

Severe multisystem inflammatory syndrome in a vaccinated adult with COVID-19

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Accepted 17 April 2022

SUMMARY

The ability of SARS-CoV-2 to trigger hyperinflammatory response in children and adults is increasingly recognised. However, the detailed features that distinguish severe COVID-19-associated hyperinflammation from multisystem inflammatory syndrome in adults (MIS-A) is not yet known. We describe a young, vaccinated patient with no prior SARS-CoV-2 exposure who developed COVID-19 and MIS-A. We also provide a review of the current literature on MIS-A and COVID-19-associated hyperinflammation.

BACKGROUND

COVID-19 continues to pose a global public health crisis. Yet, its full clinical and pathophysiological characterisation is still not clearly defined. In May 2020, multisystem inflammatory syndrome in children (MIS-C) was described.^{1,2} The illness was characterised by cardiac dysfunction, shock, severely elevated inflammatory markers and positive SARS-CoV-2 serology. In October 2020, an illness referred to as multisystem inflammatory syndrome in adults (MIS-A) was described.³ Recently, there have been a few case reports of multisystem inflammatory syndrome following SARS-CoV-2 vaccination (MIS-V).^{4,5} Here, we describe a unique case of a patient vaccinated against SARS-CoV-2, presenting with COVID-19 and MIS-A and provide a review of the current literature regarding this complex presentation.

CASE PRESENTATION

A healthy man in his late 20s presented to the hospital after being found down unconscious. He tested positive for SARS-CoV-2, 3 weeks prior to admission. He endorsed cough, fevers and chills. He was unable to walk unassisted due to generalised weakness. He became increasingly tachypneic and lost consciousness. He was noted to become rigid and lost bladder continence. He had no prior history of seizures. He did not take any medications at home. He had received two doses of mRNA-1273 (Moderna) SARS-CoV-2 mRNA vaccine for SARS-CoV-2, 9 months prior to presentation. He did not receive a booster dose.

En route to the hospital, he developed supraventricular tachycardia with a heart rate of the 200 beats per minute on cardiac monitor. He was given 12 mg of intravenous adenosine with improvement in heart rate. At the time of admission, his temperature was 100.7°F, heart rate 125 beats/min, BP 62/28 mm Hg and respiratory rate of 30 breaths/min. His body mass index was 44.85 kg/m². His

Glasgow Coma Scale was noted to be 3 and underwent endotracheal intubation for airway protection. Physical examination was remarkable for comatose state, mydriasis of pupils, and coarse, rhonchorous breath sounds throughout all lung fields. Conjunctivitis and skin rash were not identified. Extremities were cool to touch. Initial labs were notable for elevated lactate of 5.6 mEq/L, acute kidney injury, transaminitis and SARS-CoV-2 positivity (table 1). He was started on norepinephrine for management of shock and admitted to the medical intensive care unit. His urine drug screen was positive for fentanyl. CT scan of the chest showed low lung volumes with dependent bilateral airspace disease suspicious for atelectasis or aspiration.

He was started on levetiracetam for possible seizures and on broad spectrum antibiotics for septic shock secondary to aspiration pneumonia. Infectious diseases, cardiology and neurology services were consulted. He met the necessary criteria for MIS-A as per the Centers for Disease Control (CDC) definition. On day 3, he was given intravenous immunoglobulin (IG) and started on high-dose methylprednisolone. Subsequently, there was improvement in the levels of his inflammatory markers. The medical team decided against treatment with anakinra given clinical improvement. CT of the brain imaging revealed subtle diffuse sulcal effacement concerning for intracranial oedema. Echocardiogram (EEG) showed diffuse delta range slowing, suggestive of generalised cerebral dysfunction. He was extubated on day 8 of his hospital admission.

He was noted to be in persistent shock requiring high-dose norepinephrine. EEG revealed ejection fraction of 15%. A right heart catheterisation was performed that revealed severe biventricular failure and cardiogenic shock (cardiac output by Fick 3.4 L/min (normal 4–6 L/min), CI 1.4 (normal 2–4 L/min/m²), right ventricle 34/16, pulmonary artery 35/22 (mean 29) (normal 25/10 (15)), pulmonary capillary wedge pressure 23 mm Hg (normal 6–11 mm Hg)). Dobutamine was added to his inotropic regimen and diuresis was initiated.

OUTCOME AND FOLLOW-UP

He improved neurologically and was able to follow some commands although remained persistently weak due to critical illness myopathy. He remained on a gradual tapering regimen of methylprednisolone.

DISCUSSION

Current adult models of COVID-19 disease typically involve three clinical phases. First, there



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To cite: Selvaraj V, Finn A, Santos M, et al. *BMJ Case Rep* 2022;**15**:e249425. doi:10.1136/bcr-2022-249425

Table 1 Lab values on the day of presentation, peak values and post intervention

Labs	On presentation	Peak value	Post intervention
White blood cell count (3.5–11.0×10 ⁹ /L)	4.2	12.7	8.5
Platelets (150–400×10 ⁹ /L)	112 000	15 000	87 000
Aspartate aminotransferase (10–42 IU/L)	56	2008	209
Alanine aminotransferase (6–45 IU/L)	114	1399	942
Ferritin (22–322 NG/ML)	>16 500	>16 500	1707
C reactive protein (0–10 MG/L)	223.88	223.88	46.21
D dimer (0–230 NG/ML)	6692	12 574	3249
High-sensitive troponin (3–57 NG/L)	5298	11 295	1712
Creatine kinase (20–210 IU/L)	722	1337	174

is an initial viral response phase where patients mostly have mild constitutional symptoms, followed by a pulmonary phase where there is an overlap of host inflammatory response and viral replication effects. Lastly, there is a hyperinflammatory phase where the pathophysiology is driven by the host immune response. Such progression occurs within 1–2 weeks of SARS-CoV-2 infection.⁶ MIS-A may be a late sequela of the hyperinflammatory phase or a delayed inflammatory phase, driven by a dysregulated immune response or autoimmunity. Unlike MIS-A, COVID-19 hyperinflammatory syndrome (cHIS) does not have a defined clinical presentation and may exhibit a mix of features of severe COVID-19 disease, multi-inflammatory syndrome (MIS) and other known hyperinflammatory syndromes such as haemophagocytic lymphohistiocytosis, macrophage activation syndrome and cytokine release syndrome. Differentiation of severe COVID-19 infection and cHIS versus MIS remains a challenge.

The true incidence of MIS-A is not known. MIS-A is likely underdiagnosed due to overlapping symptoms with severe, acute biphasic COVID-19 disease and cHIS. cHIS is more difficult to define clinically and likely has a more heterogeneous presentation. Although both are similar in terms of fever, extremely elevated inflammatory markers and multiorgan dysfunction, they are clinically distinct syndromes. MIS-A likely has a more severe presentation, involving severe multiorgan failure, shock and cardiac involvement, additionally it typically occurs some time (1+ weeks) after the initial infection. The onset of cHIS is also heterogeneous: it may be concurrent with COVID-19 or take more of a delayed course. MIS-A and cHIS should be considered on a spectrum of hyperinflammation concurrent with or following after SARS-CoV-2 infection. [Table 2](#) details

differences between severe COVID-19/cHIS and MIS-A.^{7–11} Differential diagnoses should also include Kawasaki disease, hemophagocytic lymphohistiocytosis, toxic shock syndrome, macrophage activation syndrome and severe Kawasaki shock. It is critical to distinguish MIS-A from alternative diagnoses as the clinical management can differ significantly. A thorough history and physical examination, laboratory workup and high clinical suspicion can provide a degree of clinical certainty.

The exact pathophysiology is unclear. First, antibodies to SARS-CoV-2 might enhance antibody-dependent viral entry into cells and amplify viral replication. Second, there could be autoantibody or T-cell-mediated direct cell damage by attacking cells that express viral antigens or host antigens, which mimic viral antigens. Third, there can be activation of the host inflammatory response through immune complex formation. Immune complexes may also be responsible for vascular and coronary injury by activation of inflammatory responses through the Fc-γ receptor or complement activation, such as Kawasaki disease. Antibodies against SARS-CoV-2 are also associated with interleukin (IL)-16 and IL-18 activation, and activation of natural killer cell, lymphocytes and monocytes. Lastly, there may also be viral superantigen sequences that activate the host immune cells.^{12–14}

Currently, there are only preliminary definitions for MIS-A, some of which are similar to criteria used to diagnose MIS-C. Our patient met the CDC criteria for MIS-A (presence of fever, severe cardiac illness, encephalopathy, thrombocytopenia, hypotension, significantly elevated inflammatory markers and positive SARS-CoV-2 test by RT-PCR).¹⁵ There were no alternative diagnoses to explain his clinical presentation. An extensive workup revealed no other aetiologies. As per CDC criteria, MIS-A patients usually have minimal respiratory system involvement. Our patient was intubated for airway protection due to acute encephalopathy and was extubated after 8 days following treatment for aspiration pneumonia. Vogel *et al* described three categories of patients in his article on MIS-C/A. There may be SARS-CoV-2 naïve patients who are vaccinated against SARS-CoV-2 and then develop MIS-C/A; there may be patients with history of COVID-19, subsequently get vaccinated and then develop MIS-C/A; lastly, patients who have already been vaccinated may then become infected or reinfected with SARS-CoV-2 and then develop MIS-C/A.¹⁶ Our patient would fit under category three where he was already vaccinated; however, got infected with SARS-CoV-2 and developed MIS-A.

COVID-19 mRNA vaccines elicit an immune response to the spike protein, and these patients are expected to have anti-spike protein (anti-S) and anti-receptor binding domain (anti-RBD) antibodies but not antinucleocapsid antibodies. However, patients infected with COVID-19 have both antispikes and antinucleocapsid antibodies. This can be used to distinguish the

Table 2 Differences between severe COVID-19/cHIS and MIS-A

Differences	Severe COVID-19/cHIS	MIS-A
Age	Tend to be older patients	Tend to be younger patients
Comorbidities	Diabetes, hypertension, obesity	Usually healthy, minimal comorbidities
Timing after initial SARS-CoV-2 exposure	1–2 weeks	2–5 weeks
Severity of SARS-CoV-2 infection	Moderate to severe	Asymptomatic or mild
Common clinical presentation	Respiratory symptoms with thrombotic sequelae	Gastrointestinal, cardiologic, neurologic symptoms
Diagnosis	SARS-CoV-2 PCR tests	SARS-CoV-2 serologic assays, PCR tests
Management	Dexamethasone, remdesivir, tocilizumab, baricitinib	Intravenous immunoglobulin, corticosteroids, anakinra, tocilizumab
Mortality	Variable	Low

cHIS, COVID-19 hyperinflammatory syndrome; MIS-A, multisystem inflammatory syndrome in adult.

immune response to vaccination from that resulting from natural COVID-19 infection.¹⁷ Most MIS-A patients have positive anti-S IgG antibodies, and these levels are comparable to adult individuals that survived severe COVID-19, suggesting that MIS-A is associated with a strong immune response. MIS-A is also noted to have low or absent anti-S IgM, supporting the idea of a post-infectious phenomenon. Clinical response to immunomodulation with glucocorticoids, intravenous IG suggests that MIS-A is likely driven by postinfectious immune dysregulation rather than directly by the viral infection. In our patient, significantly elevated levels of anti-RBD IgG (>25 000, normal <50 AU/mL) and antinucleocapsid IgG (8.67, normal <1.40 index) antibodies and negative anti-S IgM levels were suggestive of a post-infectious immune dysregulation phenomenon. In addition, the dramatic response to the immunomodulation therapy supports an immune dysregulation pathology.

Treatment largely depends on guidelines adopted from treatment of MIS-C. It involves immunomodulation with intravenous IG, high-dose glucocorticoids, IL-1 or IL-6 antagonists either alone or in combination. Intravenous IG causes induction of regulatory T cells, which help control inflammation. The antibodies in intravenous IG might also compete with endogenous antibody and alter the immune complexes or may compete with the immune complex binding sites.¹⁸ Based on its mechanism of action, intravenous IG is considered a first-line therapy. The proposed starting dose of intravenous IG is 2 gm/kg daily. High-dose glucocorticoids are often used in conjunction with intravenous IG. Typical starting dose of methylprednisolone is 2 mg/kg/day. In patients who are refractory to these treatments or have contraindications to them, IL-1 and IL-6 antagonists can be used. Anakinra, a recombinant IL-1 receptor antagonist, is typically started at 4 mg/kg/day intravenous, with a gradual plan to taper the dose based on clinical improvement and resolution of inflammatory markers. Tocilizumab may also be alternatively used if there is a shortage of IL-1 antagonists; however, the risk of bacterial and fungal infection remains high.¹⁹

In conclusion, MIS-A and cHIS are rare but increasingly recognised, sequelae/complications of COVID-19 disease. Clinicians must have a high index of suspicion to diagnose these poorly understood conditions as initial SARS-CoV-2 PCR tests may be negative. Patients may need further serologic assays to establish prior infection with SARS-CoV-2. Early recognition of a hyperinflammatory state associated with COVID-19 (MIS-A, cHIS) is essential for timely initiation of appropriate therapy to reduce morbidity and mortality. Many questions remain regarding the immunopathogenesis and optimal management of the spectrum of hyperinflammation and delayed inflammatory

sequelae of COVID-19. Larger studies are needed to further elucidate risk factors and biomarkers to distinguish MIS-A from severe COVID-19/cHIS to help with prognostication and treatment decisions.

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Contributors VS was involved in obtaining consent and drafting the original document. AF revised the manuscript, did literature review and discussion. MS was involved in direct care of the patient, revised manuscript and edited tables and case presentation. KD-A supervised, reviewed and edited the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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Learning points

- Multisystem inflammatory syndrome in adult (MIS-A) may be a late sequela of the hyperinflammatory phase or a delayed inflammatory phase, driven by a dysregulated immune response or autoantibodies.
- Treatment of MIS-A involves immunomodulation with intravenous immunoglobulin, high-dose glucocorticoids, interleukin (IL)-1 or IL-6 antagonists either alone or in combination.
- Severe COVID-19, COVID-19 hyperinflammatory syndrome and MIS-A exist along a spectrum of inflammation with sometimes overlapping features and timelines.

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