A Diagnosis You Cannot Afford to MIS-C: Multisystem Inflammatory Syndrome in Children Within the Active Duty Population

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ABSTRACT  Multisystem inflammatory syndrome in children (MIS-C), which is associated with coronavirus disease 2019 (COVID-19) and occurs in the immediately post-infectious period, has never-before been reported within the active duty population. It typically affects children, aged 5-13 years, but has been shown to affect those up to 20 years old. We present an 18-year-old active duty male that arrived at a military treatment facility emergency department with headache, neck pain, and shock without evidence of meningococcalitis on cerebrospinal fluid analysis and with a negative COVID-19 test. He developed significant abdominal pain and cardiomyopathy. Chest computed tomography showed evidence of ground glass infiltrates, and repeat testing was positive for the COVID-19 virus. Multisystem inflammatory syndrome in children (MIS-C) was diagnosed and treated with a rapid improvement in the patient’s condition. It is a rare but potentially fatal condition that has been shown to affect patients up to the age of 20, encompassing a large part of the junior enlisted population. Multisystem inflammatory syndrome in children (MIS-C) can lead to death, yet mimic other diseases leading to delay of care. Thus, it should be considered when faced with the appropriate constellation of symptoms.

INTRODUCTION  Multisystem inflammatory syndrome in children (MIS-C) is a rare and severe multisystem inflammatory condition associated with COVID-19 that is characteristically observed in individuals under the age of 21 years and can occur weeks after infection; only 6,851 cases have been reported as of February 2022.¹ Latest data from the Centers for Disease Control and Prevention (CDC) reports that 0.1-0.2% of COVID-19 deaths caused by the active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were among children aged <18 years old.² Although children are less prone to severe respiratory disease, they can suffer from severe multiorgan failure in the recent post-infectious state known as MIS-C.³ This syndrome is not well understood and has been described in recent medical literature as resembling other diseases such as Kawasaki disease and toxic shock syndrome.³ However, patients suffering from MIS-C typically do not meet criteria for these alternate diagnoses.⁴ Diagnosis of MIS-C had been defined by a CDC health advisory as⁵:

1. An individual aged <21 years presenting with fever (fever ≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated C-reactive protein [CRP], erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, or interleukin 6; elevated neutrophils; reduced lymphocytes; and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological);
2. No alternative plausible diagnoses; and
3. Positive for current or recent SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (RT-PCR), serology, or antigen test or exposure to a suspected or confirmed COVID-19 case within the 4 weeks before the onset of symptoms.

Cases of MIS-C have never been reported within the U.S. Military population. However, given the age at which enlistment into the military is allowed, the seriousness of the condition, and its ability to be treated, it is a diagnosis requiring familiarity from military physicians. We report a case of an 18-year-old male with shock that rapidly improved after the diagnosis and treatment of MIS-C, and we describe the clinical course to help with provider recognition moving forward.

CASE REPORT  In February 2021, an 18-year-old active duty male presented to the emergency department complaining of 4 days of fevers, headache and neck pain, weakness, and abdominal pain with profuse diarrhea. Vitals on presentation included blood pressures as low as 69/40 with mean arterial pressure of 50, heart rate up to 119, and respiratory rate up to 28 although oxygen saturation of ≥97%. His lactate level was elevated to 2.5 mmol/L and he had a neutrophilia, 91%, with bandemia, 32% of neutrophils, but no leukocytosis. Septic
MIS-C in Active Duty

FIGURE 1. Computed Tomography Angiography imaging of a section of the patient’s lungs showing ground glass opacities and pleural effusions secondary to COVID-19 pneumonia.

FIGURE 2. Echocardiography of the patient’s heart showing systolic dysfunction and an estimated ejection fraction of 47%.

shock was diagnosed and the vasopressor medications, norepinephrine and vasopressin, were required to normalize his blood pressures. His initial COVID-19 testing, via RT-PCR for SARS-CoV-2 RNA, was negative. Lumbar puncture was negative for evidence of infection including cell count without red blood cells or nucleated cells and Gram stain without white blood cells or organisms seen. Bio Fire FilmArray Meningoencephalitis PCR Panel was negative (Bio Fire FilmArray Meningoencephalitis PCR Panel tests for Bacteria: Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae. Virus: Cytomegalovirus, enterovirus, herpes simplex virus 1 and 2, human herpes virus 6, human parechovirus, varicella zoster virus. Fungus: Cryptococcus neoformans/gattii). The patient denied ever having any symptoms of COVID-19 or close contacts to infected persons although he lived in close quarters in the barracks. This event occurred at a time before a COVID vaccine was available.

He was admitted to the ICU for septic shock. Broad-spectrum antibiotics, vancomycin and piperacillin–tazobactam, did not improve his condition, and piperacillin–tazobactam was later escalated to Meropenem. Inflammatory markers were significantly elevated with a CRP level of 137 mg/L (normal <6), erythrocyte sedimentation rate of 108 (normal 0-9), ferritin level of 2,266.7 ng/mL (normal 26-388), and D-dimer 10,957 ng/mL (normal <500). His abdominal pain and corresponding exam worsened to the point of peritonitis over the next 24 hours, leading to surgical exploration of his abdomen and subsequent appendectomy. No evidence of intra-abdominal pathology was discovered. His condition continued to deteriorate. Computed tomography of the chest showed patchy opacities (Fig. 1), prompting repeat COVID testing by RT-PCR, which was positive. Laboratory evaluation revealed significantly elevated troponin I levels, 0.218 ng/mL, and pro-B-type natriuretic peptide (proBNP), 10,505 pg/mL. Global left ventricular systolic dysfunction, ejection fraction estimated at 45-50%, and impaired relaxation (stage I diastolic dysfunction) were discovered on echocardiography (Fig. 2). A clinical diagnosis of MIS-C was made and he was started on human intravenous immune globulins (IVIG), 100 g as 10 g/100 mL run at 50-100 mL/hr as tolerated, and methylprednisolone IV 60 mg with rapid clinical improvement during the next 12 hours. He received one more dose of IVIG the next day due to persistent fever, although significantly clinically improved, and was continued on steroid therapy for the planned five total days. Antibody testing, on blood drawn the day after IVIG administration, later revealed immunoglobulin M “negative” antibodies to SARS-CoV-2 spike protein but immunoglobulin G “positive” to SARS-CoV-2 S1/S2 proteins, suggesting likely prior but not active infection at the time of his stay. However, it is unclear whether the IVIG administered was originally drawn from patients with previous COVID infection to cause a positive immunoglobulin G result. Repeat echocardiography, 18 days after the first, showed resolution of systolic and diastolic dysfunction. He had close follow-up with his medical officers and was requesting return to training within 2 weeks after discharge from the hospital. He was eventually returned to full military duty by cardiology after cardiac magnetic resonance imaging was without abnormalities.

DISCUSSION

This is an index case in military medicine. This is the first reported incident of a syndrome that has the potential to affect a large part of the junior enlisted population. The Department of Defense reports that 51.6% and 14.4% of the military are below the age of 25 in the enlisted and officer populations, respectively. The CDC reports clinical presentation as persistent fever, abdominal pain, vomiting, diarrhea, skin rash, and mucocutaneous lesions and, in severe cases, with hypotension and shock. Patients have elevated markers of inflammation (e.g., CRP and ferritin), and a majority of patients have laboratory evidence of damage to the heart (e.g., elevated
troponin, BNP, or proBNP). The condition may follow a characteristic progression of organ dysfunction, starting with gastrointestinal symptoms, often mimicking appendicitis. It then affects the cardiovascular system, with resulting elevated troponin levels and cardiomyopathy evidenced on echocardiogram. Progression to headache and nuchal rigidity suggesting meningoencephalitis can follow. Inflammatory marker and D-dimer elevations are present at all stages of the disease. As per the American College of Rheumatology, IVIG, high-dose steroids, antiplatelet therapy (AcetylSalicylic Acid 81 mg), and antacids are the preferred therapy which achieved rapid (hours) stabilization in hemodynamics and overall clinical improvement in our patient. Patients with a diagnosis of MIS-C should have close outpatient follow-up, including pediatric cardiology follow-up starting 2-3 weeks after discharge.

**CONCLUSION**
Multisystem inflammatory syndrome in children (MIS-C) is a poorly understood but serious complication of a potentially asymptomatic SARS-CoV-2 infection that can affect those within the military population. We hope that the description provided will help make military treatment facility providers more aware of the possibility of this condition among younger military personnel and provide them with a starting point for understanding intervention.

**ACKNOWLEDGMENTS**
None declared.

**FUNDING**
None declared.

**CONFLICT OF INTEREST STATEMENT**
The authors declare that they have no competing interests to report.

**CONSENT**
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review.

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