

## Lessons from practice

## Recent SARS-CoV-2 infection: too early to vaccinate?

## Clinical record

**W**e present two complex cases with unfortunate sequelae following early vaccination after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in New South Wales, at a time when the Delta variant was dominant and new infections were rising towards a peak of 1603 per day.

## Patient 1

A 35-year-old South Asian man with mild asthma had SARS-CoV-2 infection in August 2021. He was managed in the community and de-isolated on day 16 following a negative polymerase chain reaction (PCR) test result. He received vaccination (Comirnaty [Pfizer]) on day 35 after infection. He presented to the emergency department on day 6 after vaccination (day 41 after infection) with lethargy, chills and myalgia. Repeat SARS-CoV-2 PCR test results were negative. He had elevated inflammatory markers, but troponin, bedside electrocardiography and echocardiography results were normal. He was discharged home with advice to re-present if symptoms worsened.

He re-presented on day 7 after vaccination (day 42 after infection) and was admitted with progressive symptoms, plus profuse vomiting, diarrhoea and urticaria. Laboratory testing showed rising creatinine and inflammatory markers (C-reactive protein level, 235 mg/L; reference interval [RI], <5 mg/L), mild mixed liver function derangement (alkaline phosphatase, 98 U/L [RI, 30–100 U/L];  $\gamma$ -glutamyltransferase, 79 U/L [RI, 5–50 U/L]); alanine aminotransferase, 114 U/L [RI, 10–50 U/L]; aspartate aminotransferase, 105 U/L [RI, 10–35 U/L]), anaemia (haemoglobin level, 115 g/L; RI, 130–180 g/L), thrombocytopenia (platelet count,  $111 \times 10^9$ /L; RI, 150–400  $\times 10^9$ /L), neutrophilia (neutrophil count,  $11.1 \times 10^9$ /L; RI, 2–8  $\times 10^9$ /L), and lymphopenia (lymphocyte count,  $0.1 \times 10^9$ /L; RI, 1–4  $\times 10^9$ /L). Troponin levels were normal. Radiology showed right lower lobe infiltrate, right hilar lymphadenopathy and gallbladder wall thickening. Microbiological investigations were negative for SARS-CoV-2 (PCR) and respiratory viruses (multiplex PCR), and parvovirus B19, adenovirus and human herpesvirus 6 DNA were undetectable on nasopharyngeal aspirate.

The patient had persistent tachycardia, tachypnoea, hypotension, fevers, profuse diarrhoea and worsening rash, and was transferred to the intensive care unit (ICU) on day 9 after vaccination (day 44 after infection) for management of hypotension with vasopressors. Transthoracic echocardiography (TTE) showed mild left ventricular dilatation and a left ventricular ejection fraction of 40%. His troponin level was 1474 ng/L (RI, <14 ng/L) and B-type natriuretic peptide level

was 5600 ng/L (RI, <100 ng/L). Dobutamine and noradrenaline were commenced to treat cardiogenic shock. He was transferred to a tertiary ICU. Owing to increasing noradrenaline requirement on day 11 after vaccination (day 46 after infection), vasopressin was commenced. Dobutamine was changed to milrinone and ivabradine added to manage severe sinus tachycardia. Repeat TTE showed severe left ventricular and mild right ventricular hypokinesia and a left ventricular ejection fraction of 25%. There was progressive deterioration in his anaemia (haemoglobin level, 87 g/L), thrombocytopenia (platelet count,  $65 \times 10^9$ /L), lymphopenia (lymphocyte count,  $0.1 \times 10^9$ /L) and liver function (alkaline phosphatase, 157 U/L;  $\gamma$ -glutamyltransferase, 111 U/L; alanine aminotransferase, 195 U/L; aspartate aminotransferase, 246 U/L). With allergist/immunologist input, intravenous methylprednisolone was initiated with continuation of hydrocortisone 1 mg/kg four times daily. Over the next 24 hours, he developed atrial fibrillation, progressive pulmonary oedema and respiratory failure, and was electrically cardioverted to sinus rhythm and intubated. TTE on day 12 after vaccination (day 47 after infection) showed severe global biventricular hypokinesia and a left ventricular ejection fraction of 15%. His shock progressed and treatment was escalated to maximal doses of adrenaline, noradrenaline and vasopressin, and maximal ventilatory support, followed by commencement of venoarterial extracorporeal membrane oxygenation. Anakinra 100 mg subcutaneously was administered. Within a few hours, respiratory and haemodynamic parameters improved, and considerably less vasopressor support was required. He was transferred to a cardiac transplant centre. With no additional interventions, his cardiac function continued to improve and venoarterial extracorporeal membrane oxygenation was discontinued on day 18 after vaccination (day 53 after infection). Repeat TTE on day 19 after vaccination (day 54 after infection) showed normal ventricular size and function. He was extubated. All laboratory test results were normal on follow-up at 3 months.

## Patient 2

A 24-year-old man of Asian–African ancestry, with obesity but otherwise healthy, had SARS-CoV-2 infection in September 2021 requiring a 3-day hospital admission. He was de-isolated on day 17 after a negative PCR test result. He received vaccination (Comirnaty [Pfizer]) on day 34 after infection. He developed fever, abdominal pain and profuse vomiting and diarrhoea 8 hours after vaccination, and presented to the emergency department 3 days later with refractory symptoms (day 37 after infection). Laboratory testing showed elevated inflammatory markers (C-reactive protein

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**Brighton Collaboration criteria for multisystem inflammatory syndrome in children and adults (MIS-C/A): Level 1 of Diagnostic Certainty – Definitive Case<sup>2</sup>**

Criteria	Patient 1	Patient 2
Age < 21 years (MIS-C) or ≥ 21 years (MIS-A) AND	• ≥ 21 years	• ≥ 21 years
Fever ≥ 3 consecutive days AND	• Fever ≥ 3 consecutive days	• Fever ≥ 3 consecutive days
Two or more of the following clinical features: <ul style="list-style-type: none"> <li>• mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral non-exudative conjunctivitis, erythema/oedema of the hands and feet)</li> <li>• gastrointestinal (abdominal pain, vomiting, diarrhoea)</li> <li>• shock/hypotension</li> <li>• neurological (altered mental status, headache, weakness, paraesthesia, lethargy)</li> </ul>	<ul style="list-style-type: none"> <li>• Mucocutaneous (rash)</li> <li>• Gastrointestinal (abdominal pain, vomiting, diarrhoea)</li> <li>• shock/hypotension</li> </ul>	<ul style="list-style-type: none"> <li>• Gastrointestinal (abdominal pain, vomiting, diarrhoea)</li> <li>• Shock/hypotension</li> </ul>
AND		
Laboratory evidence of inflammation including any of the following: <ul style="list-style-type: none"> <li>• elevated CRP, ESR, ferritin or procalcitonin</li> </ul>	• Elevated CRP, ESR, ferritin and procalcitonin	• Elevated CRP, ESR, ferritin and procalcitonin
AND		
Two or more measures of disease activity: <ul style="list-style-type: none"> <li>• elevated BNP or NT-proBNP, or troponin</li> <li>• neutrophilia, lymphopenia or thrombocytopenia</li> <li>• evidence of cardiac involvement by echocardiography or physical stigmata of heart failure</li> <li>• electrocardiographic changes consistent with myocarditis or myopericarditis</li> </ul>	<ul style="list-style-type: none"> <li>• Elevated BNP and troponin</li> <li>• Neutrophilia, lymphopenia and thrombocytopenia</li> <li>• Evidence of cardiac involvement by echocardiography and physical stigmata of heart failure</li> <li>• Electrocardiographic changes consistent with myocarditis or myopericarditis</li> </ul>	<ul style="list-style-type: none"> <li>• Elevated BNP and troponin</li> <li>• Lymphopenia and thrombocytopenia</li> <li>• Evidence of cardiac involvement by echocardiography and physical stigmata of heart failure</li> <li>• Electrocardiographic changes consistent with myocarditis or myopericarditis</li> </ul>
AND		
Laboratory confirmed SARS-CoV-2 infection OR	• Laboratory confirmed SARS-CoV-2 infection	• Laboratory confirmed SARS-CoV-2 infection
Personal history of suspected COVID-19 within 12 weeks OR	AND • Following SARS-CoV-2 vaccination	AND • Following SARS-CoV-2 vaccination
Close contact with known COVID-19 case within 12 weeks OR		
Following SARS-CoV-2 vaccination		

BNP = B-type natriuretic peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; NT-proBNP = N-terminal prohormone BNP.

level, 422 mg/L; RI, < 4 mg/L) and lymphopenia (lymphocyte count,  $0.5 \times 10^9/L$ ). His troponin level was normal. Microbiological investigations were negative for SARS-CoV-2 (PCR), respiratory viruses (multiplex PCR), and urine and blood cultures. He developed dyspnoea and tachycardia, and TTE showed mild biventricular dilation and a left ventricular ejection fraction of 35%. On day 6 after vaccination (day 40 after infection), laboratory tests showed a troponin level of 670 ng/L (RI, < 50 ng/L) and thrombocytopenia (platelet count,  $84 \times 10^9/L$ ). He was transferred to the ICU on day 8 after vaccination (day 42 after infection) for management of hypotension with vasopressors. Hydrocortisone 1 mg/kg four times daily was commenced, with improved cardiorespiratory function and inflammatory markers, lymphopenia and thrombocytopenia from 24 hours. Progress TTE on day 11 after vaccination (day 45 after infection) showed normal left ventricular size and function. The patient was discharged on day

13 after vaccination (day 47 after infection), with oral prednisolone.

**Discussion**

Both cases were notified to the NSW Public Health Unit as part of the NSW vaccine safety review process, and subsequently referred for expert panel review, and to the Therapeutic Goods Administration for causality assessment.<sup>1</sup> On expert panel review, both cases were concluded to be consistent with multisystem inflammatory syndrome (MIS), a life-threatening hyper-inflammatory state of unknown pathogenesis. Both cases met Brighton Collaboration definitive case criteria (Box).<sup>2</sup> MIS is well described in children (MIS-C), first recognised in April 2020, with prevalence estimated at 2 in 100 000 children during the early 2020 COVID-19 outbreak in New York, occurring 4–6 weeks after primary infection, mostly in otherwise healthy children.<sup>2</sup> It is now also recognised in adults (MIS-A)

with unknown prevalence, occurring within 12 weeks of primary infection, mostly in adults with underlying health conditions.<sup>2</sup>

Recently, a number of cases have been described in which patients, all aged under 45 years with mostly no or mild underlying medical conditions, developed MIS following vaccination (MIS-V). However, many of these cases, and both of our cases described above, were also associated with antecedent SARS-CoV-2 infection. Therefore, it is difficult to determine in all these cases whether MIS was due to infection, vaccination or both. MIS-V has been described following the first or second dose of Comirnaty (Pfizer),<sup>3-5</sup> Vaxzevria (AstraZeneca)<sup>6</sup> and BBIBP-CorV (Sinopharm).<sup>7</sup> The timing between the most recent vaccination and onset of symptoms varied between hours<sup>7</sup> and 22 days.<sup>4</sup> Empirical treatments described comprise high dose corticosteroids, intravenous immunoglobulin and anakinra, an interleukin-1 antagonist, and are associated with significant rate of recovery.

Nonetheless, potential life-threatening adverse events following COVID-19 vaccination remain important to identify even though antecedent SARS-CoV-2 infection makes attribution to vaccination difficult. We note that following infection with the SARS-CoV-2 Delta strain, neutralising antibodies develop in most patients, persist for 6–12 months,<sup>8,9</sup> and offer 85% protection against subsequent Delta infection.<sup>10</sup> Temporary medical exemption to vaccination following recovery can be considered. However, previous infection only appears to offer 19% protection against infection with the Omicron strain.<sup>10</sup>

### Lessons from practice

- Multisystem inflammatory syndrome (MIS) is a rare hyperinflammatory state that can lead to multi-organ failure and death.
- MIS has been described 4–12 weeks after primary SARS-CoV-2 infection.
- MIS has recently been described within 22 days of COVID-19 vaccination, with about 50% of cases associated with vaccination after recovery from SARS-CoV-2 infection.

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