Multisystem Inflammatory Syndrome in an Adult With COVID-19—A Trial of Anakinra
A Case Report

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Abstract: COVID-19 disease has been a pandemic caused by a β-coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A life-threatening multisystem inflammatory syndrome (MIS), secondary to SARS-CoV-2 virus infection, sharing common features with Kawasaki disease shock syndrome, staphylococcal/streptococcal shock syndrome, and macrophage activation syndrome in pediatric patients has been described. A total of 27 cases in adults (MIS-A) with a similar presentation have been reported so far. Here we describe the case of a 21-year-old man admitted with abdominal pain, diarrhea, tachycardia, and low blood pressure. He had elevated troponin, ferritin, and interleukin-2 receptor levels and had evidence of myocarditis. He tested positive for SARS-CoV-2 IgG antibody, and a diagnosis of MIS-A was made. Our case adds to the scant literature on this topic, and to our knowledge, it is the first case where anakinra was administered. He recovered well. MIS-A should be considered when young adults present with multiorgan dysfunction.

Key Words: SARS-CoV-2, multisystem inflammatory syndrome, myocarditis

CASE DESCRIPTION

A 21-year-old man with a history of asthma, glucose-6-phosphate dehydrogenase deficiency, obesity (body mass index, 33.6 kg/m²), and no history of smoking, alcohol, or substance use disorder presented to the emergency department in April 2020 with a 2-day history of frontal headache, fever, abdominal pain, vomiting, and nonbloody diarrhea. Initial vital signs included a temperature of 103.5°F, heart rate of 177 beats/min, blood pressure of 95/56 mm Hg, and oxygen saturation of 98% on room air. Physical examination findings included a dehydrated and tachycardic patient with diffuse abdominal tenderness on deep palpation without rigidity or guarding. Prominent laboratory results (Table 1) indicated acute kidney injury, and elevated C-reactive protein (CRP) and ferritin levels on admission. He tested negative for SARS-CoV-2 by nasopharyngeal (NP) polymerase chain reaction (PCR). His mother was diagnosed with coronavirus 2019 (COVID-19) pneumonia secondary to SARS-CoV-2 3 weeks before his admission. No abnormalities were noted on chest x-ray and computed tomography of the abdomen/pelvis. Blood cultures were negative. Stool PCR panel tested positive for enteroaggregative Escherichia coli. Intravenous fluids and broad-spectrum antibiotic piperacillin-tazobactam at 4.5 g every 6 hours were started.

On day 3 of admission, he continued to be febrile to 104.8°F, had systolic blood pressure ranging between 94 and 109 mm Hg, tachycardia, and elevated troponin and ferritin (Table 1). Electrocardiography showed ST-segment elevation in lead I, lead aVL, and lateral precordial leads likely consistent with myocarditis. Transthoracic echocardiogram findings included moderately reduced global systolic function with a left ventricular ejection fraction of 38%. Because of myocarditis and concern for macrophage activation syndrome (MAS) in the setting of persistent fever and high inflammatory markers (day 3; Table 1), patient was started on a 5-day course of anakinra (interleukin-1 receptor antagonist) at 100 mg every 12 hours and then increased to every 6 hours the following day.

On day 5, he continued to be febrile but did not require vasopressor or respiratory support. Intravenous immunoglobulin (IVIG) at a dose of 1 g/kg was started, followed by a second dose at 2 g/kg 48 hours later. On day 7, piperacillin-tazobactam and anakinra were stopped and intravenous methylprednisolone 1 mg/kg every 12 hours was started. A second SARS-CoV-2 NP PCR was negative, but a SARS-CoV-2 serum IgG was positive. His soluble IL-2 receptor was 5430 pg/mL (reference range, ≤1033 pg/mL), consistent with MAS. On day 8, he became afebrile. His inflammatory markers gradually improved. He was discharged on day 10 on lisinopril 10 mg daily and a prednisone course starting from 60 mg twice a day tapering the dose by 10 mg every 2 days with a final diagnosis of multisystem inflammatory syndrome—adults (MIS-A).

At a telehealth follow-up visit 2 weeks after discharge, he reported fatigue for a day after discharge and a gradual return to baseline health a week later. A repeat echocardiogram was recommended in 2 to 3 months, but he was lost to care.

DISCUSSION

SARS-CoV-2 is a novel β-coronavirus initially isolated in Wuhan, China, and later recognized as a global threat in January 2020 after reports of a cluster of cases presenting with fever, difficulty in breathing, and chest x-rays showing extensive pulmonary lesions. The world soon got caught in the grips of this virus with an exponential surge in patients with a similar constellation of symptoms, which was later defined as COVID-19 infection. The first case of COVID-19 in the United States was reported in Washington on January 19, 2020, in a patient traveling from China. The virus was isolated from his sputum, bronchoalveolar lavage,
urine, and stool specimens. The World Health Organization officially declared COVID-19 as a pandemic in March 2020.3

SARS-CoV-2 is an aggressive virus with capacity to cause multiorgan involvement with intricate and complex clinical manifestations. Stroke,4 myocarditis,5 and acute kidney injury6 are also recognized as manifestations of COVID-19. A COVID-19-associated MIS in children (MIS-C) has been described; it shares common features with Kawasaki disease shock syndrome (KDSS), staphylococcal and streptococcal shock syndrome (TSS), bacterial sepsis, and MAS. Fever, abdominal symptoms, myocarditis, acute kidney injury, and elevated inflammatory markers are common.7 The pathogenesis of MIS-C is unclear but has been presumed to be due to endothelial damage and thromboinflammation, dysregulated immune responses, and dysregulation of renin-angiotensin-aldosterone system.8 It could also be potentially a postinfectious process, but immunophenotyping has been noted to be distinct from MAS or Kawasaki disease.9

The diagnostic criteria for MIS-C include age <21 years, fever, a positive SARS-CoV-2 test result (either positive SARS-CoV-2 PCR or antibody assay), elevated inflammatory markers, multisystem (≥2) organ involvement, and no alternative plausible diagnosis.10 Patients hospitalized for acute hypoxic respiratory failure with other organ system involvement do not fall under this category. Patients may be asymptomatic or may have had mild upper respiratory symptoms due to SARS-CoV-2 2 to 5 weeks before presenting with MIS. The majority of patients with MIS-C described in the literature were hospitalized for acute hypoxic respiratory involvement, and cardiovascular and laboratory abnormalities resembling MIS. Most of these children had COVID-19 infection-induced MIS.

COVID-19 cardiovascular involvement occurs in 8% to 28% of patients. Myocarditis has been documented, and elevated troponin and natriuretic peptide are prognostic factors for intensive care unit admittance, mechanical ventilation, and death.13 SARS-CoV-2 is dependent on the glycoprotein angiotensin-converting enzyme 2 (ACE2) protein found in the lung and cardiac tissue as a cellular entry receptor that binds to its spike protein. ACE2 expression protects myocardium from injury as it converts angiotensin II into angiotensin I, a vasodilator and a counterregulator of the renin-angiotensin-aldosterone system. The ACE2 action is downregulated by binding of SARS-CoV-2 via its spike protein. ACE2 expression protects myocardium from injury as it converts angiotensin II into angiotensin I, a vasodilator and a counterregulator of the renin-angiotensin-aldosterone system. The ACE2 action is downregulated by binding of SARS-CoV-2 via its spike protein. ACE2 expression

Most of our patient's laboratory findings were compatible with MAS, a life-threatening type of multisystem inflammation characterized by fever, elevated ferritin, elevated interleukins including soluble IL-2 levels,15 cytopenia, liver dysfunction, and fibrinolytic coagulopathy secondary to increased IL-6 levels. Elevated ferritin level is associated with increased mortality.16 Cardiovascular involvement is not associated with this syndrome unless it is complicated with KDSS and coronary aneurysms.17

Our young adult case had similarities to a cluster of cases reported in 8 children with vasogenic shock, lack of significant respiratory involvement, and cardiovascular and laboratory abnormalities resembling MIS. Most of these children had COVID-19 or were contacts of family members with COVID.18 Our patient's initial SARS-CoV-2 NP PCR was negative, but his SARS-CoV-2

### TABLE 1. Laboratory Tests and Treatment During Hospitalization

| Test                     | Reference Range | Day 1 | Day 3 Anakinra | Day 5 Anakinra and IVIG | Day 7 Anakinra and IVIG | Day 8 Prednisolone | Day 10 Prednisolone |
|--------------------------|-----------------|-------|----------------|-------------------------|-------------------------|-------------------|---------------------|
| WBC, k/μL                | 4.0–11.0        | 8.6   | 5.6            | 10.8                    | 8.8                     | 9.9               | 9.4                 |
| ALC, k/μL                | 1.1–3.5         | 0.5   | 0.4            | 0.9                     | 0.9                     | 1.3               | 3                   |
| Hemoglobin, g/dL         | 13.5–17.5       | 15.3  | 11.9           | 10.8                    | 8.9                     | 9.6               | 9.3                 |
| Platelets, k/μL          | 150–400         | 223   | 145            | 165                     | 333                     | 447               | 523                 |
| CRP, mg/L                | 0–5             | 210   | 237            | 327                     | 153                     | 93                | 39                  |
| Fibrinogen, mg/dL        | <0.50           | 3.14  | 8.10           | 17.44                   |                         |                   |                     |
| Procalcitonin, ng/mL     | 26–209          | 413   | 1885           | 3896                    | 3223                    | 2635              | 1544                |
| Ferritin, ng/mL          | 1.2–1.3         | 1.14  | 1.20           | 1.16                    | 0.98                    | 0.83              | 0.74                |
| LDH, μL                  | 171–308         | 156   | 277            | 262                     | 270                     | 254               |                     |
| Fibrinogen, mg/dL        | 180–460         | 683   | 609            | >800                    | 481                     | 406               | 271                 |
| D-dimer, ng/mL DDU       | <243            | 833   | 640            | 359                     | 479                     | 469               | 831                 |
| AST, μ/L                 | 13–39           | 34    | 31             | 25                      | 32                      | 44                | 49                  |
| ALT, μ/L                 | 9.0–67.0        | 17    | 27             | 23                      | 24                      | 33                | 45                  |
| Creatinine, mg/dL        | 0.7–1.3         | 1.14  | 1.20           | 1.16                    | 0.98                    | 0.83              | 0.74                |
| Total bilirubin, mg/dL   | 0.3–1.2         | 1.3   | 2.1            | 1.9                     | 0.6                     | 0.7               | 0.7                 |
| Troponin I, ng/mL        | <0.033          | ~0.006| 0.074          | 0.299                    | 0.109                    | 0.080             |                     |
| BNP, pg/mL               | 33.3–11        | 30    | 656            | 843                     | 500                     |                   |                     |
| PT, s                    | 9.2–13.5        | 15.9  | 16.2           | 14.9                    |                         |                   | 14.3                |
| INR                      | 0.83–1.20       | 1.19  | 1.34           | 1.24                    |                         |                   | 1.19                |
| PTT, s                   | 27–37           | 33    | 29             |                         |                         |                   |                     |
| Triglyceride, mg/dL      | 40–200          | 135   | 209            |                         |                         |                   |                     |

ALC indicates absolute lymphocyte count; ALC, alanine aminotransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CRP, C-Reactive Protein; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood count.

It is unknown if patients with respiratory or GI symptoms or both are prone to develop symptoms compatible with COVID-19 infection-induced MIS.

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serum IgG was positive, supporting the diagnosis of SARS-CoV-2–induced MIS that shares features with KDSS and TSS.

Our case also had similarities to MIS cases described previously in adults and now recognized as MIS-A by the Centers for Disease Control and Prevention (CDC). Three case series have been published on MIS-A.19,20 The CDC Morbidity and Mortality Week Report reviewed them along with the 9 cases directly registered with the CDC and 7 individually published case reports, tallying to a total of 27 reported cases of MIS-A.18 Twenty-four patients recovered, 2 received tocilizumab (IL-6 receptor antagonist), and the remainder received either corticosteroids or IVIG. Our case adds to the limited literature of reported MIS-A cases and is the only case where anakinra was administered because of clear progression to MAS. Anakinra has been approved for use in MIS-C29 but not reportedly even been used in adults for MIS-A. We believe that in our patient, the outcome was influenced by the use of anakinra as noted by improvement in ferritin, CRP, troponin, and creatinine levels by the end of anakinra course (Table 1). This patient presented earlier in the pandemic (in April 2020) when the knowledge of cytokine inhibitors for use in COVID-19 was limited. Also, further decision to pursue Anakinra therapy was supported by demonstration of favorable response to anakinra in a cross-sectional study in adult patients admitted for MAS.30

In conclusion, SARS-CoV-2 can affect multiple organs predisposing individuals to a life-threatening multisystem inflammation along with elevated inflammatory markers that resemble a mixture of KS/TSS with laboratory evidence of a cytokine storm. Early recognition of the clinical manifestations and imaging and laboratory abnormalities are crucial to initiating prompt therapy in these patients. Multisystem inflammatory syndrome secondary to SARS-CoV-2 infection should be considered in all patients presenting with multiple-organ involvement or multiple extrapulmonary manifestations especially if the initial COVID 19 PCR is negative, highlighting the importance of obtaining a SARS-CoV-2 IgG in these patients.

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