Delayed Coronary Dilation with Multisystem Inflammatory Syndrome in Children

Meghan Corrigan Nelson, DO, Justine Mrosak, MD, Sassan Hashemi, MD, Cynthia Manos, MD, MSCE, Sampath Prahalad, MD, MSc, Sarah Varghese, MD, and Matthew E. Oster, MD, MPH, Atlanta, Georgia

INTRODUCTION

Since the outbreak of coronavirus disease 2019, there have been reports of systemic inflammation and cardiac dysfunction with multiorgan involvement in pediatric patients, temporally associated with severe acute respiratory syndrome coronavirus-2. This entity has collectively been referred to as multisystem inflammatory syndrome in children (MIS-C).

Further reports identified a clinically distinct phenotype of these patients with a Kawasaki disease (KD)–like syndrome complicated by coronary dilation. A subset of these patients have proved refractory to conventional therapies, with either development or progression of coronary artery dilation. Coronary artery dilation or aneurysms have been described in 8% to 24% of these patients. Aneurysmal progression despite current standard therapy, however, is a less common entity, with limited reports. We describe this phenomenon in our MIS-C population.

CASE PRESENTATIONS

Patient 1

A 17-year-old boy with Klippel-Feil syndrome presented with 3 days of fever, myalgia, and sore throat. Initial echocardiography showed a dilated left main coronary artery (LMCA) and left anterior descending coronary artery (LAD), with normal biventricular function (Z-scores of 2.09 and 3.48, respectively; Figure 1A and 1B, Video 1A and 1B). Following the administration of intravenous immunoglobulin (IVIG) 2 g/kg on day 4, he developed signs of heart failure and was transferred to the pediatric intensive care unit for inotropic support. Repeat echocardiography revealed severely depressed left ventricular function with persistent coronary artery dilation. He was started on methylprednisolone 2 mg/kg/d, with improvement in systolic function, but developed worsening dilation of the LMCA (Z-score = 5.05) on day 8 (Figure 1C and 1D, Video 1C and 1D). He received methylprednisolone 2 mg/kg/d for 5 days, followed by transition to a prednisone taper. Five months following discharge, the patient had persistently stable LMCA dilation on cardiac magnetic resonance imaging.

Patient 2

A 6-year-old boy presented with 6 days of fever, conjunctival injection, abdominal pain, emesis, and diarrhea. He was admitted briefly to the intensive care unit for vasopressor support, and findings on initial echocardiography were normal. He was given IVIG 2 g/kg and dexamethasone 0.15 mg/kg followed by methylprednisolone 2 mg/kg/d. On day 9, echocardiography revealed dilation of the LAD (Z-score = 2.7; Figure 2, Video 2) for which he received infliximab 10 mg/kg and methylprednisolone was increased to 4 mg/kg/d. Echocardiography on day 12 revealed worsening LAD dilation, prompting initiation of methylprednisolone 30 mg/kg for 3 days with subsequent stabilization of LAD dilation (Z-score = 4.18). He was discharged on day 14 on clopidogrel, low-dose aspirin, and a prolonged prednisolone taper. Echocardiography on day 28 showed normal coronary arteries.

Patient 3

A 4-year-old boy presented with colitis, conjunctival injection, oral mucosa erythema, and fever for 5 days. He received IVIG 2 g/kg and methylprednisolone 2 mg/kg/d for 4 days, followed by a prednisolone taper. Echocardiography showed normal coronary arteries. Four days following discharge, he redeveloped fever, abdominal pain, and scrotal edema, with increasing inflammatory markers and brain natriuretic peptide, prompting readmission (Figure 3). Echocardiography on day 14 revealed diffuse proximal coronary artery dilation (LAD Z-score = 2.38, LMCA Z-score = 2.37, right main coronary artery Z-score = 2.52; Figure 3, Video 3). He was given methylprednisolone 30 mg/kg/d for 3 days and infliximab 10 mg/kg. Echocardiography 48 hours following infliximab infusion revealed resolution of coronary artery dilation. He was discharged home on low-dose aspirin and prednisolone taper. Echocardiography on day 27 showed normal coronary arteries.

DISCUSSION

We present a series of cases of pediatric patients with delayed coronary involvement secondary to MIS-C despite treatment with IVIG and steroids. MIS-C has been described as a post–coronavirus disease 2019 hyperinflammatory syndrome with variability of expression and multiorgan system involvement. Cardiovascular involvement in

From the Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia (M.C.N., J.M., C.M., S.P., S.V., M.E.O.); Children’s Healthcare of Atlanta, Atlanta, Georgia (J.M., S.H., S.V., M.E.O.); and the Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia (S.P.).
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Drs. Nelson, Mrosak, Varghese, and Oster contributed equally to this work.
Dr. Prahalad serves on the Macrophage Activation Syndrome Adjudication Committee for Novartis Pharmaceuticals.
Reprint requests: Meghan Corrigan Nelson, DO, Department of Pediatrics, Emory University School of Medicine, 1400 Tullie Road, Atlanta, GA 30329. (E-mail: macorn07@gmail.com).
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MIS-C is common, including acute myocardial and valvular dysfunction, myocarditis, and cardiogenic and vasodilatory shock, with many patients requiring vasoactive support and intensive care unit admission. Coronary artery dilation and aneurysm formation have also been described as cardiac complications of MIS-C, with varied incidence. Although the exact mechanism is not clear, some hypothesize that coronary involvement may be secondary to circulating inflammatory cytokines that disrupt the arterial wall, as similarly seen in KD. Alternatively, because coronary manifestations described with MIS-C have been relatively mild and quick to resolve, others believe that coronary enlargement may result from vasodilation in the setting of a proinflammatory environment.

To date, management of MIS-C has involved the use of corticosteroids, IVIG, and biologic agents, based largely on overlap of features between KD and a Kawasaki-like phenotype of MIS-C. In comparison to patients with KD-related coronary artery aneurysm development, Whittaker et al reported that patients with MIS-C who developed coronary changes were generally older (median age, 9 years), had higher levels of inflammatory markers (specifically C-reactive protein and ferritin), and had higher levels of cardiac injury...
markers. Kelly et al. reported that cardiac biomarker elevation may be an indicator of overall illness severity as well as echocardiographic changes, including reduced left ventricular ejection fraction. This was reflected in our patient population, with reduced ejection fraction being associated with higher brain natriuretic peptide and troponin levels (Figure 4). Further studies have suggested that patients with MIS-C have significantly reduced left ventricular function at presentation, a phenomenon also overall reflected in our patient cohort. Furthermore, abnormalities in longitudinal strain persisted after normalization of ejection fraction between hospital days 5 and 9.8 This suggests possible separate etiologies for coronary injury that may require different treatment approaches than those used in KD. Although IVIG is thought to prevent coronary artery dilation and aneurysm formation in patients with KD, all of our patients developed either primary or worsening dilation after initial treatment with this therapeutic modality.9,10 Infliximab, along with other tumor necrosis factor inhibitors and cytokine modulators, has been used in patients with MIS-C as adjunct therapy.11 Infliximab use has been associated with improvement of coronary artery aneurysms in patients with MIS-C, particularly those in whom initial IVIG therapy failed.11,12 Ultimately, two out of the three patients in our case series received infliximab for progression of coronary involvement, with either stabilization or improvement on short-term follow-up (see Table 1).

CONCLUSION

We describe the development of delayed coronary artery dilation and/or aneurysm following timely administration of current first-line therapeutics for MIS-C, adding to limited reports.5,10 Studies have elucidated persistent left ventricular strain even at 10-week follow-up, indicating that patients can continue to exhibit myocardial dysfunction beyond inpatient hospitalization.13 These cases highlight the importance of early cardiac disease detection as well as continued serial monitoring of this patient population. As evidenced in this report, development of cardiac sequelae may occur even in patients receiving current standard therapies and otherwise exhibiting clinical improvement. In addition, patients can present with a wide spectrum of clinical disease, making it difficult to predict clinical course. A high index of suspicion and vigilant follow-up are indicated for these patients as we continue to learn more about the course of disease and long-term complications of MIS-C.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2021.08.002.
Figure 3 2D TTE, basal parasternal short axis images of patient 3 at early presentation, showing normal left (A, arrow) and right (B, arrow) coronary arteries. One-week follow up imaging, showing mild (Z-score = 2.4) left (C, arrow) and mild (Z-score = 2.5) right (D, arrow) coronary artery dilation.

Figure 4 Coronary size and medications throughout the disease course. Coronary Z score versus time for each patient is shown. The top rows indicate medications used throughout disease course. The bottom rows indicate laboratory parameters corresponding to day of illness. BNP, Brain natriuretic peptide; CRP, C-reactive protein; LCX, left circumflex coronary artery; RCA, right coronary artery.
Table 1: Characteristics of patients with MIS-C with delayed coronary involvement

| Patient 1 | Patient 2 | Patient 3 |
|-----------|-----------|-----------|
| Age, y    | 17        | 6         | 4         |
| Sex       | Male      | Male      | Male      |
| Weight, kg| 64        | 25        | 17        |
| Comorbidities | Klippel-Feil syndrome, spinal fusion | None | None |
| COVID-19 status | PCR+, IgG+ | PCR+, IgG+ | PCR−, IgG+ |

**Presentation**

| Fever | 3 d | 6 d | 5 d |
| Conjunctivitis | + | + | + |
| Peripheral edema | + | + | + |
| Abdominal pain | + | + | + |
| Vomiting/diarrhea | + | + | + |
| Myalgia | + | + | + |
| Shortness of breath | + | + | + |

**Initial support**

- Epinephrine and milrinone drops, high-flow nasal canula
- Epinephrine drops
- None

**Initial treatment**

- Methylprednisolone (1 mg/kg every 12 h), IVIG (2 g/kg)
- Dexamethasone 6 mg IV × 48 h, methylprednisolone 1 mg/kg every 12 h, IVIG (2 g/kg)
- Methylprednisolone 1 mg/kg every 12 h, IVIG (2 g/kg)

**Return of symptoms**

- No
- No
- Fever and scrotal edema 4 d postdischarge

**Readmission**

- No
- No
- Yes

**LOS**

- 9 d
- 10 d
- 3 d, 3 d (two admissions)

This table depicts patient demographics, clinical features, and management of MIS-C both before and after the development of delayed coronary dilation.

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