Multisystem inflammatory syndrome in an adult following the SARS-CoV-2 vaccine (MIS-V)

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SUMMARY
SARS-CoV-2 vaccine roll-out has been successful in the UK and other parts of the world; however, there are increasing concerns about adverse events. A 44-year-old woman presented to a UK hospital with left upper arm pain at the vaccine site a couple of days after receiving the Pfizer-BioNTech mRNA vaccine, which progressed to fever, diarrhoea and abdominal pain over the next few days. She had an erythematous rash on the chest with subcutaneous oedema. Her C reactive protein was 539 mg/L, white cell count of 17×109/L (1.8–7.5), troponin-T of 1013 ng/L and creatine kinase of 572 u/L. She developed an unprovoked pulmonary embolism with acute kidney injury. After administration of intravenous methylprednisolone, the muscle oedema, skin rashes and acute kidney injury resolved. Although multisystem inflammatory syndrome (MIS) is described in children (MIS-C) and adults (MIS-A) following SARS-CoV-2 infection, we highlight the first reported MIS-V case after the SARS-CoV-2 vaccine.

BACKGROUND
Available literature data suggest that SARS-CoV-2 vaccines are generally safe and well tolerated.1–3 However, there is an increasing focus on adverse events following immunisation (AEFI) after the SARS-CoV-2 vaccine recently. In the UK, over 43 million of the adult population have been vaccinated so far in the fight to end the pandemic.4 Reported data indicate that 1 in 15 patients may develop mild to moderate self-limiting side effects for few days, mimicking influenza or low-grade COVID-19 infection following SARS-CoV-2 vaccination. The most common side effects are sore arm, localised swelling, headache, fever, swollen glands, muscle pains and fatigue.5 Reassuringly, severe AEFI is rare with COVID-19 vaccines, but recent reports suggest that a small number of individuals have sustained severe adverse events.

Pfizer-BioNTech m-RNA SARS-CoV-2 vaccination is known to cause rare allergic reactions, ranging from hives, tongue swelling and life-threatening anaphylaxis (1 in 100 000), particularly in individuals with known allergies.3 5 6 Recently, new concerns have been raised about thromboembolism (TE) risk following the AstraZeneca-Oxford SARS-CoV-2 vaccine.7–9 The Medicines and Healthcare products Regulatory Agency revealed in April 2021 that 7 out of 18 million adults in the UK have died from TE after receiving the AstraZeneca-SARS-CoV-2 vaccine. Further reports in the global media highlighting cerebrovascular sinus thromboses (CVST) and potential causal relationship with the AstraZeneca-Oxford SARS-CoV-2 vaccine have caused worldwide concern. Current evidence suggests that the risk of CVST is overall low, with an estimated risk of 13.2 cases per million per year.10

Multisystem inflammatory syndrome (MIS) associated with COVID-19 infection also generated much interest, mainly in children (MIS-C) and, more recently, adults (MIS-A).11–13 We highlight a first reported case of an MIS following the Pfizer-BioNTech m-RNA SARS-CoV-2 vaccine, successfully treated with intravenous corticosteroid therapy. There is currently limited information about the prevalence of MIS-A. Therefore, we feel it is essential to report an MIS case due to the SARS-CoV-2 vaccine. We will explain the disease’s course, discuss the differences compared with MIS-A and MIS-C, and its management in our patient. The available literature is reviewed.

CASE PRESENTATION
A 44-year-old woman with a history of mild asthma was admitted to our local hospital with left upper arm/chest pain in January 2021, 2 days after receiving the Pfizer-BioNTech m-RNA SARS-CoV-2 vaccine. She reported constant left arm pain, which was worse on limb movement. Symptoms progressed to involve the left axilla and abdominal wall over the next few days. She reported that she was unable to lift her left arm due to pain. She also had bilious vomiting, loose stools and chest tightness. During the hospital admission, the patient developed an erythematous skin rash on the left chest wall (figure 1). The initial suspicion was that this could be a herpes zoster rash, but it was felt unlikely following a dermatology review.

The patient denied any history of skin rashes, Raynaud’s, photosensitivity or mouth ulcers before hospital admission. She reported being well before receiving the SARS-CoV-2 vaccine. She denied any nose bleeds, ear discharge or hearing loss. She previously had influenza and yellow fever vaccines without any reaction. The patient did not have any allergies. She had three first trimester miscarriages and one ectopic pregnancy before she delivered her healthy full-term first child. The patient denied having a history of TE.

She was admitted to the intensive therapy unit (ITU) with a temperature of 38°C. She was hypotensive with a blood pressure of 81/38 mm Hg and a pulse rate of 100 beats/min. The patient had tenderness in the left axilla, chest wall and loin. Left-arm abduction was limited due to pain, with weakness of 4/5 on the Medical Research Council scale. She had normal heart sounds and her chest was clear to
auscultation. The patient continued to have temperature spikes >38°C.

INVESTIGATIONS
Her admission electrocardiography (ECG) showed no evidence of ischaemia. Serum creatinine was 193 μmol/L (54–79) with an estimated glomerular filtration rate of 27 mL/min/1.73 m² (normal >60). The white cell count was 17.1 × 10⁹/L (4.1–11.0) with a neutrophil count of 8 × 10⁹/L (1.8–7.5). Lymphocyte and eosinophil counts were normal. The C reactive protein (CRP) was elevated at 539 mg/L (0–5), and troponin-T was 1013 ng/L (0–15). D-dimer was raised at 2564 units (n<540) (table 1).

The patient had a negative SARS-CoV-2 real-time reverse transcriptase-PCR test following a nasopharyngeal swab, including tests for influenza and respiratory syncytial virus. The creatinine kinase (CK) was moderately elevated at 572 u/L (0–200), which peaked at 865 u/L. The patient also had a positive varicella immunoglobulin G (IgG) test. CT of the chest revealed left chest wall muscle oedema (figure 2).

DIFFERENTIAL DIAGNOSIS
The first impression was that of septic shock in view of hypotension and raised CRP. Elevated CK and acute kidney injury raised the possibility of rhabdomyolysis. However, urine was visibly clear and repeat CK was not significantly elevated. Due to the presence of fever, COVID-19 infection was sought. A CT evidence of subsegmental pulmonary embolism and elevated troponin also strengthened this suspicion. However, the patient did not have any typical respiratory symptoms, such as cough and breathlessness, had multiple negative SARS-CoV-2 nasopharyngeal swabs and antibody tests, and the CT of the chest showed no evidence of COVID-19 pneumonitis. Finally, with the elevated CK and the CT scan evidence of muscle oedema, we explored the possibility of inflammatory myositis. Due to the lack of symmetrical upper and lower limb proximal muscle involvement and normal connective tissue disease screen, including ANA and extractable-nuclear antigens, we ruled this out. Due to the patient’s normal ferritin, macrophage activation syndrome was also ruled out.

Overall, the patient’s clinical features and biochemical markers were consistent with the Centers for Disease Control and Prevention (CDC) definition of MIS. Although to date, MIS has been described in children and adults in the context of infection with COVID-19, it is a syndrome that can have various presentations. Our patient had a fever, elevated inflammatory
A systematic review by the Brighton Collaboration and several case studies have reported instances of Kawasaki disease associated with vaccines such as diphtheria-tetanus-pertussis, influenza and hepatitis vaccines. The Brighton Collaboration network recently recommended criteria to identify MIS cases in adults and children associated with SARS-CoV-2 vaccines. As per these criteria, to diagnose SARS-CoV-2 vaccination-induced MIS, patients should have onset of MIS symptoms within 4–6 weeks of SARS-CoV-2 vaccination for MIS-C and up to 12 weeks for MIS-A.17

A study from NEJM reports that 12 individuals developed delayed hypersensitivity reactions, called the ‘COVID-19 arm’, after receiving Moderna mRNA SARS-CoV-2 vaccine.25 As demonstrated in the present case, the patient’s symptoms started as a ‘COVID-19 arm’ which evolved as MIS. This emphasises that MIS can manifest following SARS-CoV-2 vaccination. Unlike the longer duration between acute COVID-19 and MIS-C and MIS-A in reported cases so far, our patient’s symptoms suggest MIS-V (MIS due to vaccination) developing within a week after an mRNA, SARS-CoV-2 vaccine. However, we suspect similar pathophysiology seen in MIS-C and MIS-A may play a key role in patients with MIS-V, causing immune system dysregulation and cytokine storm, leading to multiorgan dysfunction.26 As demonstrated in managing this patient, a diagnosis of MIS-V is a decision of exclusion that requires a high index of clinical suspicion. Hyperinflammatory syndromes such as acute COVID-19, macrophage activation syndrome and sepsis must be ruled out before considering MIS-V in patients who receive SARS-CoV-2 vaccinations. Being aware of the higher prevalence of MIS in children than adults, it remains to be seen whether SARS-CoV-2 vaccination in children would pose a greater risk of MIS-V.

The ideal management of MIS-V will become clearer once more cases are detected and reported. The fact that our patient responded exceptionally well to high-dose intravenous steroids raises the possibility that the mechanism of MIS-V is probably similar to MIS-C and MIS-A. Since steroids, intravenous immunoglobulins and other immunomodulatory medications have all been successfully used to treat cases of MIS-C and MIS-A, we anticipate further studies into their use for treating future cases of MIS-V.

We hope that our case sets a precedent for clinicians globally to identify and report cases of MIS associated with immunisation against SARS-CoV-2 infection. Recently published guidelines to define MIS-V should help raise awareness among clinicians to recognise MIS-V early during the patients’ illness and distinguish this new syndrome from similar conditions. We envisage that the CDC will play a key role in collating the suspected cases of multisystem hyperinflammatory syndromes with circulatory...
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shock to identify MIS-V cases, helping understand the pathophysiology and natural course of illness. This will help to find suitable treatments and better clinical outcomes in patients with MIS-V.

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