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INTERMEDIATE

CASE REPORT: CLINICAL CASE

Reversible Coronary Artery Aneurysm With Delayed Anti-inflammatory Therapy in Multisystem Inflammatory Syndrome in Children

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ABSTRACT

A 4-year-old boy with multisystem inflammatory syndrome in children before widespread recognition of this disease developed complications, including coronary artery aneurysm, without anti-inflammatory treatment. With delayed treatment, all sequelae resolved. This case demonstrates a natural history supporting the role of anti-inflammatory treatment even with delayed or equivocal diagnosis. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:550–4) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has created urgent challenges for the medical community. Although published scientific reports have focused on the adult population, the emergence of multisystem inflammatory syndrome in children (MIS-C) has brought focus to how SARS-CoV-2 can affect children (1–4). Because of the severity of MIS-C, which may present with life-threatening shock, myocarditis, and coagulopathy, the pediatric community has quickly developed management guidelines. However, as we await further studies, treatment remains founded on limited evidence and expert consensus (5,6).

LEARNING OBJECTIVES

- To understand the potential natural history of untreated MIS-C, including coronary artery aneurysm formation, and compare it to that of KD.
- To review the importance of anti-inflammatory treatment of MIS-C in aneurysm prevention and treatment and to evaluate the role of treatment even with delayed or equivocal diagnosis.

Current guidelines for MIS-C emphasize its similarities to Kawasaki disease (KD), a rare childhood vasculitis associated with coronary artery aneurysm formation. Typical KD is marked by prolonged fever and diffuse mucocutaneous inflammation, whereas incomplete KD presents with fever and derangements in inflammatory markers. We describe a patient with MIS-C who presented before widespread recognition of this disease, leading to delayed diagnosis. To our knowledge, this is the only described case of

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untreated MIS-C with sequelae, including coronary artery aneurysm, that all resolved upon eventual initiation of treatment.

HISTORY OF PRESENTATION

A 4-year-old boy presented to a pediatric emergency department with dyspnea, fatigue, diarrhea, decreased urination, and 4 days of fever (maximum temperature: 40°C). He had no rashes, mucous membrane or extremity changes, conjunctival injection, or lymphadenopathy. He was afebrile; his heart rate was 137 beats/min, blood pressure was 54/36 mm Hg, and respiratory rate was 50 breaths/min. Initial oxygen saturation was not detected by pulse oximetry because of poor perfusion. He was somnolent, with dry mucous membranes, abdominal distension, and labored breathing. He received 40 ml/kg of isotonic fluid, dopamine, empiric vancomycin and ceftriaxone, and oxygen via a non-rebreather mask for persistent desaturations to 80%.

MEDICAL HISTORY

There was no significant medical history.

DIFFERENTIAL DIAGNOSIS

Presumed diagnosis was viral sepsis due to acute SARS-CoV-2 infection. Bacterial pneumonia and viral myocarditis were also high on the differential diagnosis.

INVESTIGATIONS

Chest radiograph showed bilateral patchy perihilar and bibasilar opacities. Transthoracic echocardiogram showed normal left ventricular systolic function, mildly decreased right ventricular systolic function, and no evidence of coronary artery dilation. A 15-lead electrocardiogram and serum troponin were unremarkable. N-terminal pro-B-type natriuretic peptide level (NT-proBNP) was elevated

ABBREVIATIONS AND ACRONYMS

HD = hospital day

KD = Kawasaki disease

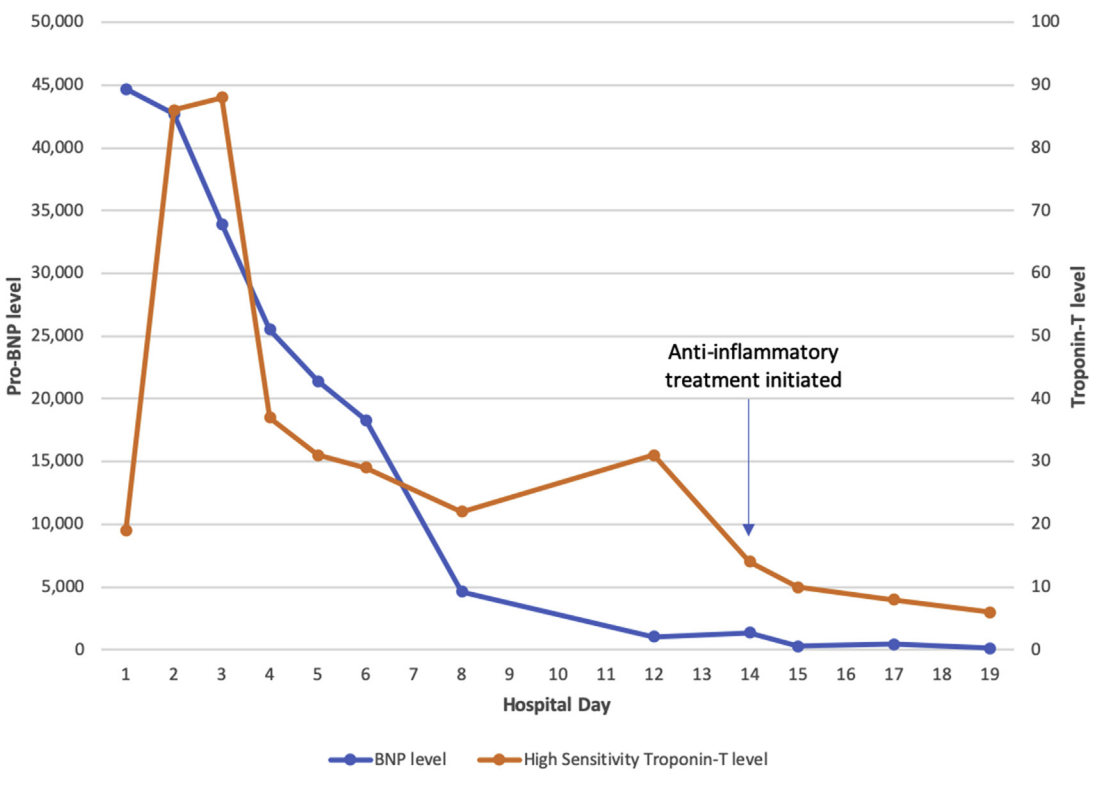
LAD = left anterior descending

MIS-C = multisystem inflammatory syndrome in children

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

FIGURE 1 Pro-BNP and High Sensitivity Troponin-T Trend



BNP = B-type natriuretic peptide.

TABLE 1 Admission Laboratory Test Values

Admission Laboratory Tests	Results	Normal Range
Complete blood count		
White blood cell ($\times 10^3/\mu l$)	12.0	5.14–13.38
Hemoglobin (g/dl)	11.5	10.2–12.7
Platelet ($\times 10^3/\mu l$)	105	202–403
Basic metabolic panel		
Sodium (mmol/l)	141	137–145
Potassium (mmol/l)	3.9	3.5–5.1
Chloride (mmol/l)	101	98–107
Carbon dioxide (mmol/l)	14	19–27
Blood urea nitrogen (mg/dl)	63	3–16
Creatinine (mg/dl)	3.6	0.50–0.80
Glucose (mg/dl)	119	60–100
Calcium (mg/dl)	8.0	8.8–10.3
Hepatic function panel		
Protein total (g/dl)	5.2	5.7–8.0
Albumin level (g/dl)	2.5	3.9–5.2
Globulin (g/dl)	2.7	2.0–3.5
Bilirubin total (mg/dl)	0.4	0.2–1.3
Bilirubin direct (mg/dl)	0.3	0.0–0.3
Aspartate aminotransferase (U/l)	28	10–37
Alanine aminotransferase (U/l)	38	9–50
Alkaline phosphatase (U/l)	142	142–335
Coagulation profile		
Prothrombin time (s)	18.7	11.9–14.4
International normalization ratio	1.6	0.9–1.1
Activated partial thromboplastin time (s)	38.8	23.9–34.7
Fibrinogen (mg/dl)	684	191–430
Venous blood gas		
pH	7.18	7.36–7.41
P_{CO_2} (mm Hg)	57	40–45
Lactate (mmol/l)	6.2	0.50–2.20
Cardiac biomarkers		
N-terminal pro-B-type natriuretic peptide (pg/ml)	44,677.0	23.0–327.0
Troponin-T, high sensitivity (ng/l)	19	≤22
Inflammatory markers		
Creatine kinase (U/l)	64.0	64.0–499.0
Lactate dehydrogenase (U/l)	476	155–345
C-reactive protein high sensitivity (mg/l)	>300.00	0.00–10.00
Procalcitonin (ng/l)	126.92	≤0.08
Ferritin level (ng/l)	1,195.0	30.0–400.0
D-dimer (μg/ml FEU)	1.39	≤0.80
COVID-19 testing		
SARS-CoV-2 RT-PCR	Not detected	Not detected

COVID-19 = coronavirus disease-2019; FEU = fibrinogen equivalent units; P_{CO_2}, partial pressure of carbon dioxide; RT-PCR = reverse-transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2.

to 44,677 pg/ml (Figure 1). Laboratory study results (Table 1) showed a mixed metabolic and respiratory acidosis, acute kidney injury, thrombocytopenia, elevated inflammatory markers, hyperferritinemia, elevated fibrinogen, elevated D-dimer, and prolonged coagulation studies. The result of a nasopharyngeal SARS-CoV-2 polymerase chain reaction test had been positive 2 days prior at urgent care but was negative when the test was repeated.

The patient was admitted to the pediatric intensive care unit and received supportive care per the local acute SARS-CoV-2 protocol. Dopamine, epinephrine, norepinephrine, vasopressin, and stress-dose hydrocortisone were required to maintain systemic blood pressures. He received 10 days of antibiotics for presumed culture-negative bacterial sepsis. Abdominal ultrasonography obtained on hospital day (HD) 3 for pain and distension showed ascites and gallbladder wall thickening. He developed a mild transaminitis while in the pediatric intensive care unit consistent with ischemic hepatopathy, which resolved by HD 5.

On HD 4, he developed respiratory failure requiring bilevel positive airway pressure. Serum SARS-CoV-2 antibody testing result was positive. On HD 6 he was weaned to continuous positive airway pressure, and vasopressor support was discontinued; respiratory support was ultimately discontinued on HD 9. Physical examination showed muscle weakness out of proportion to the duration of hemodynamic shock, with minimal spontaneous movements even when agitated.

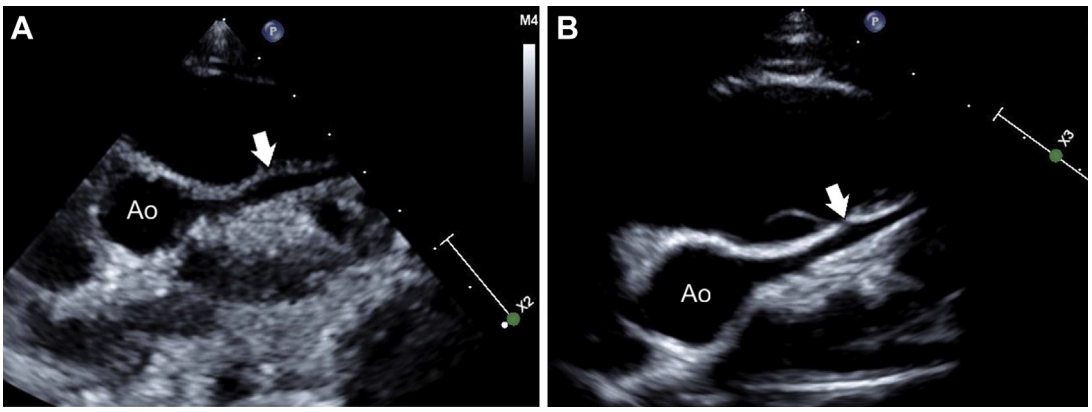
On HD 10, he was transferred to the intermediate care unit. On HD 12, physical examination showed 4/5 strength bilaterally, wide-based antalgic gait, right ankle clonus, bilateral lower extremity tenderness, right knee swelling limiting range of motion, and inability to rise from seated without assistance. Serum creatine phosphokinase, aldolase, and lactate dehydrogenase levels were normal.

On HD 14, he developed increasing tachypnea, scrotal edema, ascites, and serositis concerning for fluid retention. A transthoracic echocardiogram showed normal left ventricular systolic function but revealed a diffuse, medium-sized aneurysm of the left anterior descending (LAD) coronary artery (*z* score: 5.2) that was not present on his initial transthoracic echocardiogram.

MANAGEMENT

Based on his myopathy, synovitis, history of shock, and new finding of coronary artery aneurysm, the patient was diagnosed with MIS-C. He received intravenous immunoglobulin, anakinra, pulse-dose methylprednisolone, and anticoagulation with enoxaparin. Two days after initiation of anti-inflammatory treatment, his weakness, abdominal pain, distension, tachypnea, and knee effusion resolved. Repeat echocardiogram 6 days after initiating treatment

FIGURE 2 Echocardiogram Images Demonstrating Coronary Artery Changes During Hospitalization



(A) Hospital day 14: diffuse, medium-sized aneurysm of the left anterior descending coronary artery measuring 3.7 mm (*z*-score: 5.2, based on Boston Children's Hospital *z*-score system). **(B)** Hospital day 20: resolution of aneurysm with left anterior descending coronary artery measuring 2.5 mm (*z*-score: 1.1). Ao = aorta.

showed resolution of the LAD aneurysm (2.5 mm; *z*-score: 1.1) (Figure 2).

FOLLOW-UP

The patient was discharged on HD 20. A transthoracic echocardiogram 2 weeks after discharge showed further decrease in LAD luminal dimension (*z*-score: 0.7). The patient's mother reported that his strength, activity, and energy had returned to baseline.

DISCUSSION

This represents the only reported case to date of untreated, severe MIS-C and demonstrates that multisystem sequelae may develop without anti-inflammatory treatment, even after hemodynamic resuscitation and clinical improvement. Our patient developed a medium-sized coronary artery aneurysm, a novel and important finding. As with KD, the most feared complication of MIS-C is the development of coronary artery aneurysms. There is robust evidence of increased mortality in untreated KD, and KD-related coronary artery aneurysms account for 5% of acute coronary syndromes in adults younger than 40 years old (7–9). Although there is evidence of extensive cardiac involvement in MIS-C, including hemodynamic shock, coagulopathy, and myocarditis with dramatically elevated NT-pro-BNP and troponin-T, few significant coronary artery changes have been described (1–4,10).

One notable divergence between this case and KD-related coronary artery aneurysms is the rapid return to normal luminal dimension <1 week after initiation of treatment. Current treatment pathways for KD recommend anti-inflammatory management until at least 10 days after presentation for maximal efficacy in preventing coronary artery formation (8,9). In our case, treatment was delayed well beyond the typical windows for KD yet resulted in even faster aneurysm resolution than is typically seen in KD, where comparable aneurysms demonstrate improvement 6 to 18 months after treatment (8). The complete resolution of the patient's symptoms immediately after initiating treatment suggests a persistent hyperinflammatory state in untreated MIS-C.

Our case demonstrates the importance of considering MIS-C in patients with positive SARS-CoV-2 polymerase chain reaction swabs, because prolonged viral shedding can overlap with positive antibody testing (10). MIS-C is a diagnosis that cannot be missed, often rapidly progressing to hemodynamic shock (1–4,10). This case provides new evidence that coronary artery aneurysms are another potentially life-threatening complication of MIS-C, highlighting the importance of early disease detection. Crucially, this patient had complete resolution of coronary artery aneurysms and all other symptoms, which supports initiation of anti-inflammatory therapy as soon as the diagnosis of MIS-C is made, even if delayed.

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