CASE REPORT

Management of SARS-CoV-2 Multisystem Inflammatory Syndrome in Adult with Intravenous Immunoglobulin

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Abstract

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to evolve creating management dilemmas as time passes. Multisystem inflammatory syndrome in adults (MIS-A) unlike multisystem inflammatory syndrome in children and adolescents (MIS-C) has not been well characterized. Multisystem inflammatory syndrome in adults is a rare but potentially life-threatening hyperinflammatory syndrome affecting adults of all ages. Multisystem inflammatory syndrome in adults can occur in current or previous SARS-CoV-2 infection. Here we present a case of an elderly male with previous SARS-CoV-2 infection who had an unusual presentation with high fever, neck swelling, and skin rashes and recovered after intravenous immunoglobulin (IVIG) therapy. Clinicians should be aware of this postinfectious multisystem inflammatory illness after COVID-19. Intravenous immunoglobulin has an important role to play in the management of MIS-A.

Keywords: Adult, COVID-19, Fever, Intravenous immunoglobulin, Lymphadenopathy, Multisystem inflammatory syndrome in adults, SARS-CoV-2, Skin rash.

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Introduction

Coronavirus disease 2019 is an infectious disease caused by SARS-CoV-2. The COVID-19 pandemic has affected tens of millions of people across the world. A new MIS-C emerged during the pandemic. In this rare syndrome, affected children develop a significant inflammatory response similar to other inflammatory conditions like Kawasaki disease, bacterial sepsis, staphylococcal and streptococcal toxic syndromes, and macrophage activation syndrome.[1] There is a similar multisystem inflammatory syndrome affecting adults. In October 2020, Centers for Disease Control and Prevention (CDC) published a case series of MIS-A associated with SARS-CoV-2 infection. Clinical features have included fever, chills, throat and neck pain, skin rash, abdominal symptoms, shock, cardiac dysfunction, electrocardiogram changes, and raised inflammatory markers including C-reactive protein (CRP), ferritin, and interleukin-6 (IL-6).[2] Multisystem inflammatory syndrome in adults has a more heterogeneous clinical presentation. Disease can be serious, requiring intensive care treatment. Intravenous immunoglobulin, corticosteroids, and IL-6 inhibitors have been used in the management.

Incidence of MIS-A is unknown. There is limited information currently available about risk factors, pathogenesis, clinical course, and treatment of MIS-A. Long-term effects of this condition are unknown. High clinical suspicion is needed to detect MIS-A as many patients may have had a silent or mild acute infection. Antibody testing may be required to identify SARS-CoV-2 infection. Here we present a unique case report of a patient with MIS-A successfully managed with IVIG.

Case Description

A 68-year-old man presented to the medicine outpatient department with complaints of high-grade fever for 4 days, left-sided neck swelling for 3 days followed by rash for 1 day. Past medical history included diabetes mellitus and treatment for mild flu-like symptoms and suspected COVID-19 infection 3 weeks prior to this admission. Computed tomography (CT) chest (plain) at that time had shown features suggestive of viral pneumonitis, and mild lung involvement with CT severity score 8/25. He had recovered completely at home, not requiring hospital admission. He is a nonsmoker, did not drink alcohol, and had no known allergies. For this episode of illness, he was evaluated outside with laboratory investigations and COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) test was negative. Tests for malaria antigen, typhoid antibodies (IgM and IgG), dengue antibodies (NS1 and IgM) were negative, erythrocyte sedimentation rate (ESR) 65 mm after 1 hour, and CRP was 114.9 mg/dL. He had received antibiotics (tablet Co-amoxiclav) and paracetamol as part of the treatment. He was admitted to the ward. On evaluation, he was alert and oriented to self, time, and place, SpO_2 96%, respiratory rate 20/min, heart rate 92/min, blood pressure 110/70 mm Hg, and temperature 100°F. Physical examination was notable for multiple erythematous maculopapular lesions over the trunk and extremities. Swelling on the left side of the neck in the posterior

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triangle with enlarged multiple lymph nodes. Lungs were clear to auscultation bilaterally. Laboratory investigations were significant for thrombocytopenia 100,000/µL, elevated D-dimer 3.07 µg/mL, procalcitonin 3.26 ng/mL, hs Troponin I 73.75 pg/mL, and NT-proBNP 3030 pg/mL. Ultrasonography of the abdomen and pelvis showed grade I fatty infiltration of the liver, mild splenomegaly, and prostatomegaly. Electrocardiogram showed sinus tachycardia. Blood and urine cultures were sent. Patient was started on a broad-spectrum antibiotic.

Day 1 of admission, he continued to have fever up to 103°F. Contrast-enhanced CT imaging of the neck, chest, and abdomen was performed. Computed tomography of the neck showed diffuse edema in the retropharyngeal space, inflammation/cellulitis with no abscess or collection, and multiple enlarged left deep cervical lymph nodes. Computed tomography of the chest showed minimal fibrotic changes in bilateral lungs and no acute lung infection changes. Computed tomography of the abdomen showed fatty hepatomegaly, mild splenomegaly and bilateral perinephric fat stranding, and prostatomegaly. He was evaluated for other causes like malaria, leptospirosis, brucellosis, Lyme disease, and scrub typhus, and reports were negative. Antineutrophil cytoplasmic antibody (indirect immunofluorescence method) was also negative. Ear, nose, and throat flexible laryngoscopy examination revealed a normal nasopharynx, uniform pharyngeal bulge at the level of oropharynx, and no pus point. Ultrasound-guided left cervical lymph node biopsy showed reactive changes and no evidence of lymphoma. The Gene Xpert test of the sample was also negative for tuberculosis. Day 2, there was gradual deterioration in health with persisting fever, hypoxemia requiring oxygen, and generalized weakness. Neck swelling and skin rashes had decreased. Patient was shifted to the intensive care unit. There was an increase in white cell count 15,130/µL, CRP 34.28 mg/dL, serum procalcitonin 21.16 ng/mL, and platelet count remained low at 104,000/µL. Repeated D-dimer 7.99 µg/mL, hs Troponin I 264.8 pg/mL, and NT-proBNP 7390 pg/mL, all showed increasing trend. Blood peripheral smear was unremarkable except for neutrophilic leukocytosis and thrombocytopenia. COVID-19 antibodies were positive. Interleukin-6 level was high, 634.3 pg/mL. Serum fibrinogen was elevated at 7.36 g/L. There was concern for MIS-A. Examination and investigations had shown involvement of skin, lymph nodes, pharynx, lungs, heart, and abdomen with elevated inflammatory markers. Cultures of blood and urine had not shown any bacterial growth. A risk-benefit discussion was held with the patient and family members regarding treatment with IVIG. Potential risks including hypercoagulability were discussed. After consent, he was treated with IVIG 1 gm/kg/day on hospital days 4 and 5. Patient's clinical symptoms gradually improved. Fever subsided and he was weaned off oxygen. Repeat investigations showed decrease in CRP 15.22 mg/dL, D-dimer 4.10 µg/mL, and increase in platelet count 192,000/µL. Day 6, he was shifted to the ward. He continued to make good improvement, CRP, IL-6, and D-dimer showing a declining trend and no thrombocytopenia. Patient was discharged home on day 10.

Discussion

Multisystem inflammatory syndrome in adults is a new syndrome being more commonly recognized in patients with current or previous SARS-CoV-2 infection. Centers for Disease Control and Prevention has published a case definition for MIS-A. A patient aged ≥21 years hospitalized for ≥24 hours, or with an illness resulting in death, should meet the required clinical and laboratory criteria and the patient should not have a more likely alternative diagnosis for the illness.[3] Our patient was positive for COVID-19 antibodies and had fever, rash, thrombocytopenia, and elevated inflammatory markers ESR, CRP, IL-6, and procalcitonin. During the pandemic, recognizing SARS-CoV-2 infection can be challenging. High clinical suspicion is needed to detect MIS-A as many patients may have had a silent or mild acute infection. Our patient COVID-19 RT-PCR test was negative but COVID-19 antibodies test was positive. The interval between infection and development of MIS-A is unclear. In a single-center, retrospective cohort study of patients with SARS-CoV-2 related admission, patients with MIS-A were predominantly male (66.7%) and younger with a median age of 45.1 years. For patients with prior admission for acute COVID-19, the median interval between acute COVID-19 admission and MIS-A admission was 23 days. The median number of organ systems involved was 4 with the gastrointestinal, hematologic, and kidney systems being commonly affected.[4] Our patient developed symptoms 3 weeks after the previously suspected COVID-19 infection and had multiorgan involvement.

In elderly patients with multiple comorbidities, recognizing MIS-A can be challenging. Wide spectrum of presentation in the absence of management guidelines makes treatment decisions challenging. Multidisciplinary team approach is recommended. Early recognition by evaluation for hemophagocytic lymphohistiocytosis (HLH), thrombotic microangiopathies most commonly thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome, malignancy, and ruling out infections will aid in the management. Secondary HLH has been reported with SARS-CoV-2 infection.[5] Our patient did not have abnormal ferritin, triglycerides and lactate dehydrogenase, and no hemophagocytosis. Underlying malignancy can mimic vasculitis and multisystem involvement; however, lymph node biopsy was negative for lymphoma.

Procalcitonin is one of the inflammatory markers suggested by the CDC in the case definition of MIS-A for the presence of laboratory evidence of inflammation.[3] Procalcitonin is a biomarker that can be used to diagnose bacterial infection and monitor treatment. Many clinical practice guidelines endorse the use of procalcitonin in differential diagnosis of bacterial infections and/or to monitor antibiotic therapy.[6] Procalcitonin levels are elevated in COVID-19 patients also.[7] A systematic review and meta-analysis of COVID-19 patients showed increased procalcitonin, D-dimer, and thrombocytopenia as predictors of severe infection.[8] Duration of elevation of procalcitonin in SARS-CoV-2 infection is unknown.

Corticosteroids, IVIG, IL-6 inhibitor, and Tocilizumab have been used in the management of MIS-A.[2] Tocilizumab and corticosteroids are a concern in patients with proven or suspected infection. Our patient had increased procalcitonin and previous use of antibiotics had raised the concern of false-negative culture reports.

Since the syndrome is similar to MIS-C, treatment modalities have been extrapolated from suggested therapies for MIS-C. The American College of Rheumatology has developed clinical guidance for pediatric patients diagnosed with MIS-C associated with SARS-CoV-2 infection. A stepwise progression of immunomodulatory therapies has been suggested to treat MIS-C with IVIG considered as first-tier therapy and glucocorticoids to be used as adjunctive therapy. High-dose IVIG, typically 2 gm/kg based on ideal body weight, is recommended.[9] Intravenous immunoglobulin has been used in various autoimmune and inflammatory conditions. The immunomodulatory actions of high-dose IVIG in autoimmune

and inflammatory conditions are highly complex and differ in different diseases. In general, high-dose IVIG paradoxically leads to immunosuppressive and anti-inflammatory effects.[10] Intravenous immunoglobulin is easy to administer and well tolerated by many patients. Availability, adverse reactions, and cost are important points to be considered when considering IVIG.

Conclusion

This case highlights the important role of IVIG in the management of MIS-A. The optimal treatment of MIS-A remains unknown. Further research is needed to identify potential opportunities for targeted treatment of this multisystem inflammatory syndrome. Potential changes in disease characteristics with evolving virus mutations may create an ever-changing challenge.

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