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A case of multisystem inflammatory syndrome in adults following natural infection and subsequent immunization

Anthony Lieu^{a,*}, Jordan Mah^b, Deirdre Church^{a,b}

^a Division of Infectious Diseases, Department of Medicine, Cummings School of Medicine, University of Calgary, Calgary, Alberta, Canada

^b Division of Microbiology, Department of Pathology, Cummings School of Medicine, University of Calgary, Calgary, Alberta, Canada

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ABSTRACT

Multisystem inflammatory syndrome in adults is a rare and life-threatening complication that follows natural COVID-19 infection and primarily affects young unvaccinated adults. This complication is seldom described following vaccination, which would have important implications for the vaccination timing and platform in this population. COVID-19 vaccines are extremely effective; however, the risk of rare adverse events needs to be balanced with the vaccination benefits.

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Case Presentation

A 21-year-old woman presented to the emergency department (ED) with a 2-day history of chest pain, dyspnea, and leg edema. She had previously received positive test results for the SARS-CoV-2 alpha variant through nasopharyngeal (NP) polymerase chain reaction (PCR) testing 6 weeks before this acute illness. She was asymptomatic at the time of testing, with the test performed in the context of workplace exposure. Notably, 27 days after she tested positive, she received her first dose of the messenger RNA (mRNA) vaccine (Moderna) without immediate adverse reactions. Ten days after her vaccination, she experienced an acute-onset frontal headache associated with nausea, vomiting, and diarrhea. Over the next 7 days, she developed a rash with fever and therefore sought medical attention from her general practitioner who diagnosed her with an allergic reaction. Her symptoms were later associated with progressive shortness of breath and chest pain, leading to her ED presentation (Figure 1).

She was a previously healthy, life-long nonsmoker and her ethnicity was Haitian. On examination, her temperature was 38.0 °C with a blood pressure of 80/50 mm Hg, heart rate of 120

beats/min, respiratory rate of 28 breaths/min, and normal oxygen saturation on ambient air. Physical examination revealed a convalescent, pink maculopapular rash involving the trunk and extremities, mild erythema of the tongue, and moderate bilateral leg edema.

Her initial laboratory results revealed leukocytosis, elevated inflammatory markers, and cardiac troponins. IgG serological test for antibodies directed toward the SARS-CoV-2 nucleocapsid protein was positive. A chest x-ray was unremarkable, and a transthoracic echocardiogram (TTE) showed early signs of pericarditis, including reduced left ventricular ejection function (LVEF) with global hypokinesis and trace pericardial effusion. Respiratory pathogen panel testing and SARS-CoV-2 PCR performed from the NP swab were negative, including for enterovirus and adenovirus.

Given her clinical picture of shock, she received fluid resuscitation, broad-spectrum antibiotics, and was admitted to the intensive care unit (ICU) to initiate inotropes. She fulfilled the Centers for Disease Control and Prevention (CDC) case definition of multisystem inflammatory syndrome in adults (MIS-A). The patient was started on a 5-day course of intravenous glucocorticoids with a taper, intravenous immunoglobulins, and aspirin (Figure 1). Cardiogenic shock ensued over the next 48 hours despite inotropic support, and the patient required intubation because of hypoxic respiratory failure. The patient had a precipitous decline in cardiac function, as documented on serial TTEs, with her nadir LVEF

* Corresponding author: Anthony Lieu, Division of Infectious Diseases, Department of Medicine, University of Calgary, 1403 – 29th Street NW, Calgary, Alberta, T2N 2T8. Telephone: (403) 944-2325; fax: (403) 944-3364.

E-mail address: anthony.lieu@albertahealthservices.ca (A. Lieu).

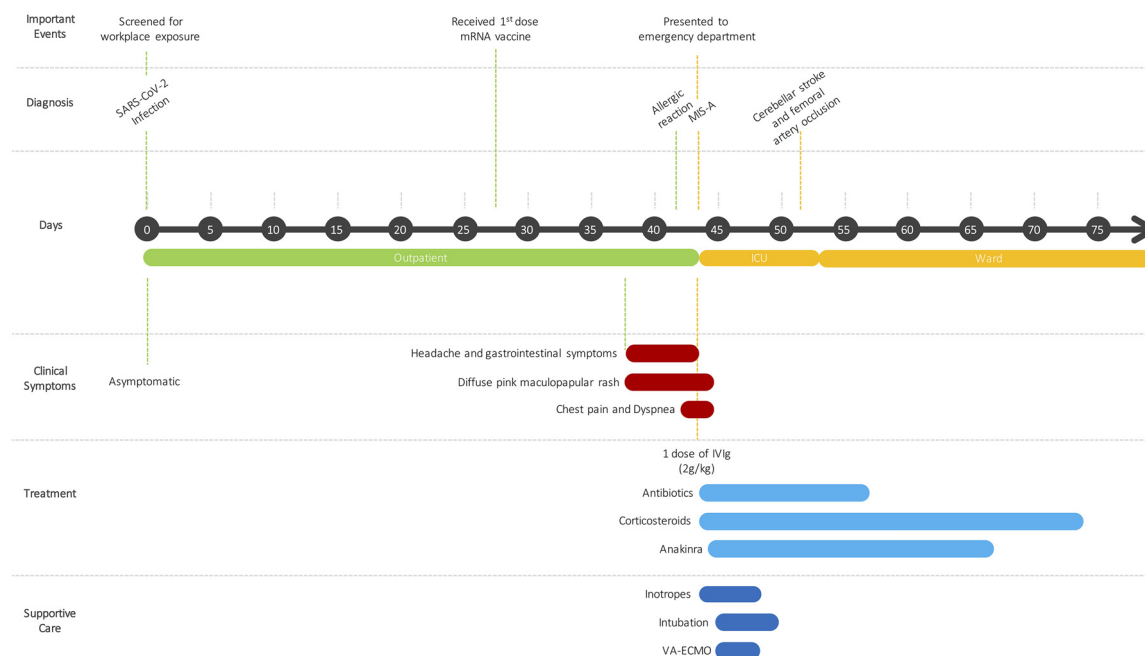


Figure 1. Timeline of clinical presentation and medical interventions.

Table 1
Longitudinal laboratory results.

Laboratory test	Day(s) since admission							Reference range
	0 IVIG Steroids	1	2 Anakinra	3	4	6	10	
Hemoglobin (g/L)	119	89	71	79	103	98	79	120–160
Leucocytes ($10^9/L$)	17.7	21.2	17.6	21.5	16.6	16.2	19.0	4.0–11.0
Neutrophils ($10^9/L$)	15.7	19.2	15.5	18.4	15.7	14.5	16.7	2.0–9.0
Lymphocytes ($10^9/L$)	0.8	0.2	0.3	1.6	0.2	0.6	1.5	0.5–3.3
Platelet count ($10^9/L$)	186	202	251	270	144	130	388	150–400
C-reactive protein (mg/L)	315.0	292.5	281.1	213.1	154.0	85.6		0.0–8.0
Ferritin (ug/L)	668		1342	1042		880		20–300
ALT (U/L)	74	51	102	188				<39
Alkaline phosphatase (U/L)	59	44	63	42				40–120
Total bilirubin ($\mu\text{mol/L}$)	17	22	14	10				20–300
Creatinine ($\mu\text{mol/L}$)	89	73	75	82	55	151	48	40–100
Troponin (ng/L)	808	1306	689	679				0–13
NT-proBNP (ng/L)	1641		27699					<300
CK (U/L)	363	554	182	1864	20859	17525		30–200

Abnormal results with trends over the first 10-days of ICU hospitalization are highlighted in gray.

ALT, alanine transaminase; CK, creatine kinase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

falling to 5%. On multidisciplinary discussion with various subspecialties, Anakinra, an interleukin-1 inhibitor, was initiated for the cytokine storm and MIS-A. In spite of these therapies, the patient had persistent hypoxic failure and vasoplegia, which required venous-arterial extracorporeal membrane oxygenation (VA-ECMO). Her clinical status improved over the next few days, and repeated echocardiograms demonstrated LVEF recovery and improvement in inflammatory markers (Tables 1 and 2). She was weaned off vasopressors, inotropes, VA-ECMO, and extubated. Her ICU stay was complicated by a cerebellar stroke, right common femoral artery thrombus, and critical illness polyneuropathy.

Discussion

MIS-A is a rare and potentially life-threatening complication of a natural infection of COVID-19, commonly requiring acute care and often intensive care with hemodynamic support. Despite many case reports and case series, the true incidence is not known (Morris et al, 2020). However, there have only been a handful of case reports describing this severe complication fol-

lowing SARS-CoV-2 immunization, all of which occurred following a previous exposure to COVID-19 or a positive serological test for SARS-CoV-2 nucleocapsid IgG antibodies (Salzman et al, 2021; Uwaydah et al, 2021). Common features of these patients include their young age (18–44 years), previous mild or asymptomatic COVID-19 infection, and the type of vaccine received (mRNA) (Salzman et al, 2021). Younger age and mRNA vaccine platforms are associated with immunogenicity and a potentially higher risk of inducing MIS-A after natural infection (Salzman et al, 2021). However, given the scarcity of MIS-A cases following vaccination, little is understood about this entity, and suspected cases should be reported to the CDC.

It is well described that after natural COVID-19 infections in individuals, vaccination elicits a more robust immune response than in those not previously exposed and is often associated with systemic symptoms, including fever (Krammer et al, 2021). We associate this potent immune response with the generation of better immunity; however, this can also theoretically lead to hyperinflammation and a dysregulated immune system that can paradoxically cause harm to the host. Of the 2 mRNA vaccines, Moderna

Table 2

Rapid cardiac deterioration and recovery of myocarditis/pericarditis on serial TTE.

Day(s) since admission	Ejection fraction	Valvulopathy	Others
0	Left ventricular (LV [7]): 45%–50% Preserved right ventricular (RV [20]) function	Mild to moderate tricuspid regurgitation (TR)	Trace pericardial effusion, lateral wall and apex are hypokinetic
1	LV: 30%–35% RV function significantly impaired	Severe TR	Small pericardial effusion, LV dysfunction of a cardiomyopathic pattern
2	LV: 25–30% RV function moderate to severely reduced	Severe TR	Stable pericardial effusion, global hypokinesis LV
3	LV: <5% RV: severely reduced	Moderate TR	Small pericardial effusion, severe global hypokinesis LV
4	LV: 5%–10% RV: severely reduced	Moderate TR	Small pericardial effusion
6	LV: 15–25% RV: mildly reduced	Mild TR/MR	Moderate pericardial effusion
10	LV: EF 45%–50% RV: normal in size and function	Normal valve	Small posterior pericardial effusions

has been reported to be more immunogenic, which is the vaccine that our patient had received (Steensels et al, 2021). The vaccine may have triggered an already primed immune system, causing a cytokine storm that led to a rapidly progressing, severe cardiac illness in an otherwise healthy young adult. This may raise questions about the optimal timing of vaccination following natural infection among young adults. It is important to note that all cases of MIS-A that occurred after vaccination were described after natural infection with COVID-19, and it is impossible to determine the causality based on these reports.

The CDC and many health care jurisdictions suggest that vaccination following SARS-CoV-2 infection should occur after clinical recovery of the patient and completion of the isolation period (CDC, 2021; Alberta Health Services, 2021). However, for patients diagnosed with MIS-A/C, the CDC recommends delaying vaccination by 90 days after diagnosis and clinical recovery but excludes patients who developed MIS-A/C following vaccination (CDC, 2021). There is general agreement that individuals who have been infected previously with SARS-CoV-2 should be vaccinated. However, there is little guidance on which vaccine is appropriate and how many doses are required. Several studies have shown that most recovered COVID-19 patients develop antibodies against SARS-CoV-2, lasting at least 4 to 8 months (Dan et al, 2021). This raises questions about the optimal timing of vaccination following SARS-CoV-2 infection, particularly in young and healthy adults. Until further studies have been conducted, we propose that a delay in immunization by 90 days following natural infection should be considered, given the rare but potentially severe risk of exacerbating MIS-A if the vaccine is given too prematurely.

There is evidence to suggest that there are long-lasting neutralizing antibody responses that may last up to 8 to 12 months in individuals who previously had a severe COVID-19 infection (Lau et al, 2021; Sherina et al, 2021). Our case may represent an exceptionally rare circumstance in which vaccination potentially could have been deferred by 90 days after previous infection. Because COVID-19 vaccines have been demonstrated to be extremely effective in preventing infection, the risk for rare adverse events following immunization needs to be balanced with the benefits of vaccination.

We report a case of MIS-A that followed natural COVID-19 infection and subsequent SARS-CoV-2 mRNA immunization, which was associated with high morbidity. Clinician reporting of MIS-A following vaccination is crucial in monitoring this potentially rare and unrecognized adverse event. Only a handful of case reports have, so far, described severe progressive MIS-A following vaccination, all of which have followed natural infection, and the optimal timing of COVID-19 immunization in this young population remains to be elucidated.

Author Contributions

A.L. and J.M. contributed equally to the conception and writing of the manuscript. D.C. contributed to the editing and revision of the manuscript.

Conflict of Interest

The authors have no conflict of interest to declare.

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Ethics Approval Statement

We obtained direct consent from the patient for publication of this case report. No ethics approval was sought for the writing of this manuscript.

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References

- Alberta Health Services. COVID-19 Vaccine Frequently Asked Questions 2021. COVID-19 Vaccine 2021 <https://www.albertahealthservices.ca/topics/Page17389.aspx>. November 2021 (accessed 2 December 2021).
- Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html/>, November 2021 (accessed 2 December 2021)
- Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, Grifoni A, Ramirez SI, Haupt S, Frazier A, Nakao C, Rayaprolu V, Rawlings SA, Peters B, Krammer F, Simon V, Saphire EO, Smith DM, Weiskopf D, Sette A, Crotty S. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science*. 2021;371(6529):eabf4063 Epub 2021 Jan 4066 4010.1126/science.abf4063.
- Krammer F, Srivastava K, Alshammary H, Amoako AA, Awawda MH, Beach KF, Bermúdez-González MC, Bielak DA, Carreño JM, Chernet RL, Eaker LQ, Ferreri ED, Floda DL, Gleason CR, Hamburger JZ, Jiang K, Kleiner G, Jurczyszak D, Matthews JC, Mendez WA, Nabeel I, Mulder LCF, Raskin AJ, Russo KT, Salimban-gon AT, Saksena M, Shin AS, Singh G, Sominsky LA, Stadlbauer D, Wajnberg A, Simon V. Antibody Responses in Seropositive Persons after a Single Dose of SARS-CoV-2 mRNA Vaccine. *N Engl J Med*. 2021;384(14):1372–4 Epub 2102021 Mar 2101610, 1310.1056/NEJMc2101667.
- Lau EHY, Tsang OTY, Hui DSC, Kwan MYW, Chan WH, Chiu SS, Ko RLW, Chan KH, Cheng SMS, Perera R, Cowling BJ, Poon LLM, Peiris M. Neutralizing antibody titres in SARS-CoV-2 infections. *Nat Commun*. 2021;12(1):63. doi:10.1038/s41467-41020-20247-41464.

- Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, Lee EH, Paneth-Polak R, Geevarughese A, Lash MK, Dorsinville MS, Ballen V, Eiras DP, Newton-Cheh C, Smith E, Robinson S, Stogsdill P, Lim S, Fox SE, Richardson G, Hand J, Oliver NT, Kofman A, Bryant B, Ende Z, Datta D, Belay E, Godfred-Cato S. Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection - United Kingdom and United States, March-August 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(40):1450–6 1410.15585/mmwr.mm16940e15581.
- Salzman MB, Huang CW, O'Brien CM, Castillo RD. Multisystem Inflammatory Syndrome after SARS-CoV-2 Infection and COVID-19 Vaccination. *Emerg Infect Dis.* 2021;27(7):1944–8 Epub 212021 May 210525 1910.3201/eid2707.210594.
- Sherina N, Piralla A, Du L, Wan H, Kumagai-Braesch M, Andréll J, Braesch-Andersen S, Cassaniti I, Percivalle E, Sarasini A, Bergami F, Di Martino R, Colaneri M, Vecchia M, Sambo M, Zuccaro V, Bruno R, Sachs M, Oggionni T, Meloni F, Abolhassani H, Bertoglio F, Schubert M, Byrne-Steele M, Han J, Hust M, Xue Y, Hammarström L, Baldanti F, Marcotte H, Pan-Hammarström Q. Persistence of SARS-CoV-2-specific B and T cell responses in convalescent COVID-19 patients 6-8 months after the infection. *Med (N Y).* 2021;2(3):281–95 e284Epub 2021 Feb 1010 210.1016/j.medj.2021.1002.1001.
- Steensels D, Pierlet N, Penders J, Mesotten D, Heylen L. Comparison of SARS-CoV-2 Antibody Response Following Vaccination With BNT162b2 and mRNA-1273. *JAMA.* 2021;326(15):1533–5 1510.1001/jama.2021.15125.
- Uwaydah AK, Hassan NMM, Abu Ghoush MS, Shahin KMM. Adult multisystem inflammatory syndrome in a patient who recovered from COVID-19 postvaccination. *BMJ Case Rep.* 2021;14(4) 242010.241136/bcr-242021-242060.