Case of adult-onset Kawasaki disease and multisystem inflammatory syndrome following SARS-CoV-2 vaccination

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SUMMARY

Kawasaki disease (KD) and multisystem inflammatory syndrome (MIS) are rare conditions that occur predominately in children. Recent reports document KD and MIS in adult patients following infection with SARS-CoV-2. Rarely, MIS is observed following vaccination against SARS-CoV-2, mostly in patients with prior SARS-CoV-2 infection. We report a case of KD in a man after a second SARS-CoV-2 vaccine dose, in absence of concurrent or prior SARS-CoV-2 infection. This patient also met criteria for probable MIS associated with vaccination. He tested negative for SARS-CoV-2 RNA via reverse transcriptase PCR, negative for SARS-CoV-2 nucleocapsid antibodies and demonstrated high levels SARS-CoV-2 spike protein antibodies, commonly used to assess vaccine response. Symptom improvement followed treatment with intravenous immunoglobulin, including desquamation of the hands and feet. As widespread vaccination against SARS-CoV-2 continues, increased vigilance and prompt intervention is necessary to limit the effects of postvaccination inflammatory syndromes.

BACKGROUND

Kawasaki disease (KD) is a small to medium-sized vessel vasculitis that may occur in children following infection with SARS-CoV-2.1 2 Classically observed in young children following bacterial or viral infection, KD occurs rarely in adults.3 Current theories propose that KD results from an exaggerated inflammatory response to environmental triggers in genetically susceptible individuals; environmental triggers are believed to be infectious antigens in the majority of cases.4 Prior reports document the occurrence of KD following exposure to vaccines, though systematic literature reviews have not found sufficient evidence to establish a causal link.5 6

A novel inflammatory syndrome that may mimic KD, termed multisystem inflammatory syndrome (MIS), also occurs in children and adults following infection with SARS-CoV-2.7 8 High fever, elevated serum inflammatory markers and diffuse rash characterise both syndromes. While KD is typically a mild condition that may result in cardiac disease, MIS often results in severe illness characterised by multiorgan dysfunction.10 Notably, patients with SARS-CoV-2-associated KD or MIS rarely experience severe respiratory failure, distinguishing them from patients with typical COVID-19.

Nucleoside-modified mRNA transcripts of the SARS-CoV-2 spike protein are used to produce COVID-19 vaccines.11 The SARS-CoV-2 spike protein is known to be highly immunogenic, particularly via mechanisms that activate innate inflammatory responses.12 To date, most reported cases of SARS-CoV-2-associated KD and MIS have resulted from infection with native SARS-CoV-2, though cases of MIS in children and adults have been reported following delivery of spike protein-based SARS-CoV-2 vaccines.13–18 Termed MIS associated with vaccination (MIS-V), most of these reported patients were previously infected with SARS-CoV-2 and developed fever, rash, elevated inflammatory markers and multiorgan dysfunction shortly after receiving a vaccine dose. Rapid improvement was observed following administration of high-dose steroids or intravenous immunoglobulin (IVIg) in each case.

We report a case of KD following vaccination against SARS-CoV-2 in a man after the second dose of the Pfizer-BioNTech mRNA SARS-CoV-2 vaccine. In addition, this patient met criteria for probable MIS-V by the current case definition.10 This patient had no history of COVID-19, tested negative for evidence of concurrent or prior SARS-CoV-2 infection and demonstrated high levels of SARS-CoV-2 spike protein antibodies, commonly used to assess vaccine response. Our objectives in reporting this case are to describe the initial clinical presentation and the exclusion of alternative diagnoses, as well as to demonstrate prompt response to treatment. Early recognition and intervention in both KD and MIS may limit progression and forestall the development of cardiac or other organ dysfunction, and are therefore essential to the safe use of effective vaccines.

CASE PRESENTATION

A man in his 40s presented to our hospital complaining of 1 day of fever, sore throat, abdominal pain associated with loose stools and a diffuse erythematous rash. The rash was non-tender, non-pruritic, blanching, and had progressed from his right thigh to include diffuse areas of his chest, abdomen, back, and the palms and soles of his hands and feet (figure 1). He denied prodromal symptoms prior to the onset of rash and denied prior COVID-19 infection. He received the second dose in a two-dose series of the Pfizer-BioNTech mRNA SARS-CoV-2 vaccine approximately 4 weeks prior to the onset of symptoms. A SARS-CoV-2 RNA reverse transcriptase (RT)-PCR assay of a nasopharyngeal swab specimen was negative. A presumptive diagnosis of bacterial pharyngitis was
considered and throat specimens were obtained for culture. He was prescribed a short course of oral amoxicillin and released without hospital admission.

Three days later, the patient returned to the hospital complaining of persistent fever, sore throat, non-productive cough, ongoing abdominal pain and loose stools, worsening rash, and new-onset painful joint swelling in the hands and feet. He reported full compliance with recently prescribed amoxicillin.

On further questioning, the patient denied chronic medical conditions and reported no known allergies to medications or environmental allergens. He denied family history of autoimmune or inflammatory disease, and denied recent contact with sick individuals or individuals exposed to SARS-CoV-2. He denied recent travel, recent outdoor activities, or exposure to wildlife or livestock. He denied intravenous drug use, new sexual partners or a history of tattoos. He denied use of tobacco products, alcohol or illicit substances, and stated that he does not use medications or supplements regularly. He did not know details of prior vaccinations though denied adverse reactions to vaccines in the past.

Examination revealed extension of the erythematous rash to encompass both thighs and approximately half of the torso and chest surface. Symmetric involvement of the palms and soles of the hands and feet was present. Conjunctival injection without exudate was present bilaterally and oral examination revealed angular cheilitis, erythematous strawberry tongue, dry mucous membranes without ulceration and enlarged tonsils without exudate (figure 1). Diffuse cervical lymphadenopathy was present. Joint examination revealed bilateral shoulder pain on passive range of motion testing, swelling and tenderness in bilateral wrists, bilateral proximal phalangeal joints associated with inability to make a fist, bilateral ankles and bilateral metatarsophalangeal joints associated with difficulty walking.

Empiric antibiotic therapy with oral doxycycline was initiated on the first day of hospitalisation. Symptoms persisted despite antibiotic treatment, including fever to a maximum temperature of 38.9°C.

Figure 1 Diffuse erythematous rash (A). Erythema and oedema of the hands and feet (B, C). Strawberry tongue (D).

TREATMENT
Daily aspirin and a 3 day course of IVIg were initiated on the second day of hospitalisation. Over the ensuing 6 days sustained defervescence and progressive abatement of rash were observed, marked by desquamation of the palms and soles (figure 2). Reduced swelling and return of full range of motion in the joints of hands and feet accompanied resolution of the rash. Tongue erythema and conjunctival injection resolved over a period of 5 days following initiation of IVIg. Oral prednisone was initiated on the fifth day, following completion of IVIg.

OUTCOME AND FOLLOW-UP
Laboratory analysis on the fifth day of hospitalisation revealed reduced inflammatory markers and mild thrombocytosis that peaked on the seventh day. A transthoracic echocardiogram performed on the second day revealed no evidence of cardiac dysfunction, and CT coronary angiogram performed on the seventh day did not demonstrate coronary aneurysms or stenosis.

On discharge from acute care on the seventh day of hospitalisation, the patient reported significant improvement in symptoms including complete resolution of fever, joint pain, abdominal pain and erythematous rash. Painless desquamation of the palms and soles of the hands and feet was present. The patient was instructed to continue daily aspirin and complete a taper of oral prednisone over 3 weeks.

One month after discharge the patient reported sustained resolution of symptoms, though did demonstrate ongoing painless desquamation of the palms and soles. Two months after discharge the patient reported resolution of desquamation. Laboratory analysis revealed resolution of thrombocytosis and normalisation of inflammatory markers. Results of a serum assay revealed an extremely high concentration of SARS-CoV-2 spike protein antibodies.

DISCUSSION
We report a man that demonstrated symptoms consistent with KD and concerning for MIS-V 4 weeks after the second dose of the Pfizer-BioNTech mRNA SARS-CoV-2 vaccine. No evidence of concurrent or prior SARS-CoV-2 infection was detected, though high levels of antibodies against the SARS-CoV-2 spike protein, measured to assess immune response to vaccination, were detected. Extensive investigation did not reveal evidence of an alternative aetiology and resolution of symptoms followed courses of IVIg and oral prednisone.

MIS is a rare response to SARS-CoV-2 exposure in children and adults. The recently proposed Brighton Collaborative case

INVESTIGATIONS
Initial laboratory analysis revealed a mild leucocytosis and increased band cells. Mild elevations in liver chemistry tests and acute phase reactants were detected, including a C reactive protein (CRP) level of 13.72 (mg/dL). Urinalysis detected few red blood cells and a urine drug screen was negative. A SARS-CoV-2 nasopharyngeal swab RT-PCR and a SARS-CoV-2 nucleocapsid antibody serology assay were both negative. Acute autoimmune and infectious aetiologies were excluded (table 1).

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**Case report**

Table 1  
**Laboratory analysis**

| Test                          | Value   | Reference ranges |
|-------------------------------|---------|-----------------|
| White cell count (x10^9/L)    | 11.19   | 4.80–10.90      |
| Neutrophils (%)               | 68.0    | 45–75           |
| Lymphocytes (%)               | 4.0     | 20–50           |
| Eosinophils (%)               | 4.0     | 0.0–5.0         |
| Bands (%)                     | 19.0    |                 |
| Haemoglobin (g/L)             | 137     | 133–177         |
| Platelet count (x10^9/L)      | 200     | 150–400         |
| Alanine aminotransferase (units/L) | 127 | 5–41         |
| Aspartate aminotransferase (units/L) | 36   | 5–40           |
| Bilirubin, total (mg/dL)      | 1.9     | 0.0–1.2         |
| Bilirubin, direct (mg/dL)     | 1.4     | 0.0–0.3         |
| Alkaline phosphatase (units/L)| 206     | 40–130          |
| Gamma glutamyl transferase (units/L) | 292 | 4–39            |
| Creatinine (mg/dL)            | 0.88    | 0.70–1.30       |
| eGFR (mL/min/1.73 m²)         | >90     | >60             |
| Vitamin D, 25-OH (ng/mL)     | 14.8    | >30.0           |
| Thyroid stimulating hormone (mIU/L) | 1.58   | 0.27–4.20      |
| Haemoglobin A1c (%)           | 5.6     | 4.0–6.4         |
| Lactate, venous (mmol/L)      | 2.1     | 0.5–1.6         |
| Prothrombin time (s)          | 11.5    | 10–13           |
| Activated partial thromboplastin time (s) | 32.9 | 26.6–36.5 |
| Fibrinogen (mg/dL)            | 1104    | 250–490         |
| D-dimer (mg/mL)               | 609     | 0–229           |
| Serum ferritin (ng/mL)        | 858     | 30–400          |
| C reactive protein (mg/dL)    | 13.72   | 0.00–0.49       |
| Erythrocyte sedimentation rate (mm) | 58 | 0–15           |
| Lactate dehydrogenase (units/L) | 233   | 135–225        |
| Creatine kinase (units/L)     | 170     | 20–200          |
| Troponin-I (ng/mL)            | <0.010  | <0.010          |
| B-type natriuretic, N-terminal (pg/mL) | 108 | 0–125          |

**Autoimmune disease studies**

| Test                        | Value |
|-----------------------------|-------|
| Antinuclear antibody        | Negative |
| Rheumatoid factor (IU/mL)   | 17.1  |
| RNA polymerase III antibody (AU/mL) | 11 | 0–19       |
| Centromere antibody (AU/mL) | 0     |
| Topoisomerase I antibody; SCL-70 (AU/mL) | 0 | 0–0.40  |
| Protease-3 antibody (AU/mL) | 4.0   |
| Myeloperoxidase antibody (AU/mL) | 1.0 | 0.0–0.19  |
| SSA-52; Ro52 antibody (AU/mL) | 1.0   | 0.0–0.40  |
| SSA-50; Ro60 antibody (AU/mL) | 0.0   |
| SSb; La antibody (AU/mL)     | 0.0   |
| Beta-2-microglobulin        | 3.7   |
| C3 complement (mg/dL)       | 144   |
| C4 complement (mg/dL)       | 28    |
| Lupus anticoagulant screen  | Negative |
| IgA (mg/dL)                 | 187   |
| IgM (mg/dL)                 | 59    |
| IgG (mg/dL)                 | 1047  |

**Infectious disease studies**

| Test                          | Value |
|-------------------------------|-------|
| SARS-CoV-2 RT-PCR             | Not detected |
| SARS-CoV-2 nucleocapsid antibody ECLIA assay | Negative |
| SARS-CoV-2 spike antibody (units/mL) | 1186 | <0.8 |

**Table 1 Continued**

| Test                        | Value   |
|-------------------------------|---------|
| Anaplasma phagocytophilum IgG (titre) | <1.64 |

**Figure 2**  
Desquamation of the hands and feet during resolution of rash (A, B).
of hospital admission, he had experienced persistent fevers for more than 5 days and met all five of the additional American Heart Association (AHA) criteria proposed for the diagnosis of KD: painful erythematous swelling of the hands and feet, extensive erythematous rash, oropharyngeal erythema marked by cheilitis and strawberry tongue, cervical lymphadenopathy, and conjunctival injection without exudate. Desquamation of the palms and soles of the hands and feet during convalescence is considered pathognomonic of KD. Treatment with IVIg and steroids resulted in prompt improvement in symptoms and disease markers.

The overlap of non-specific features that characterise both KD and MIS limits clear differentiation of the two conditions. Both believed to result from untoward immune activation following an infectious trigger, these conditions may be considered related manifestations of similar underlying mechanisms in response to SARS-CoV-2 antigens. Reports document response to immunomodulatory therapies in both conditions, and therefore each may be treated similarly with IVIg and steroids, among other therapies. The presence of gastrointestinal symptoms, elevated liver chemistry tests, haematuria, highly elevated CRP and the absence of coronary artery involvement are more typical of MIS; nonetheless, this patient fulfilled all criteria for the diagnosis of complete KD and was therefore managed in accordance with guidelines for the treatment of KD. Designating this patient as probable MIS-V in addition to KD increased vigilance for progressive multiorgan dysfunction and for resistance to treatment with IVIg, neither of which occurred. The use of steroids in KD is associated with decreased duration of symptoms and improved cardiac outcomes; therefore, the use of prednisone in this patient may have affected early symptom control. No cardiac sequelae have been detected during 3 months of surveillance.

Novel to the growing reports of inflammatory syndromes associated with SARS-CoV-2 is the manifestation of KD in an adult following vaccination in absence of concurrent or prior SARS-CoV-2 infection. While we cannot entirely exclude the possibility of occult SARS-CoV-2 infection, this patient experienced no prodromal or concomitant features of COVID-19, tested negative for infection via RT-PCR of nasopharyngeal swab specimens, tested negative for SARS-CoV-2 nucleocapsid antibodies and demonstrated extremely high levels of SARS-CoV-2 spike protein antibodies. The onset of symptoms occurred between 4 and 6 weeks after the second dose of vaccine, approximately the same interval over which inflammatory syndromes are expected to occur following exposure to SARS-CoV-2 viral triggers. The patient denied exposure to sick individuals in the weeks prior to presentation, including exposure to known or suspected cases of COVID-19. SARS-CoV-2 spike protein antibody levels have been used in prior investigations to assess the immune response to vaccination, particularly when accompanied by the absence of SARS-CoV-2 nucleocapsid antibodies and the absence of viral RNA detected by RT-PCR to exclude prior or concurrent infection.

While KD has been described following SARS-CoV-2 infection in adults and children, only one prior report documents KD following vaccination against SARS-CoV-2. That man in his teens experienced symptoms 3 weeks after the first dose of a SARS-CoV-2 vaccine and similarly responded to treatment with IVIg. Exclusion of prior or concurrent SARS-CoV-2 infection was not specified. Prior to the COVID-19 pandemic KD was observed following vaccination, and although multiple investigations failed to establish a causal link, a temporal relationship between vaccination and KD persisted. Recent reports describe MIS-V in adult patients after receiving SARS-CoV-2 vaccines, many of whom experienced multiorgan failure and responded to high-dose steroids or IVIg. Most of these patients had prior SARS-CoV-2 infections and develop symptoms shortly after vaccination. Few among these patients experienced minor erythematous rashes on their torso or extremities; however, they did not demonstrate additional features of KD.

Alternative aetiologies appear unlikely in this patient. Though the rash involved maculopapular surfaces, no ulceration, necrosis or vesicular changes were observed and the appearance of rash predated the use of antibiotics, altogether suggesting against a drug allergy syndrome. The patient denied any history to suggest autoimmune disease and rheumatological serum studies including markers of systemic vasculitis were negative. He denied prodromal symptoms to suggest infection and the results of multiple microbial cultures were negative. He denied exposure to ticks, no bite wounds were evident, and extensive investigation revealed no evidence of concurrent tick-borne or occult viral, bacterial, or plasmodial disease. Increased band cells were noted, a non-specific finding that has been observed in KD. Short courses of amoxicillin and doxycycline were ineffective; fever and other symptoms persisted until administration of IVIg. Although serum inflammatory markers were mildly elevated, peak levels and absence of severe illness suggest against severe immune hyperactivation syndromes such as macrophage activation syndrome or haemophagocytic lymphohistiocytosis. Considering the absence of alternative explanations, the temporal relationships between symptom onset and vaccination, and the isolated elevation in spike protein antibody levels without evidence of concurrent or prior SARS-CoV-2 infection, a postvaccination inflammatory syndrome presenting as KD and meeting criteria for MIS-V appears most likely.

Importantly, temporal association between inflammatory syndromes and vaccination is not tantamount to causation. Vaccine hesitancy that results from misattribution of rare inflammatory syndromes to vaccination may indeed blunt the use of an essential tool in the battle against COVID-19. Thorough investigation of temporally related events, as presented in this report, and ongoing efforts to support widespread vaccination against SARS-CoV-2 are critical to safely and effectively combating COVID-19. Nonetheless, early recognition and intervention may limit progression in both MIS and KD and may forestall the development of cardiac dysfunction after KD. As widespread

Learning points

- Kawasaki disease may occur following vaccination against the SARS-CoV-2 virus in adults without evidence of concurrent or prior infection.
- Kawasaki disease and multisystem inflammatory syndrome share many non-specific clinical features and likely share similar underlying mechanisms in response to SARS-CoV-2 viral triggers.
- Treatment with intravenous immunoglobulin resulted in prompt improvement in symptoms and disease markers in this case of adult Kawasaki disease and multisystem inflammatory syndrome following vaccination against SARS-CoV-2.
- Temporal association does not ensure causation and thorough investigation of inflammatory syndromes that occur after vaccination is essential to the widespread use of effective SARS-CoV-2 vaccines.
vaccination against SARS-CoV-2 continues, increased vigilance and prompt intervention is necessary to limit the effects of rare postvaccination inflammatory syndromes.

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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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