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Multisystem Inflammatory Syndrome in Adults (MIS-A) After COVID-19 Infection and Recent Vaccination with Recombinant Adenoviral Vector Encoding the Spike Protein Antigen of SARS-CoV-2 (ChAdOx1 nCoV-19, Vaxzevria)

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Abstract

The clinical spectrum of Coronavirus 2019 (COVID-19) includes acute COVID-19, long covid and multisystem inflammatory syndrome in children and adults (MISC/A). The rapid roll-out of COVID-19 vaccination has the potential to affect the clinical presentation of COVID-19 and case reports document rare occurrences of MIS-A after COVID-19 infection and recent vaccination with m-RNA vaccines. We describe 2 cases of MIS-A after COVID-19 infection and recent vaccination with ChAdOx1 nCoV-19.

Keywords

adverse events, coronavirus 2019, multisystem inflammatory syndrome in adults, COVID-19 vaccine

Background

Coronavirus 2019 (COVID-19) disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 in Wuhan, China.[1] The clinical presentation of acute COVID-19 varies from asymptomatic to pneumonia with acute respiratory distress syndrome (ARDS) and death.[2] Severe COVID-19 occurs in approximately 15% persons infected with SARS-CoV-2 but reports from South Africa suggest that a more recent variant of concern, Omicron, may be less virulent.[3] Persistent symptoms or "long covid" have been reported after SARS-CoV-2 infection including among persons with mild acute COVID-19. Long covid can involve multiple organ systems with[4] varying combinations of symptoms such as chronic cough, shortness of breath, fatigue, cognitive impairment or brain fog, myalgias, palpitations and dizziness.[4–6] Older persons, women, as well as persons with pre-existing conditions, high body mass index, lower socioeconomic status, HIV infection or severe acute COVID-19 have increase risk of long COVID.[7]

Mild disease with lower mortality is characteristic of the pediatric population but cases of multisystem inflammatory syndrome in children (MIS-C) similar to Kawasaki Disease are reported.[8] This rare syndrome is also described in adults (MIS-A) and is characterized by a post-infectious hyperinflammatory disorder with multi-organ failure occurring 2 to 6 weeks after COVID-19 infection.[9,10]

PCR testing is the gold standard for diagnosis of acute COVID-19 but the roll-out of rapid antigen test kits, albeit with a lower sensitivity than PCR, has improved the diagnostic capacity of countries overwhelmed by surges. Antibody testing is considered to have limited use in diagnosis of acute COVID-19 as IGg and IgM antibodies begin to increase after

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the first week of symptom onset.[11] However, serological tests are often needed for diagnosis of MIS C/A.[12]

Novel therapeutics and vaccination against SARS-CoV-2 infection have reduced COVID-19 related mortality. However, the pathogenesis, clinical spectrum and the associated immunological response to SARS-CoV-2 infection are still not completely understood. While the effectiveness and safety of COVID-19 vaccines are well documented in population-based studies including among pregnant women and other vulnerable populations, severe adverse effects have been reported.[13] One such concern is the occurrence of MIS-A after COVID 19 infection and recent COVID-19 vaccination with mRNA vaccines (BNT162b2 or Pfizer BiOnTech and Moderna). We describe 2 cases of MIS-A after COVID-19 infection and recent vaccination with recombinant adenoviral vector encoding the spike protein antigen of SARS-CoV-2 (ChAdOx1 nCov-19, Vaxzevria).

Case Reports

Patient 1 is a 22 year-old previously healthy Afro-Caribbean male who was vaccinated with the recombinant adenoviral vector encoding the spike protein antigen of SARS-CoV-2 (ChAdOx1 nCov-19, Vaxzevria) on March 10, 2021 and May 5, 2021. He complained of headache and malaise a day prior to presentation on May 28, 2021 at a local medical facility. He presented with seizure like activity followed by loss of consciousness. On presentation, he was pulseless and cardiopulmonary resuscitation (CPR) was commenced. Three automated external defibrillator (AED) shocks were delivered with return of spontaneous circulation and he was transported to the hospital for further management.

On arrival the patient was tachycardic, tachypnoeic and hypotensive with hypoxia on oxygen 10L/minute (SpO_2 79%). Glasgow Coma Scale (GCS) was 3/15. He was intubated and inotropic support was commenced. During his ICU admission he experienced recurrent pulmonary haemorrhage with clots and malignant ventricular arrhythmias.

Laboratory studies revealed elevated inflammatory biomarkers (Table 1). SARS-CoV-2 PCR was negative. SARS-CoV-2 IgG antibody was positive. ECG on admission showed peak T waves and chest x-ray showed cephalization with patchy infiltrates in left lower and right upper zones. CT Brain revealed global cerebral oedema with no acute intracranial event. Echocardiogram was normal. He responded well to therapy with methylprednisolone.

Patient 2 is a 42 year-old Afro-Caribbean male with no chronic illnesses or prior history of COVID-19 infection. He was vaccinated with ChAdOx1 nCov-19 on March 13, 2021 and May 8, 2021. Three (3) weeks after receiving the second dose of the vaccine he developed a sore throat followed by fever. Two (2) days later he experienced dyspepsia with epigastric fullness, vomiting, and increasing chest tightness. Four (4) days after symptom onset he presented to hospital and experienced worsening dyspnea during admission.

Cardiac enzymes were elevated (Troponin I 13041.4pg/mL (0 −34.2), CK 538 and 896 (39-308), CKMB 68.[7–25] SARS-COV2 PCR done May 31, 2021 and June 3, 2021 were negative. SARS COV2 IgG antibody was positive and SARS COV2 IgM antibody negative.

ECG and echocardiogram suggested myocardial ischemia. Echocardiogram revealed mild septal hypokinesia, no valvulopathy, no evidence of pulmonary hypertension and a left ventricle ejection fraction (LVEF) of 47%. Coronary occlusion was not detected on coronary angiogram. CT pulmonary angiogram (CTPA) showed a small pleural effusion and basal pulmonary oedema but no evidence of pulmonary embolism. He was treated with intravenous furosemide and oxygen (O_2) therapy at 15L /min which gave relief of symptoms initially. He subsequently experienced worsening tachypnea, tachyarrhythmias and worsening hypoxia. He was assessed as having severe myopericarditis likely due to viral origin, with multi-organ dysfunction and transferred to ICU for further management.

On admission to ICU treatment was started with methylprednisolone. Non-invasive ventilation alternating with high flow nasal cannula (HFNC) oxygen therapy was used. He experienced bradyarrhythmias and hypotension. He was intubated and received dual inotropic support. Intra-aortic balloon pump (IABP) was placed. He was transferred to a facility in the United States of America where he continued to receive supportive care for multi-organ failure. He was discharged from hospital 3 months after his transfer.

Discussion

The clinical spectrum of COVID-19 disease is not completely understood and includes acute COVID-19, MIS- A/C and long covid. Atypical presentations have been described including extrapulmonary manifestations without respiratory symptoms and thromobolembolism.[14] Case reports of MIS-A after SARS-CoV2 infection and COVID-19 vaccination with mRNA and inactivated SARS-CoV-2 vaccine (Sinopharm) vaccines have been published.[15,16,17]

We describe 2 cases of COVID-19 which met the criteria for MIS-A based on the World Health Organization and Brighton criteria[12,18] after COVID-19 infection and recent vaccination with ChAdOx1 nCov-19. Hypotension and shock were prominent features of presentation and led to pulmonary edema, respiratory distress and hypoxia. PCR tests were negative despite clinical presentations which resembled severe COVID-19 infection but positive IgG antibody tests suggests that the persons had prior COVID-19 infection despite having no prior history of acute COVID-19 infection.

Differential Diagnoses

Other common causes of cardiogenic shock were considered and ruled out including myocardial infarction and septic shock. CT angiogram on initial presentation showed no evidence of thromboembolism. Viral panels ruled out severe dengue. Myocarditis is reported in acute COVID-19 and up to 1 year after diagnosis.[19] Acute covid-19 is less likely in view of the negative IgM antibodies. Complications of long COVID in both patients cannot be ruled out but acute multi-organ failure due to long COVID is

Table 1. Characteristics of patients with MIS-A after recent COVID-19 infection and SARS-CoV-2 vaccination, Jamaica

	Patient 1	Patient 2
Age/Sex	22/M	42/M
Underlying medical conditions	No	No
Clinical signs and symptoms	Headache, malaise, seizure like activity, syncope	Sore throat, fever, dyspepsia, vomiting and chest tightness
Previous respiratory illness/COVID-19	No/Unknown	No
COVID-19 Vaccination	Yes	Yes
Imaging Studies	ECG: peak T waves; chest radiograph: cephalization with patchy infiltrates in left lower zone and right upper zone; CT Brain: global cerebral oedema with no acute intracranial event: Echocardiogram: normal	Echocardiogram: mild septal hypokinesia, no valvulopathy, EF 47%; Coronary angiogram: no occlusion; CTPA: small pleural effusion and basal pulmonary oedema, no evidence of pulmonary embolism.
Initial Lab results (reference range)		
Hemoglobin, g/dL (13.5-18.0)	16.3	12.1
Neutrophils (1.63-6.96)	17.25	17.98
Lymphocytes (1.09-2.99)	0.6	1.19
Eosinophils (0.03-0.440)	0.013	0.004
Platelet × 10e9/L (150 -450)	170	139
INR	1.29	1.38
Sodium mmol/L (135-145)	140	136
Potassium mmol/L (3.5 -5.0)	4.1	4.7
Chloride mmol/L (95-105)	105	100
Bicarbonate mmol/L (20-28)	20	11
Urea mmol/L (2.5-6.7)	4.6	13.6
Creatinine umol/L (9-124)	184	257
Magnesium mmol/L (0.64-1.06)	0.54	0.96
Calcium mmol/L (2.25-2.75)	2.12	2.1
Phosphorous mmol/L (0.8 -1.4)	0.6	2.7
Alkaline Phosphatase, U/L (15-105)	57	42
GGT, U/L (10 -70)	124	138
ALT, U/L (6-21)	n/a	2917
AST, U/L (7 -32)	143	560
Creatinine Kinase, U/L (40-240)	705	896
LDH, U/L (105 -200)	331	1400
D dimer, ng/mL (<500)	15171	3158
Interleukin 6 ng/mL (0.000-7.000)	67.5	48.6
Procalcitonin, ng/mL (0.000-0.046)	7.13	2.26
C- reactive protein, mg/dL (<1.0)	n/a	7.73
hsCRP, ng/mL (0.000-5.000)	171	102
High sensitive troponin ng/L (0.000-14.000)	n/a	5140
SARS-C0V-2 PCR	Not detected	Not detected
SARS-C0V-2 IGg	Positive	Positive
SARS-C0V-2 IGM	Negative	Negative
Hepatitis B surface antigen	n/a	Negative
Blood cultures	Negative	Negative
Anti HCV antibody	n/a	Negative
Treatment	Methylprednisone	Methylprednisone, IV furosemide
Outcome	Discharged	Transferred

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; EF, ejection fraction; ECG, electrocardiogram; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase; LV, left ventricle; MR, mitral regurgitation; n/a, not available or not applicable; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

not described. Myocarditis after ChAdOx1 nCov-19 has been reported but is rare and usually mild.[20] However, further research is needed to understand the clinical presentation, pathophysiology and diagnosis of MIS-A, subacute COVID and long COVID.

In low resource settings, the use of serological tests is limited to community surveillance (serosurveys), research and diagnosis of MIS-A/C. Clinicians should be aware of the importance of serological tests in identifying the clinical spectrum of COVID-19 including atypical presentations and distinguishing between severe acute COVID-19, long covid and MIS-A. Case reports and studies confirm that MIS-A has a heteregenous clinical presentation which often overlaps with severe COVID-19.[9] These case presentations reinforce the relevance of SARS-CoV-2 antibody tests for diagnosis of COVID-19

related disease when PCR is negative in patients with suspected acute COVID-19. Zhao et al also found that PCR combined with antibody tests improved timely diagnosis of COVID-19, particularly severe COVID-19 disease.[21] Underutilization of antibody tests may result in missed diagnoses of MIS-A and concomitant poor outcomes since this severe secondary inflammatory syndrome may improve or resolve after treatment with corticosteroids.[22]

The role of COVID-19 vaccination in the presentation of these cases is not clear and may be coincidental but should be explored further. As of January 6, 2022, 9.33 billion doses of COVID-19 vaccines have been administered worldwide with high effectiveness against hospitalization and deaths for variants of concern that have emerged (Ritchie et al, 2020; WHO, 2021). Adverse effects such as Thrombosis with Thrombocytopenia Syndrome (TTS) and myocarditis have emerged with the rapid roll-out of COVID-19 vaccines but these are rare.[26,27] Concerns have been raised that COVID-19 vaccination might trigger/potentiate MISC A/C due to immunopathy or result in atypical presentations.[16] These concerns have implications for the dosage and optimal timing of vaccination after COVID-19 infection. Additionally, the impact of vaccinations and therapeutics on the natural history and clinical spectrum of COVID-19 disease needs further evaluation and should be considered in clinical management.

Conclusion

Serological evidence of current or past COVID-19 infection should be sought in persons presenting with illness resembling severe COVID-19 or MIS-A when PCR test is negative. Further studies are needed to determine if vaccination may affect the natural history or clinical presentation of COVID-19.

Declaration of Conflicting Interests

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Appendix

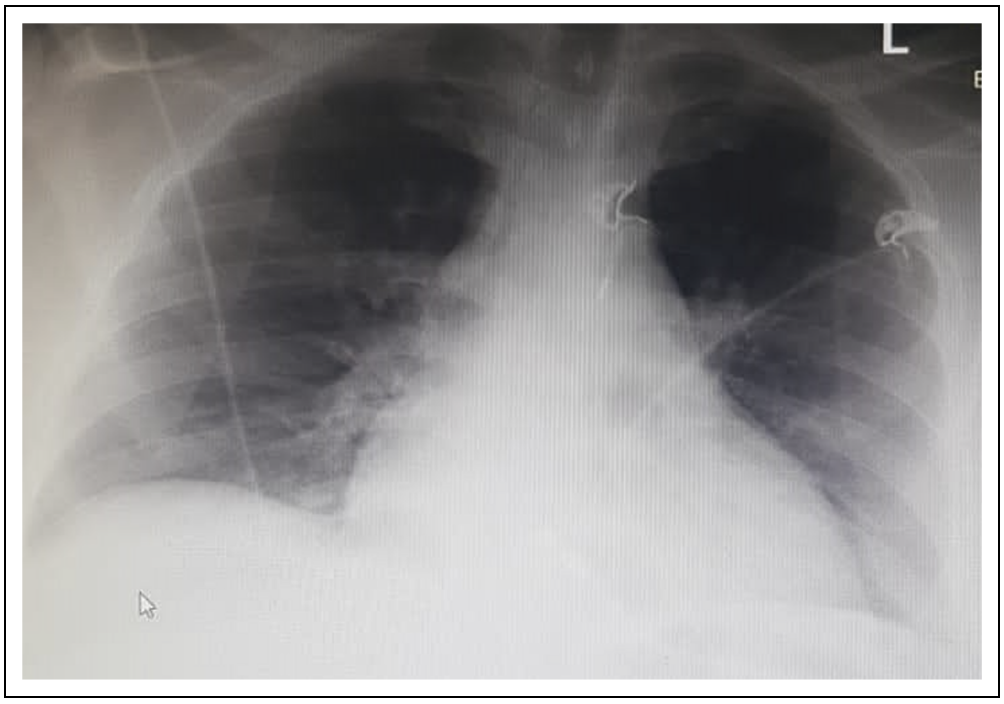

Figure 1. Chest X-ray of Patient 2 showing cardiomegaly.

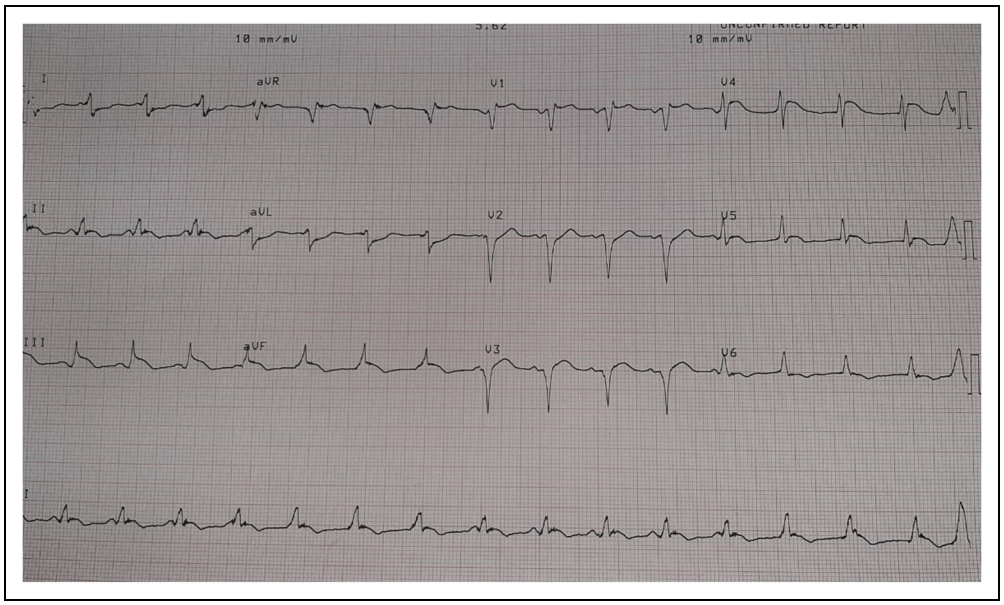

Figure 2. ECG of Patient 2 suggesting possible pericarditis or myocardial infarction (anterior/inferior wall).