Multisystem Inflammatory Syndrome in Children during the COVID-19 Pandemic: A Case Report on Managing the Hyperinflammation

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ABSTRACT  The novel human coronavirus of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has quickly swept throughout the entire world. As the ongoing pandemic has spread, recent studies have described children presenting with multisystem inflammatory disorder sharing the features of Kawasaki disease (KD) and toxic shock syndrome, now named Multisystem Inflammatory Syndrome in Children (MIS-C). These cases report a similar phenotype of prolonged fever, multisystem involvement, and biomarkers demonstrating marked hyperinflammation that occurs temporally in association with local community spread of SARS-CoV-2. Herein, we describe the presentation, clinical characteristics, and management of an 11-year-old boy with prolonged fever, strikingly elevated inflammatory markers, and profound, early coronary artery aneurysm consistent with a hyperinflammatory, multisystem disease temporally associated with coronavirus disease 2019. We highlight our multidisciplinary team’s management with intravenous immunoglobulin, methylprednisolone, and an interleukin-1 receptor antagonist, anakinra, as a strategy to manage this multisystem, hyperinflammatory disease process.

INTRODUCTION
The ongoing coronavirus disease 2019 (COVID-19) pandemic started in December 2019 in the Wuhan province of China and has quickly swept across the globe. In March 2020, the USA began seeing increasing numbers of COVID-19 cases in localized clusters with widespread outbreaks by April. The pathophysiology and clinical course of this new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children are still unknown. Children made up approximately 2% of all COVID-19 confirmed cases and <10% of those cases required hospitalization, in contrast to adults who had significantly higher morbidity and mortality rates.\(^1\)\(^–\)\(^3\)

There have been increasing reports of children presenting with a novel syndrome consisting of fever and multisystem organ involvement due to excessive inflammation, with features commonly seen in both Kawasaki disease (KD) and toxic shock syndrome. Initially referred to as Pediatric Inflammatory Multisystem Syndrome, the U.S. Center for Disease Control published a case definition naming this as Multisystem Inflammatory Syndrome in Children (MIS-C). The MIS-C diagnostic criteria require evidence of SARS-CoV-2 infection or exposure to a close contact with confirmed COVID-19, which presents challenges as diagnostic test accuracy is still uncertain. The increase in MIS-C cases has been temporally associated 4 to 6 weeks following a spike in local community spread of COVID-19. Despite the ongoing spread of the pandemic, MIS-C remains rare. To date, only case series and case reports of Pediatric Inflammatory Multisystem Syndrome/MIS-C are published.\(^4\)\(^–\)\(^15\) Many, but not all, report that children with this disease either tested positive for SARS-CoV-2 via PCR or had evidence of previous exposure based on serology. Little is known about the exact pathophysiology or long-term implications of MIS-C, and it is unclear at this time what role SARS-CoV-2 may play, if any. Here we describe the presentation and hospital course for an 11-year-old child with a hyperinflammatory state involving multiple organ systems that occurred temporally associated with our local region’s peak community spread of COVID-19. This is the first such case reported in the Military Health System (MHS) and could serve as a management guidance for other clinicians in the MHS who may only see sporadic cases.

CASE REPORT
A previously healthy 11-year-old Caucasian male presented to the emergency department (ED) with a 10-day history of fever of 39.2°C 102.6 °F, dry cough, nonmigratory bilateral ankle pain, non-bloody diarrhea, and 2 days of bilateral non-exudative conjunctivitis. He was previously seen
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in the ED on day 4 of illness where his physical exam was unrevealing, a chest x-ray (CXR) was normal, and the SARS-CoV-2 nasopharyngeal RT-PCR (Cobas 6800 platform: Roche Molecular Systems, Branchburg, NJ) and respiratory pathogen multiplex PCR (BioFire FilmArray 2.0: BioFire Defense, Salt Lake City, UT, USA) were both negative. The fever continued, and ankle pain progressed to impair ambulation. His family became concerned by a new onset of labored breathing and bilateral eye redness which prompted his return to the ED. He had dry lips and appeared tired, but reported no history of photophobia, nasal congestion, rhinorrhea, sore throat, chest pain, dyspnea, abdominal pain, swelling or redness of hands or feet, rash, irritability, neck pain, or neurological changes. He had no smoke, dust, or provoking airborne particulate exposure. There was no family history of vasculitis, autoimmune disorders, or aneurysms. There were no currently sick contacts identified. However, his younger brother had a brief febrile upper respiratory infection 3 weeks before the patient’s symptoms, and he lived in a region with extensive community spread of the SARS-CoV-2 during the preceding 5 weeks. The patient remained at home with his immediate family during the local region’s “stay-at-home” order. His father is a physician who was required to report to the hospital daily for work, but had remained well and asymptomatic.

On presentation, he was febrile to 101.7 °F, with tachycardia of 105 beats per minute, a blood pressure of 102/62 mm Hg, a respiratory rate of 20, and pulse oximetry of 93% on room air. His exam was notable for bilateral non-exudative bulbar conjunctivitis, dry lips, and oropharyngeal hyperemia with a right tonsillar exudate. He did not display irritability or meningeal signs. There was no cervical lymphadenopathy or abnormal tongue manifestations. His lungs were clear and he had no murmurs or cardiac friction rub. His abdomen was soft without tenderness or hepatosplenomegaly. There were no skin findings, peripheral edema, lymphadenitis, or synovitis.

Repeat respiratory pathogen multiplex PCR and SARS-CoV-2 RT-PCR (BioFire Defense, Salt Lake City, UT, USA) were both negative. Initial laboratory results revealed hyponatremia (134 mmol/L), hypoalbuminemia, leukocytosis with neutrophilia and lymphopenia, mild elevation of transaminases, and significantly elevated inflammatory markers (Table I). Urinalysis had mild proteinuria (30 mg/dL) but was otherwise negative. Troponin and pro-Brain Natriuretic Peptide N-Terminal (pro-BNP) were both markedly elevated (Table I). An electrocardiogram demonstrated sinus tachycardia with prolongation of his corrected QT interval (QTc) to 500 ms with biphasic and inverted T-waves in the precordial leads. His CXR demonstrated bilateral peripheral patchy opacities with central peribronchial cuffing but no focal consolidation, effusion, or pneumothorax.

He was initially admitted to the general pediatrics ward for further evaluation and management of incomplete KD and concern for MIS-C. He was immediately treated with intravenous immunoglobulin (IVIG) (2 g/kg) and aspirin (ASA) (80 mg/kg/day high dose), after which he defervesced and his diarrhea and ankle pain resolved. He was also treated with

| Laboratory | Ref range | 1 | 2 | 3 | 4 | 5 | 7 | 10 | 14 | 16 | 18 |
|------------|-----------|---|---|---|---|---|---|----|----|----|----|
| pro-BNP    | 5–125 pg/mL | 13.822 | 20.536 | 15.039 | 7.186 | 4.300 | 1.512 | 286.2 |
| Troponin   | 0–19 ng/L  | 102.5 | 129.5 | 123.5 | 73.9 | 94 | 88.1 | 14.2 |
| WBC        | 4.5–13.5 K/UL | 17.4 | 16.8 | 16.3 | 27.6 | 28.5 | 35.7 | 27.2 | 28.6 | 28.9 |
| Neutrophils| 9%–75%     | 79% | 77% | 88% | 88% | 72% | 80% | 80% | 75% | 56% | 62% |
| Bands      | 0%–10%     | 4% | 5% | 4% | 3% | 1% | 2% | 3% | 3% | 4% | 3% |
| Lymphocytes| 16%–75%    | 8% | 1% | 2% | 4% | 12% | 9% | 15% | 12% | 26% | 27% |
| Hematocrit | 35%–45%    | 36.8 | 28.9 | 35.2 | 22.9 | 31.2 | 26.9 | 29.8 | 26 | 30.4 | 31.7 |
| Platelets  | 150–450 K/UL | 363 | 420 | 377 | 641 | 642 | 607 | 567 | 499 | 384 | 364 |
| CRP        | <0.03 mg/dL | 23.77 | 23.23 | 17.69 | 16.35 | 7.48 | 3.28 | 1.49 | 0.6 | 0.22 | 0.11 |
| ESR        | 0–20 mm/HR | 113 | >120 | 75 | >120 | >120 | >120 | >120 |
| Ferritin   | 7–140 mg/mL | 559 | 778 | 1393 | 1302 | 1111 | 762 | 455 | 305 |
| Fibrinogen | 207–454 mg/dL | 688 | 773 | 765 | 825 | 651 | 624 | 590 | 388 |
| D-dimer    | <0.5 µg/mL | 3.97 | 5.07 | 3.98 | 3.25 | 3.56 | 2.31 | 1.34 | 0.8 | 0.73 |
| VWF        | 50%–150%   | 216 | 326 | 326 | 281 |
| LDH        | 135–223 U/L | 297 | 254 | 197 | 220 | 185 |
| Albumin    | 3.5–5.2 g/dL | 2.6 | 2.2 | 2 | 2.4 | 2.5 | 2.8 | 3.1 | 3.4 |
| ALT        | 0–41 U/L   | 84 | 78 | 105 | 98 | 104 | 121 | 138 | 46 |
| AST        | 0–40 U/L   | 163 | 183 | 268 | 180 | 174 | 113 | 99 | 46 |

All laboratory values listed as absolute values corresponding to units of measurement are listed under “Ref range” column.
Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; pro-BNP = pro-Brain Natriuretic Peptide N-Terminal; VWF = von Willebrand factor Ag; WBC = white blood cell.
empiric antibiotics (clindamycin and ceftriaxone) for possible toxic shock syndrome. He developed mild hypoxia and tachypnea requiring supplemental oxygen. Despite oxygen therapy, his tachypnea persisted, prompting transfer to the Pediatric Intensive Care Unit for high-flow nasal cannula. Repeat CXR showed new small bilateral pleural effusions, patchy bilateral infiltrates, prominent peribronchial cuffing, and retrocardiac atelectasis.

His initial echocardiogram on hospital day (HD)-1 demonstrated coronary artery aneurysm of the left anterior descending (LAD) coronary artery, initially measuring 4 mm (Boston z-score +3.3), which then progressed to 4.5 mm (z-score +4.6) on HD-2 (Table II). He demonstrated an evolving myocarditis with rising troponin and pro-BNP levels, and his echocardiogram showed low-normal biventricular function (left ventricular ejection fraction 55%), without valvulitis or pericardial effusion. With a clinical picture more concerning for MIS-C than incomplete KD, anakinra, an interleukin (IL)-1 receptor antagonist, was started at 2 mg/kg subcutaneously (SQ) twice daily and quickly increased to 10 mg/kg IV twice daily after continued rise of inflammatory and cardiac markers (Table I, Fig. 1).

Twenty-seven hours after completing IVIG, he had an isolated fever of 102 °F; pro-BNP and most inflammatory markers were downtrending aside from ferritin, which continued to rise (Table I, Fig. 1). Methylprednisolone 2 mg/kg IV once a day was added, and he continued on high-dose ASA. He remained on this treatment regimen for 6 days with gradual improvement. By HD-3, his electrocardiogram normalized and his ventricular function improved (left ventricular fraction 70%), all of the while showing slow normalization of inflammatory markers and cardiac enzymes. By HD-5, his respiratory support was weaned and he was stable on room air by HD-7.

Anakinra dosing was decreased to once daily on HD-9. Echocardiogram on HD-10 showed increased LAD aneurysm measuring 5.0 mm (z-score +5.9) (Fig. 2). The size increase of the LAD was unexpected, as his inflammatory markers had started to downtrend in the preceding days. This progression was viewed as a surrogate for the initial level of vascular inflammation causing likely ongoing vessel damage. As a result, he was given a second dose of IVIG 2 g/kg and 3 days of high-dose methylprednisolone (10 mg/kg once daily).

On HD-15, echocardiogram showed improvement with LAD aneurysm that decreased to 4.7 mm (z-score +5.2). Once all the inflammatory markers normalized, medication dosing was slowly decreased over the subsequent 4 days. He was discharged home on anakinra 200 mg/day SQ, oral prednisone 60 mg/day, ASA 162 mg/day, and clopidogrel 37.5 mg/day due to moderate aneurysm of coronary artery. Prednisone and anakinra were slowly tapered and then stopped after a total of 6 weeks of therapy. Serial outpatient echocardiograms showed that the LAD aneurysm was unchanged at 4 weeks but reduced to 4.2 mm (z-score +3.6) after 7 weeks. Clopidogrel was stopped but he continues on low-dose ASA daily due to the persistent small coronary artery aneurysm.

He had two blood cultures that were negative, a negative pharyngeal rapid group A streptococcal antigen, negative throat culture, negative Legionella urine antigen, and negative monospot. His blood type is A +. Serum obtained on HD-3, post-IVIG and initiation of anakinra, demonstrated increased IL-6 at 202 pg/ml (normal<7), IL-8 at 34 pg/ml (normal<21), IL-18 at 1770 pg/ml (normal<90), and sIL-2R at 3259 pg/ml (normal<3830). His IL-1b, IL-2, IL-4, IL-5, IL-10, TNF-alpha, and GM-CSF levels were all normal.

During his hospital stay, there was a detailed investigation on potential COVID-19 exposure. The younger sibling’s preceding febrile respiratory illness was intriguing and corresponded with the local region’s peak community spread. Unfortunately, the younger sibling was not tested for acute COVID-19 at the time of illness due to limited testing availability secondary to resource preservation. Our patient had a total of three separate SARS-CoV-2 RT-PCR tests performed (two Cobas and one BioFire) on nasopharyngeal specimens, all of which were negative. He also had two separate negative sets of SARS-CoV-2 IgA, IgM, and IgG serology (Abbott Diagnostics, Chicago, USA). No other identifiable cause for his hyperinflammatory state was identified.

### DISCUSSION

The differential diagnosis for an otherwise healthy 11-year-old child with prolonged fevers, mucocutaneous findings, multisystem involvement, and markedly elevated inflammatory biomarkers is broad, including a wide range of infectious, postinfectious, and autoimmune inflammatory diseases. The presence of marked coronary artery aneurysmal changes significantly narrows the differential to a handful of diseases including KD +/− macrophage activation syndrome, polyarteritis nodosa, and the newly described MIS-C. The clinical presentation of this patient was not compatible with the conventional diagnosis of polyarteritis nodosa. Initial ferritin and LDH elevations were modest and did not suggest the severity usually seen with macrophage activation syndrome.

### TABLE II. Coronary Artery Size and Z-scores

| Hospital day | LAD Size | LAD z-Score | LMCA Size | LMCA z-Score |
|--------------|----------|-------------|-----------|-------------|
| 1            | 4.0 mm   | +3.3        | 4.0 mm    | +1.2        |
| 2*           | 4.5 mm   | +4.6        | 4.1 mm    | +1.4        |
| 3            | 4.5 mm   | +4.6        | 4.6 mm    | +2.3        |
| 7*           | 4.5 mm   | +4.6        | 3.9 mm    | +1.0        |
| 10*          | 5.0 mm   | +5.9        | 4.7 mm    | +2.5        |
| 15           | 4.7 mm   | +5.2        | 4.1 mm    | +1.4        |

Trans-thoracic echocardiogram performed throughout hospitalization monitoring for coronary artery ectasia and aneurysm. Boston criteria used to calculate z-score.

*Change in intervention based on echocardiogram findings (refer to text and Fig. 1).

Abbreviations: LAD = left anterior descending artery; LMCA = left main coronary artery.
It is strikingly unusual for KD to present in this demographic and age with prominent gastrointestinal symptoms as well as respiratory symptoms. Based on his demographics, temporal relationship following peak local spread of COVID-19, laboratory data, and clinical course, our presumed diagnosis was MIS-C, with therapy directed at this new syndrome. We must point out that both KD and MIS-C are clinical syndromes with no definitive confirmatory tests.

During this pandemic, there has been an unprecedented increase in the number of reported cases analogous to our patient, which at best overlap with the findings previously described in KD. Similar to MIS-C, the cause of KD is unknown. One center in Italy reported a 30-fold increase of KD cases during the COVID-19 outbreak as compared to the previous years.\(^4\) Half of these cases met atypical KD criteria, which themselves are somewhat inexact in nature, suggesting a possibly different pathogenic trigger. These children had a more severe form of KD with higher rates of cardiac involvement and the features of macrophage activation syndrome, and 80% had evidence of concurrent or previous infection with SARS-CoV-2. Reports from Europe and the USA describe numerous children with MIS-C who also met atypical KD criteria.\(^10,12–14\) Our patient met diagnostic criteria for atypical KD. However, we recognize him as a marked outlier with his older age, early formation of coronary artery aneurysm, severe elevation of inflammatory markers, and pulmonary radiographic findings, the latter being rare in all forms of KD. His presenting characteristics, specifically age, fevers,
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FIGURE 2. Transthoracic echocardiogram parasternal short axis view of the aorta and left coronary artery system on hospital day 10. The left anterior descending artery measures 0.50 cm (z-score + 5.9). Ao = aorta; LAD = left anterior descending artery; LCx = left circumflex artery; LMCA = left main coronary artery.

diarrhea, asthenia, and biomarkers are consistent with the published data to date describing the cases of MIS-C.4 In the USA, KD has an estimated incidence range of 9 to 20 per 100,000 per year, with 76% cases occurring in children under 5 years old.16 While KD is 3 to 15 times more prevalent in Taiwan and Japan, neither country has reported any MIS-C case, refuting the proposal that MIS-C is a variant of KD. Since the emergence of COVID-19, both Taiwan and Singapore have reported lower rates of KD as compared to pre-COVID era, another enigmatic finding.17,18

Despite the negative SARS-CoV-2 nasopharyngeal PCR and negative serology, we strongly feel our case meets the intent behind the definition of MIS-C based on the above-mentioned findings. He met the diagnostic criteria for Pediatric Inflammatory Multisystem Syndrome, which preceded MIS-C and did not require SARS-CoV-2 confirmation. Although we do not have a confirmed epidemiologic link to a COVID-19 positive person, the local area had its highest peak of community spread 4 weeks before our patient’s illness, coinciding with his younger sibling’s febrile respiratory illness, where case positivity rate was 32.14%.19 Face coverings and increased distancing were just beginning to be mandated in public at this time, and there was less recognition of the potential impact of asymptomatic spread, thus we cannot fully rule out COVID-19 exposure from the community.

We initially treated our patient with IVIG and high-dose ASA in accordance with the 2017 American Heart Association’s KD guidelines.16 For KD, IVIG resistance is not assumed until fever is persistent or recrudescent at least 36 hours after the end of the first IVIG infusion. The Kobayashi scoring model is a risk stratification tool used to identify children at high risk for IVIG resistance, and a score ≥5 is considered high risk.20 At baseline, our patient had a Kobayashi score of 5 due to his elevated CRP, elevated transaminases, and neutrophilia. This is consistent with the aforementioned Italian cohort, where they found 70% of KD cases in 2020 had a Kobayashi score >5, as compared to only 10% of KD cases in the 5 years preceding the COVID-19 pandemic (P = .0021).4 We were concerned about resistance and the need for additional treatment when his inflammatory markers remained elevated despite his fever and arthralgia improving with IVIG. Interleukin-1 (IL-1) was identified as a potential therapeutic target, with elevated IL-1 levels driving the systemic inflammation as noted in similar patients. Anakinra was chosen for its rapid onset, short half-life, favorable side-effect profile, and our team’s experience with its use in similar prolonged inflammatory illnesses. Dosing of anakinra was driven by laboratory markers and expert experience. Initially, we started at 100 mg (2 mg/kg/day) of anakinra based on adult studies and then increased to the final dose of 20 mg/kg/day divided twice daily to achieve the desired effect.21,22 After the initial improvement in inflammatory markers to anakinra, IV methylprednisolone was added approximately 48 hours after IVIG completion to continue driving down the systemic inflammatory process with favorable results (Fig. 1).

In addition to a hyperinflammatory state, our patient’s d-dimer and von Willebrand Factor antigen (VWF Ag) were also elevated. This has been recently described in other MIS-C cases in the literature.4,11,15 Elevated d-dimer and VWF Ag demonstrate concurrent ongoing endothelial damage which is a risk factor for thrombosis. There are increasing reports of thrombotic events in moderate-severe COVID-19 adult patients, including strokes in those without the risk factors.23-25 In addition to anti-platelet dosing of ASA for his atypical KD with coronary artery aneurysm, we added Low Molecular Weight Heparin (Enoxaparin) for thrombotic prophylaxis until his d-dimer normalized and invasive intravascular catheters could be removed. Our patient was discharged home with dual anti-platelet therapy of clopidogrel and low-dose ASA to prevent thrombosis within his coronary artery aneurysm. Clopidogrel was stopped after 7 weeks of therapy when the coronary artery aneurysm regressed from medium-sized to small; he remains on daily low-dose aspirin indefinitely as directed by the Pediatric Cardiology.

The MHS has the pediatric subspecialists available and the resources necessary to appropriately manage children presenting in a hyperinflammatory state associated temporally with COVID-19. As can be seen with this case, both the recognition of the syndrome and the choice and dosing of the multiple therapeutic agents requires a true multidisciplinary team with excellent communication between each other and with patients and their families. As acute cases of COVID-19 spread across our nation, the numbers of cases of MIS-C will periodically rise in proportion to the levels of regional activity. This will undoubtedly occur in communities where large active duty military components are located, and MHS medical providers should be aware of the broad range of pediatric subspecialty experts required and available for consultation to appropriately guide the management approach.
CONCLUSIONS

Our case highlights the complexity of children presenting with multisystem inflammation temporally associated with the local community’s COVID-19 activity and its initial diagnostic and medical management. It is important to have early specialty involvement with Pediatric Critical Care, Allergy/Immunology, Cardiology, Hematology and Oncology, Infectious Diseases, and Rheumatology to provide a multidisciplinary approach to treatment for this novel syndrome, especially when there is myocardial involvement. All of these subspecialists are available within the MHS and able to provide consultation in-person or via telemedicine globally. The immunopathology for this hyperinflammatory state is yet to be completely elucidated, and the ideal treatment regimen has not yet been proven. Our report describes the first detailed case of a hyperinflammatory, multisystem disease in a child temporally associated with COVID-19 in the MHS. We believe more children will present with this inflammatory syndrome in the weeks to months ahead and would like to highlight our combination of IVIG, ASA, anakinra, and methylprednisolone as a potential management strategy for children who present in a similar hyperinflammatory state. However, continued disease assessment and tailored treatment is essential, and may lead to an introduction of additional agents such as anti-tumor necrosis factor alpha, anti-IL-6, or other biologic response modifiers.

ACKNOWLEDGMENTS

We thank Ms. Farahnaz Ghias, RDCS (AE/PE), for the outstanding echocardiographic images obtained on this child. We thank the entire multidisciplinary pediatric inpatient team at the Walter Reed National Military Medical Center who helped care for this patient. We thank COL (Ret.) Martin Ottolini, CPT Jeremy McMurray, CPT Ashley Packett, and CPT Nelson Vick for comments on the case report.

FUNDING

None declared.

CONFLICT OF INTEREST STATEMENT

None declared.

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