



Case report

Recovery does not always signal the end of the battle: A case of post SARS-CoV-2 multisystem inflammatory syndrome in an adult



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ABSTRACT

We describe a case of SARS-CoV-2 post-infectious inflammatory syndrome in an adult who presented with multiorgan failure two months following his initial diagnosis of SARS-CoV-2 infection. This case highlights clinician's early recognition of this devastating sequela and challenges in appropriate management of this patient.

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Introduction

Multisystem inflammatory syndrome can follow current or prior SARS-CoV-2 infection, with emerging reports of Kawasaki-like multisystem inflammatory syndrome described in adults [2,3] and the more recent case series of nine patients (officially reported) by the Centre for Disease Control and Prevention (CDC) [4]. We describe the clinical presentation, treatment, and response of an adult with history of SARS-CoV-2 infection presenting with multiorgan failure two months following recovery from acute illness with no preceding respiratory symptoms. We believe this is the first case in Miami, Florida. We aim to raise clinical awareness of this post infectious multisystem inflammatory sequelae which we believe is related to SARS-CoV-2 infection.

Case presentation

A 46-year-old man with obesity (body mass index 42 kg/m²) presented to our emergency department (ED) in July 2020 with right lower extremity weakness, nausea and generalized weakness beginning 24 h prior to arrival. He had been diagnosed with SARS-CoV-2 infection 60 days prior to this admission, after experiencing mild flu-like symptoms for a few days and was seen by his primary care physician. He was found to have positive total antibodies and two negative nasopharyngeal polymerase chain reaction (PCR) for SARS-CoV-2 on 4/24/2020 and 5/10/2020, which were confirmed by the Florida Department of Health. Upon hospital admission, he was alert and oriented to self, time and place, hypotensive with blood pressure 88/37 mmHg, and hypoxic with oxygen saturation 89 % on nasal cannula at 3 L/min. Physical exam was notable for bilateral rhonchi on auscultation of lungs with right lower extremity strength 3/5, no skin rashes evident. Initial labs revealed a negative nasopharyngeal PCR and a positive total antibody test for SARS-CoV-2. SARS-CoV-2 total antibodies were measured to be 238 signal/cut-off (s/co) ratio, and IgG of 11 s/co ratio, both defined as high per our reference range (0.00–0.99). Inflammatory markers were elevated, ferritin 962 ng/mL, IL-6 121.09 pg/mL, C-reactive protein (CRP) 2.9 mg/dL, lactate dehydrogenase (LDH) 802

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units/L with increase in procalcitonin 0.678 ng/mL. He was found to have acute kidney injury with an elevated creatinine of 4.10 mg/dL from baseline of 2.90 mg/dL, high anion gap metabolic acidosis and lactic acidosis. Chest x-ray showed left retrocardiac opacity with no evidence of overt edema. Electrocardiogram (EKG) demonstrated signs of non-ST elevation myocardial infarction (NSTEMI) with elevated troponin 0.282 ng/mL and brain natriuretic peptide (BNP) 3590 pg/mL. Transthoracic echocardiography (TTE) demonstrated grossly normal ejection fraction with borderline elevated right ventricular systolic pressure (RVSP). Computed tomography (CT) of the chest showed dependent ground glass opacities in bilateral upper lobes, right middle lobe and in bilateral lower lobes with a more confluent patchy airspace opacity noted in the left upper lobe. CT abdomen showed hepatic steatosis. There was concern for potential posterior circulation stroke as he was found to have right ataxia, mild right hemiparesis and left hemianesthesia; however, CT head was unremarkable. He continued to experience hypoxia while in the ED and required oxygen support with 6 L of nasal cannula (O2 saturation fluctuating between 84–91 %). On hospitalization day 1, chest x-ray revealed diffuse bilateral mixed interstitial and airspace opacities worsened in the right lung compared to admission. The patient was tachypneic with worsening hypoxemia and required 40 L/min high-flow nasal cannula (O2 saturation fluctuating between 85–99 %) and was transferred to the Intensive Care Unit (ICU). He underwent invasive mechanical ventilation and was started on norepinephrine to maintain perfusion for possible septic shock. Additionally, he was initiated on intravenous ceftriaxone 2 gm daily, oral azithromycin 500 mg daily, and oral dexamethasone 6 mg daily, along with unfractionated heparin in a continuous infusion of 12 unit/kg/hr for suspected NSTEMI. A repeat nasopharyngeal SARS-CoV-2 PCR was performed and was negative. On hospitalization day 3, a third SARS-CoV-2 PCR from bronchoalveolar lavage (BAL) sample was tested and returned negative. After consultation with the CDC regarding atypical cases being recently reported in New York and London [1–3,5] and based on our clinical and laboratory evidence, we had a high suspicion for Multisystem Inflammatory Syndrome in adults (MIS-A), a syndrome that had not been defined at that time. Our hospital

multidisciplinary COVID-19 team decided to treat with tocilizumab 8 mg/kg and steroids. Cardiac enzymes continued to show elevations from 0.282 ng/mL to 2.1 ng/mL with BNP elevation of 5940 pg/mL. Repeat TTE demonstrated RVSP 39.4 mmHg (upper limit of normal), normal left ventricle, normal left ventricular wall thickness, normal left ventricular wall motion and normal right ventricle. Kidney function continued to deteriorate resulting in commencement of continuous veno-venous hemodialysis (CVVH). On hospitalization day 4 and 5, the patient had no documented clinical improvement after receiving tocilizumab. Inflammatory markers continued to uptrend ferritin 1993 ng/mL, IL-6 1412.44 pg/mL, LDH 4773 units/L, D-dimer 0.62 mcg/mL with the exception of CRP 8.3 mg/dL. Liver and kidney function continued to worsen, and troponins were persistently elevated, consistent with multiorgan failure. However, on hospitalization day 6, the patient started showing signs of clinical improvement by requiring less ventilator support and no longer needing pressors. On hospitalization day 8, the patient became hypotensive and febrile with thick foul-smelling respiratory secretions, respiratory cultures only grew *Candida albicans* with normal respiratory flora. Empiric broad spectrum antibiotics with intravenous vancomycin and cefepime were initiated and norepinephrine was restarted. Labs were notable for ferritin >100,000 ng/mL and LDH > 12,000 units/L. Due to ongoing concern for MIS-A, SARS-CoV-2 RT PCR (plasma) was repeated and reported as below limit of detection. Whole genome sequencing of Spike (S) gene from BAL for suspected re-infection/false negative PCR was attempted but failed to detect the SARS-CoV-2 RNA. On hospitalization day 9, the ICU team switched dexamethasone 6 mg to hydrocortisone 50 mg q6h. The patient continued to have severe refractory acidosis and hyperkalemia despite CVVH and suffered an arrhythmia on day 10 leading to his death. Hospital course with pertinent laboratory results summarized in Timeline (Fig. 1). Inflammatory markers trend over time and response to treatment depicted in Fig. 2.

Discussion

Multisystem Inflammatory syndrome (MIS) can occur in patients with past mild or asymptomatic SARS-CoV-2 infection.

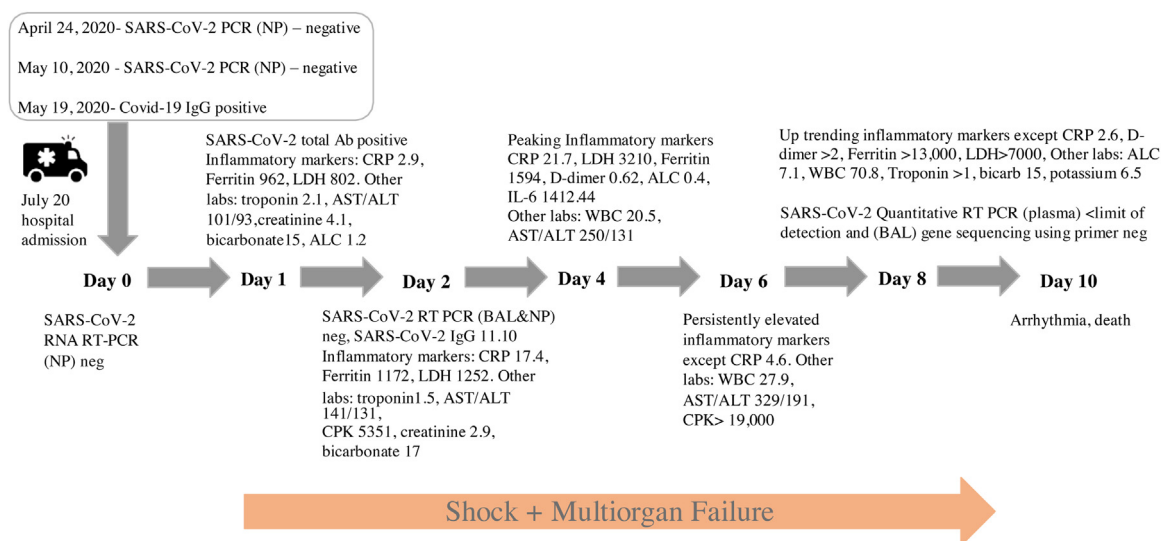


Fig. 1. Timeline of the patient's clinical course with focus on pertinent labs and clinical events over time.

Abbreviations: NP, nasopharyngeal; CRP, C-reactive protein; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALC, absolute lymphocyte count; IL-6, interleukin-6; WBC, white blood cell; CPK, creatine phosphokinase; RT-PCR, reverse transcription polymerase chain reaction; PCR, polymerase chain reaction; RNA, ribonucleic acid; BAL, bronchoalveolar lavage; IgG, immunoglobulin G; Ab, antibody.
 Lab (Units): CRP (mg/dL), LDH (unit/L), D-dimer (mcg/mL), ferritin (ng/mL), AST (unit/L), ALT (unit/L), IL-6 (pg/mL), troponin (ng/mL), bicarbonate (mmol/L), ALC (x103/mcl), WBC (x103/mcl), CPK (unit/L), creatinine (mg/dL), potassium (mmol/L), IgG (s/co ratio).

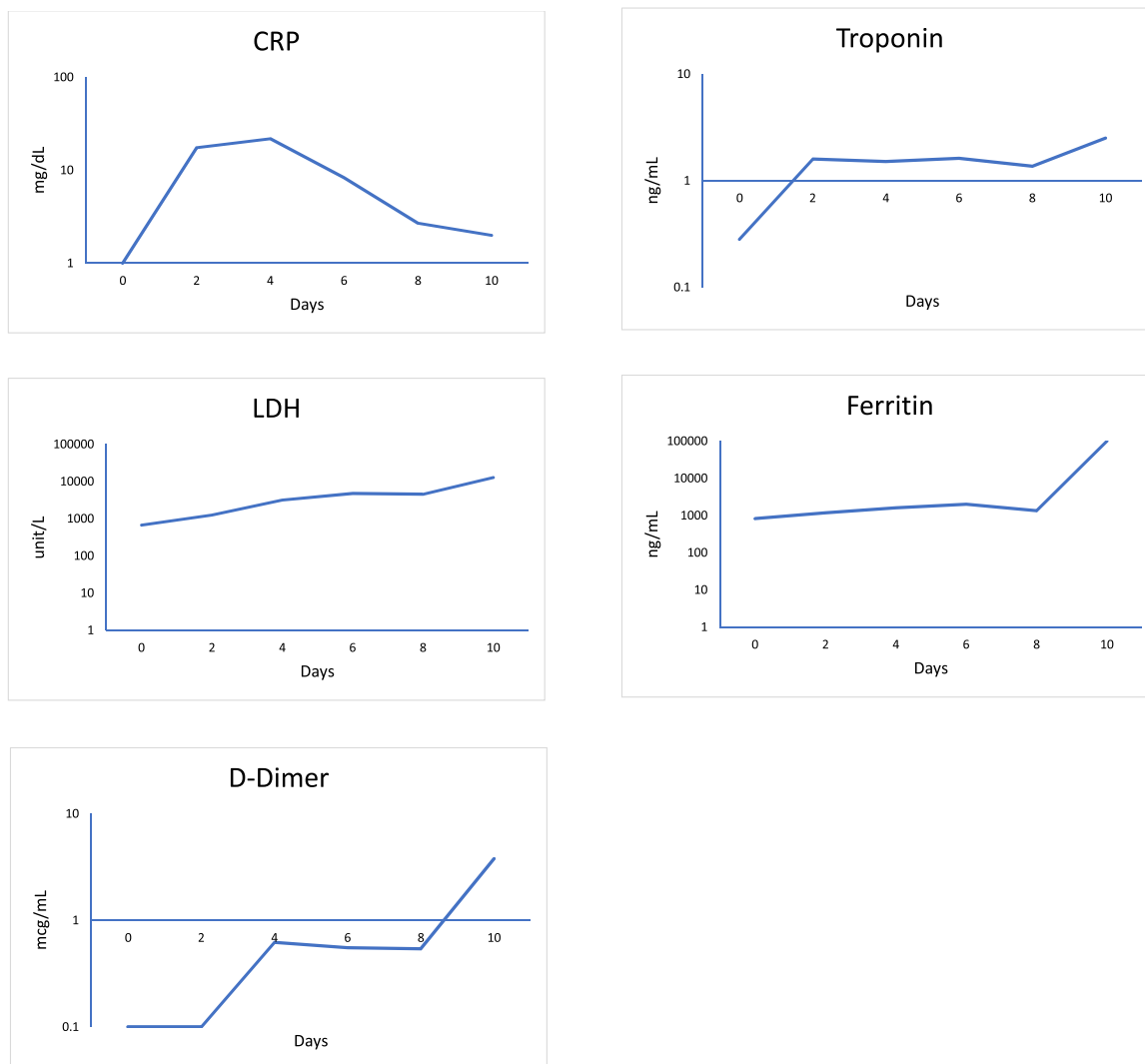


Fig. 2. Individual trend of inflammatory markers- CRP(C-reactive protein), LDH (lactate dehydrogenase), troponin, ferritin and D-dimer over time.

Although no diagnostic criteria for MIS-A has been established, our adult patient had a clinical presentation consistent with the CDC [6] and WHO [7] criteria for MIS-C. He had more than one organ system involvement on admission (cardiac and renal) with positive serology test for SARS-CoV-2 and negative SARS-CoV-2 PCR from NP and BAL samples with laboratory evidence of severe inflammation and absence of severe respiratory illness prior to admission. Furthermore, our patient developed this multisystem involvement two months after the initial diagnosis of SARS-CoV-2 with no other proven etiology.

Clinically, vascular dysfunction related to SARS-CoV-2 manifests beyond the lung in different ways, including deep venous thrombosis, pulmonary embolism, large arterial thrombosis, and multiorgan venous and arterial thromboses, and these manifestations have been attributed to factors such as hypoxemia, viral sepsis, immobility, and occasionally vasculitis [8].

Pulmonary venous thromboembolism well described in SARS-CoV-2 [9–11] could manifest with systemic emboli with organ ischemia and mimic vasculitis with similar presentation like our patient. This would be ideally confirmed with a CT pulmonary angiography which is gold standard, as our patient was hemodynamically unstable this was not performed. However, our patient empirically received anticoagulation for NSTEMI noted on EKG, that would have treated possible micro emboli/thrombus if indeed

present. Potential vasculitic involvement of other organs such as heart, brain, kidneys and skin seemed less likely due to the absence of pericarditis on exam and TTE, no acute infarctions on CT brain or renal ultrasound and lack of skin lesions respectively. Additionally, autopsy would have enabled clarification on the likelihood of alternative etiologies of this presentation, unfortunately not performed.

The borderline elevated right ventricular systolic pressures on TTE along with elevated troponins could suggest early pulmonary hypertension related to thromboembolism however this could have alternate explanations as well such as sleep apnea (obesity with BMI > 40) or heart failure (elevated BNP), and would warrant further diagnostics such as right heart catheterization which was not pursued in our case due to rapid clinical deterioration.

Another possibility is underlying malignancy which can also mimic vasculitis and manifest with multisystem thrombosis however CT chest, abdomen and pelvis were negative making it unlikely in this case.

Secondary hemophagocytic lymphohistiocytosis (sHLH) is shown to be associated with severe SARS-CoV-2 infection and can present with immune system activation rapidly progressing to multi-organ failure [12,13]. Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia, pulmonary involvement including acute respiratory distress syndrome (ARDS)

seen in approximately 50 % of patients [14]. Although fever and elevated ferritin levels in our patient may be suggestive of HLH, absence of splenomegaly, labs without cytopenia, hypofibrinogenemia does not favor this diagnosis although should be interpreted with caution due to limitation in failing to obtain triglycerides and soluble IL-2 receptor levels. The treatment of HLH is based on HLH-2004 guidelines and modified based on underlying cause and course of disease. Given the parallel cytokine profile between HLH and SARS-CoV-2, our patient was treated for potential sHLH as he received high dose steroids on admission to mitigate the hyperactive immune system in addition to IL-6 inhibitor, unfortunately without significant benefit. Additionally, sHLH is associated with other viral illnesses, our patient was screened for HIV, hepatitis C and respiratory viral panel including influenza all of which were negative.

The specific pathogenic mechanisms of this delayed clinical presentation may be similar to MIS-C or sHLH, however remains unknown. In adult cohorts, it is known that those with severe disease have higher abundance, breadth and neutralizing activity of SARS-CoV-2 antibodies compared to adults who recovered from mild disease. Multiple factors such as specificity, concentration, affinity and isotype determine whether antibodies are protective vs pathogenic [15]. Though SARS-CoV-2 antibodies are presumed to have protective and neutralizing properties, elevated levels of non-neutralizing antibodies through mechanism of antibody dependent enhancement (ADE) of infection [15] known to occur in viral infections could have played a pathogenic role in the observed hyperinflammatory response. Additionally we speculate an autoimmune process promoting aberrant immune responses leading to systemic inflammation also observed in children with MIS-C [16,17]. We believe that our patient's clinical picture was not consistent with cytokine storm because of the long timeframe between initial infection to development of symptoms.

To address the concern of possible re-infection and confirm PCR negativity on several nasal and BAL specimens, we attempted to sequence the Spike (S) gene from patient's BAL. Despite recovering ample specimens, no SARS-CoV-2 RNA was detected that could be used as template for S gene sequencing.

The optimal treatment for SARS-CoV-2 associated MIS remains unknown. Case reports have demonstrated a potential role for immunomodulator agents [1–31–3,55]. For MIS-C treatment, corticosteroids, anakinra, intravenous immunoglobulin (IVIG), and tocilizumab have each been used with varying success in children; none have been compared head-to-head [18]. For adults, similar treatment modalities have been reported, with the exception of anakinra [1–4,5].

We chose to initiate steroids based on the 'RECOVERY trial [19] and tocilizumab based on elevated IL-6 levels. Additionally, at the time, there were more studies to support tocilizumab compared to other non-steroid immunomodulators for mitigating hyperinflammation due to SARS-CoV-2 [20–22]. Within 72 h of receiving tocilizumab, our patient had a reduction in CRP, required less ventilator support, and maintained stable vitals while off pressors. However, this effect was not sustained as the patient developed worsening multiorgan failure and expired a few days later. Tocilizumab was used for the management of MIS-A in only one other case besides ours in the recently reported MIS-A case series. (Table 2, patient 11) [4]. Of note, this patient also received two doses of IVIG and steroids and subsequently discharged from the hospital. It is unclear whether administering IVIG to our patient or an additional dose of tocilizumab may have led to a different outcome. High dose IVIG is probably beneficial in patients with severe SARS-CoV-2 infection [23,24] however its role in MIS-A remains to be understood. Additionally, there is data suggesting that at least two doses of tocilizumab are needed to achieve adequate plasma drug concentrations [25]. Future studies are

needed to investigate the role of immunomodulators and IVIG for treating SARS-CoV-2 associated MIS-A.

Conclusion

This case highlights the serious and life-threatening post infectious sequelae of SARS-CoV-2 infection and rapid progression of multisystem organ failure. Further research to understand the role of SARS-CoV-2 antibody response and the pathogenesis of this acute multisystem organ involvement is encouraged. Also, early recognition of HLH like syndrome in patients recovered from SARS-CoV-2 may be important for timely management to prevent an outcome similar to our patient.

Lack of adequate evidence remains an impediment to the use of IVIG or tocilizumab as first line therapeutics for management of MIS-A and further clinical trials are needed to establish the efficacy of these in mitigating this exaggerated multisystem inflammatory sequela.

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Declaration of Competing Interest

All authors declare "No Conflict" of interest related to this submission.

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