavirus disease-19 disease and subsequent multisystem inflammatory syndrome in children or Kawasaki disease development. This report offers a number of disease mechanisms and clinical evolution considerations for further elucidation to guide development of potential therapies.

Key Words: coronavirus disease-19; immune suppression; Kawasaki disease; multisystem inflammatory syndrome in children; research

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Significant disease burden in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been relatively uncommon in children with less than 5% of cases in the United States and globally under 18 years old (1–6). Although severe disease is rare, many children become infected with the SARS-CoV-2 virus and some may serve as asymptomatic reservoirs for coronavirus disease-19 (COVID-19) disease transmission (7). However, although children appear to have a less severe acute disease course, worldwide cases of a postinfectious multisystem inflammatory syndrome in children (MIS-C) and possible

atypical Kawasaki-like disease attributed to SARS-CoV-2 infection have arisen (8–10).

Preliminary evidence and hypotheses suggested that COVID-19 disease pathogenesis was driven by an overwhelming hyperinflammatory response. More recent emerging reports suggest that a robust immune suppression may be more relevant and predominant (11–13). Recently reported data on children with MIS-C have demonstrated a heterogeneity of immune phenotypes among these patients, with concern for a strong initial hyperinflammatory state; however, data are lacking to support this. In these reported cases and in our own experiences with a case of MIS-C with delayed development of an atypical Kawasaki-like disease, a number of questions have been developed.

A 12-year-old, previously healthy, fully immunized, multiracial male presented to our quaternary-care hospital after 1 week of fever and diarrhea. A nasopharyngeal COVID-19 RNA polymerase chain reaction was negative three times, and the serology of both parents was positive for SARS-CoV-2 immunoglobulin-G (IgG) (Abbott Laboratories, Chicago, IL). At admission, he had vasodilatory septic shock with multiple laboratory and cardiac abnormalities including profound lymphopenia (absolute lymphocyte count [ALC] 392), thrombocytopenia (nadir 57), hyponatremia, hypophosphatemia, and fever (**Table 1**). During his 11 day ICU course, he received empiric broad-spectrum antibiotics, hemodynamic support for catecholamine-resistant septic shock, stress dose hydrocortisone for critical illness-related corticosteroid insufficiency (two doses), and high-flow nasal cannula with subsequent noninvasive bilevel positive sirway pressure support without the need for intubation. Cardiac specific evaluation showed initial electrocardiogram findings with prolonged corrected QT interval, transthoracic echocardiogram (TTE) showed borderline left ventricle ejection fraction with dyskinetic septum, and probrain natriuretic peptide (BNP) and troponin-I were both significantly elevated (Table 1). By days 4–6, an SARS-CoV-2 IgG test was positive, he became hypertensive requiring a nitroprusside infusion and subsequent transition to lisinopril, and his left ventricular ejection fraction increased to 50%. An initial cytokine panel demonstrated tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and interleukin (IL)-6 levels below the limit of detection and elevated IL-2R and IL-10 (**Table 2**). All other cytokines were within normal limits. His nonspecific inflammatory markers all normalized including D-dimer, ferritin, C-reactive protein (CRP), and fibrinogen, and he defervesced. At day 11, a predischarge TTE revealed normal systolic function, but his left main coronary artery, left anterior descending artery, circumflex artery, and right coronary artery (RCA) were all diffusely dilated with the RCA demonstrating the greatest amount of dilation with a fusiform appearing aneurysm and proximal RCA stenosis. He was discharged on low-dose aspirin and clopidogrel with a presumed diagnosis of COVID-19 MIS-C and atypical Kawasaki-like disease. A 4-week postdischarge TTE continued to have normal systolic function with unchanged coronary artery dilation and a slightly elevated troponin-I of 0.18 ng/mL. Anticoagulation therapy was continued and antihypertensive medications stopped after normalization of blood pressure.

Recent U.S. and U.K. reports of over 500 MIS-C patients have shown findings of lymphopenia, elevated CRP, ferritin, BNP, D-dimer, IL-6, and fibrinogen (8, 10, 14, 15). However, unlike these case series, our patient had much higher nonspecific inflammatory markers (CRP, ferritin, D-dimer, and fibrinogen) without elevation in IL-6 or TNF-α cytokine levels. Previous reports have demonstrated lymphopenia between 1,000 and 2,000 cells/mm^2. In contrast, our patient had an ALC less than 400, a finding similar to that seen in AIDS. Our patient's divergent findings of elevation of some hyperinflammatory markers and depression of others highlight the presence of differing innate and adaptive immune phenotypes. In turn, this questions whether reported descriptive immune findings in adults can be accurately ascribed to children when children are presenting with different clinical manifestations over an altered time course. Likewise, prior to uniform pediatric use of therapies that have been attempted in adults, we must gain better understanding of key mechanistic pathways of SARS-CoV-2 infection and extrapolate and apply known pathologic mechanisms in other similar and previously elucidated diseases (e.g., known Kawasaki disease [KD] findings and other viruses).

Current COVID-19-induced Kawasaki-like disease may have overlapping mechanisms with canonical KD or may represent a completely different disease with overlapping clinical findings. Comparing the clinical and laboratory characteristics of these two entities has very distinct properties. From a clinical standpoint, patients with MIS-C have a broader age range with a median of 9 years, whereas KD patients have a narrower age range with a median of 2 years (8, 16). Patients with MIS-C also have a lower prevalence of developing the classic KD findings of conjunctivitis, rash, mucositis, extremity swelling, and cervical lymphadenopathy (16). Interestingly, it has been reported that patients with MIS-C compared with COVID-19-associated KD have lower WBC counts, worsened thrombocytopenia and lymphopenia, and decreased erythrocyte sedimentation rates with less anemia (higher hemoglobin values) (16). Our patient demonstrated more severe lymphopenia than previously reported and yet had hematologic findings that bridged both previously reported findings in MIS-C and KD (i.e., higher WBC counts with thrombocytopenia and anemia). Additionally, our patient developed coronary artery dilatation 11 days after acute presentation and after recovery of myocardial function. This novel finding has not been reported in case series that have focused on cardiac manifestations of MIS-C (17). This further delineates MIS-C and KD as heterogeneous syndromes with potentially differing subphenotypes.

Furthermore, canonical KD has previously demonstrated coronary vascular infiltration of neutrophils, cluster of differentiation 8 T lymphocytes, immunoglobulin-A-producing plasma cells, macrophages, and eosinophils (18–20). Numerous reports in adult COVID-19 disease have demonstrated isolated proinflammatory marker elevations but likely predominant immune suppression with T cell exhaustion and significant peripheral lymphopenia (11–13). Based on preliminary concerns of a hyperinflammatory state driving disease progression, many patients with MIS-C are treated with anti-inflammatory agents (corticosteroids, anakinra, and nonsteroidal anti-inflammatory drugs) (14, 15, 21, 22). However, if children demonstrate similar findings as in adults

TABLE 1. Laboratory and Cardiac Findings During Hospitalization

	First Emergency Department Visit	Hospital Day 1	Hospital Day 2	Hospital Day 3	Hospital Day 4	Hospital Day 7	Hospital Day 11	4-wk Postdischarge Follow-Up
Maximum temp	37.7	**40.5**	**40.4**	**39**	37.4	37.4	36.7	36.6
Coronavirus disease 2019 polymerase chain reaction	Negative[a]	Negative[a]	Negative[b]					
Severe acute respiratory syndrome coronavirus 2 immunoglobulin-G[c]					**Reactive**			
WBC (K/cumm)	7.0	9.5	**15.4**	**14.3**	**12.9**	8.0	7.0	
Absolute lymphocyte count (cells/mm^2)	392	523		**2,302**	**1,238**	**1,504**	**2,240**	
Hemoglobin (g/dL)	11.8	12.0	**10.5**	**9.8**	**9.0**	**8.8**	11.8	
Platelet Count (K/cumm)	148	**57**	**85**	**89**	**81**	191	**468**	
Sodium (mmol/L)	**126**	**123**	**130**	139	147	137		138
Potassium (mmol/L)	3.5	**3.0**	**2.2**	**3.3**	3.5	3.4		3.8
Phosphorus (mg/dL)		**2.0**	**1.9**	**2.3**	**1.5**	3.3		
Blood urea nitrogen (mg/dL)	12	**49**	**29**	11	10	9		7
Creatinine (mg/dL)	0.74	**2.04**	**1.31**	0.75	0.72	0.58		0.52
Alanine aminotransferase (Units/L)	11	27	23	21	24	**46**	**55**	16
Erythrocyte sedimentation rate (mm/hr)		**30**					**28**	9
C-reactive protein (mg/L)	**137.4**	**325.0**			**57.5**		8.7	1
Ferritin (ng/mL)		**2,758**	**3,095**	**3,764**	**2,685**	**583**		
Fibrinogen (mg/dL)		**659**	**589**	**463**	295			
D-dimer (ng/mL FEU)		**1,780**	**1,636**	**957**	**1,060**	**749**		
Peak lactate (mmol/L)		1.8	**2.7**	**3.0**	**3.1**	1.3		
Troponin-I (ng/mL)			**0.64**	**0.14**	**0.08**	0.03		**0.18**
N-terminal pro hormone brain natriuretic peptide (pg/mL)			**29,765**	**22,613**	**13,495**	**5,528**	200	
Corrected QT interval on electrocardiogram		394	**475**	**470**	446	**462**		430
Systolic function			**SF 24.77% and EF 42.59%**	**SF 22.56% and EF 39.48%**			SF 29.62% **and EF 48.03%**	SF 33.99% and EF 55.05%
Coronary arteries			Normal	Normal			**Dilated LCA, LAD, circumflex,** and **RCA**	**Dilated LCA, LAD, circumflex,** and **RCA**

EF = ejection fraction, LAD = left anterior descending, LCA = left main coronary artery, RCA = right coronary artery, SF = shortening fraction.

[a]Coronavirus disease-19 RNA nasopharyngeal.

[b]Coronavirus disease-19 RNA sputum.

[c]Severe acute respiratory syndrome coronavirus 2 (coronavirus disease-19) antibody immunoglobulin-G.

Boldface represent abnormal values.

with immune suppression, these agents may have negative effects including the potential for development of secondary infections and/or unmitigated viral tissue replication. It is unclear how this may affect development from acute disease to MIS-C or KD.

Thus, a number of considerations remain regarding the broad definition of this syndrome, mechanisms involved, and the need for targeted rather than nonspecific therapies. This underscores a need for future studies in children to better characterize alterations in innate and adaptive immune functions not solely in acute infectious disease presentation but also in disease evolution to postinflammatory syndrome. Our case describes a patient that meets Centers for Disease Control and Prevention criteria for MIS-C with evolution of delayed KD findings of coronary artery dilations. A number of questions thus arise as follows:

- What mechanistically could describe findings of MIS-C at presentation and yet delayed findings of KD with coronary artery dilatation after four echocardiograms that have not been previously reported in large case series?
- When and how often should echocardiogram surveillance occur with children that meet MIS-C criteria at admission but may not have evidence of KD?
- Why in this illustrative case do we see a clinical presentation of vasodilatory shock with increased nonspecific inflammatory biomarkers and an absence of a "cytokine storm" of IL-6, TNF-α, or related proinflammatory cytokines but with profound lymphopenia and reduction in IFN-γ demonstrating immune exhaustion? Could changes in IL-2R be more relevant than IL-6 and provide further insight into JAK1, JAK3, or other tyrosine kinase/map kinase signaling pathways?
- With oversampling of diagnostic testing including serial echocardiograms, are we unearthing a phenomenon restricted only to SARS-CoV-2 virus or would other common childhood viruses with the same testing reveal similar findings?
- Recent data suggest that children less than 10 years old have diminished nasal gene expression of angiotensin-converting enzyme 2 (ACE-2) compared with greater than 10 year olds (23). Does this age-related increase in ACE-2 expression play a role in the observation that KD-like disease in SARS-CoV-2 infection occurs more frequently in an older population compared with KD and what other potential signaling pathways may be involved?
- Would the well-established ability of other coronaviruses to block type 1 and type III IFN responses provide further insights in additional therapies that may influence Janus kinases-STAT pathways? Could further elucidation of these pathways demonstrate more refined targeted therapies with improved outcomes for this syndrome or previously described canonical KD?

Presently, our understanding of MIS-C is limited to associations temporal to the COVID-19 disease. Better elucidation of relevant signaling pathways that define transition from acute disease to MIS-C is not only important for COVID-19 disease but may provide insights into understanding KD associated with other pathogens. Further evaluation of these considerations and questions could present many avenues for further investigation.

TABLE 2. Cytokine Panel Obtained on Hospital Day 4

Cytokine Panel Results		
Cytokine	**Result**	**Reference Value**
Tumor necrosis factor-α (pg/mL)	5 (nmL)	≤ 22
IL-2 (pg/mL)	9 (nmL)	≤ 12
IL-2R (pg/mL)	**17,370 (high)**	≤ 1,033
IL-4 (pg/mL)	< 5 (nmL)	≤ 5
IL-5 (pg/mL)	< 5 (nmL)	≤ 5
IL-6 (pg/mL)	**6 (equivocal)**	≤ 5
IL-8 (pg/mL)	< 5 (nmL)	≤ 5
IL-12 (pg/mL)	< 5 (nmL)	≤ 6
Interferon-γ (pg/mL)	< 5 (nmL)	≤ 5
IL-10 (pg/mL)	**122 (high)**	≤ 18
IL-13 (pg/mL)	< 5 (nmL)	≤ 5
IL-17 (pg/mL)	11 (nmL)	≤ 11
IL-1β (pg/mL)	< 5 (nmL)	≤ 36

IL = interleukin.
Boldface represent abnormal values.

Invariably, many children will present with SARS-CoV-2 positive antibody serology testing in the fall with signs and symptoms consistent with sepsis, hemophagocytic lymphohistiocytosis, or MIS-C; differentiating between these entities diagnostically and with subsequent therapies will be important in patient management and potential outcomes.

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