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Multisystem inflammatory syndrome in children (MIS-C) possibly secondary to COVID-19 mRNA vaccination

Zoon Wangu,[1,2] Hannah Swartz,[3] Meaghan Doherty[4]

[1]Pediatric Infectious Diseases & Immunology, University of Massachusetts Medical School, Worcester, Massachusetts, USA
[2]Ratelle STD/HIV Prevention Training Center, Massachusetts Department of Public Health, Jamaica Plain, Massachusetts, USA
[3]University of Massachusetts Medical School, Worcester, Massachusetts, USA
[4]Pediatric Cardiology, University of Massachusetts Medical School, Worcester, Massachusetts, USA

Correspondence to
Dr Zoon Wangu;
zoon.wangu@umassmemorial.org

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SUMMARY

Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 is a postinfectious condition identified during the COVID-19 pandemic with specific Centers for Disease Control and Prevention and WHO criteria. Theoretical concerns have been raised whether MIS-C might also occur after COVID-19 vaccination, as the pathogenesis of MIS-C is not yet entirely understood. We present a woman in her late teens who developed MIS-C after having received two doses of Pfizer BioNTech COVID-19 vaccine 12 weeks prior, in the setting of documented anti-spike SARS-CoV-2 IgG positive, antinucleocapsid SARS-CoV-2 IgG negative, and multiple negative surveillance SARS-CoV-2 PCRs done in the 12-week period prior to development of MIS-C. While vaccination remains safe and critical in controlling the pandemic, it may be considered as a potential trigger for MIS-C in patients with no history of infection. Further surveillance is necessary to determine whether MIS-C will emerge as a confirmed adverse event after COVID-19 vaccination.

BACKGROUND

Multisystem inflammatory syndrome in children (MIS-C) was first reported in mid-April 2020 by Riphagen *et al* in the UK and Verdoni *et al* in Italy, when emerging cases of a hyperinflammatory shock syndrome following COVID-19 infection were identified in children.[1 2] Since these initial reports, over 4000 cases and 37 deaths have been reported in the USA.[3] MIS-C is considered a post-infectious inflammatory condition, given the low or nonexistent viral loads and treatment response to immunomodulation. Based on early case series, approximately 60% of patients with MIS-C have positive serology with negative PCR at the time of diagnosis, 34% are both serology and PCR positive, and 5% have negative results for both tests.[2 4–8] MIS-C has specific clinical criteria per the US Centers for Disease Control and Prevention (CDC) including age <21 years, fever ≥24 hours, laboratory markers of inflammation, involvement of two or more organ systems, no alternative plausible diagnosis and a recent or current COVID-19 infection or exposure.[9] WHO has similar criteria with minor variations including fever ≥3 days, and no specific timeframe for previous COVID-19 exposure.[10]

The pathophysiology of MIS-C is still being clarified, but it is distinct from that occurring in acute COVID-19 infection. Patients with acute severe COVID-19 show lymphopenia, T-cell activation and elevated interferon-gamma levels, whereas the summation of interleukin 10 and tumor necrosis factor alpha levels has been found to be predictive of MIS-C over acute COVID-19 infection.[11 12] Myocarditis has become a well-recognised immune-mediated vaccine reaction in younger patients. The proposed mechanisms for this include mRNA immune reactivity and antibody cross reactivity as well as hormonal differences due to the male predominant prevalence of myocarditis. Although the clinical diagnosis of MIS-C has significant overlap with Kawasaki disease (KD), the underlying immunological cascades likely differ given the differing cytokine profiles.[13]

Theoretical concerns have been raised about COVID-19 vaccine triggering MIS-C. Recently, Nune *et al* described multisystem inflammatory syndrome in an adult after COVID-19 mRNA vaccine (MIS-V) in the absence of acute COVID-19.[14] No similar reports of this entity in those younger than 21 years of age have yet been identified to our knowledge. We evaluated a patient in our medical centre with MIS-C who had no evidence of past or recent infection with COVID-19 but had received two doses of the Pfizer BioNTech COVID-19 vaccine 12 weeks prior to hospitalisation, raising the possibility that MIS-C was related to vaccination.

CASE PRESENTATION

A woman in her late teens presented to our hospital emergency department with fevers up to 40°C for 4 days, chills, sweats, tachycardia, shortness of breath, fatigue and a throbbing headache. Fevers were only briefly responsive to antipyretics. At the time of presentation, she also described mid-sternal chest pressure resolving with ambulation, diffuse myalgias, nausea, one episode of vomiting and four episodes of watery non-bloody diarrhoea.

The patient had a history of dysmenorrhea managed by oral contraceptives (ethinyl estradiol and norgestimate). Her prior surgical history included an appendectomy 6 months prior. SARS-CoV-2 PCR testing done both 3 and 2 days prior to admission were negative. She had received weekly to biweekly PCR testing in the 3-month period prior to presentation, given her employment at a long-term care facility. All PCR tests were negative. The patient received her first dose of the Pfizer BioNTech COVID-19 vaccine approximately 12 weeks prior to her presentation, with her second

Table 1 Laboratory findings during patient hospitalisation

	Patient values Note: single values indicate highest value during hospitalisation unless otherwise stated	Normal range (per reference laboratory)
WCC	7.7×10^3	4.3–10.8 x 10^9/L
Absolute lymphocytes	**0.5×10^3/µL***	0.9–3.4 x 10^3/µL
C reactive protein	**235.3** mg/L	<10 mg/L
Erythrocyte sedimentation rate	**120** mm/hour	<20 mm/hour
Troponin I	**0.23** ng/mL	0.01–0.04 ng/mL
Brain natriuretic peptide	75 pg/mL	<100 pg/mL
Creatine kinase-MB	0.7 ng/mL	<4.4 ng/mL
Lactate dehydrogenase	208 U/L	110–240 U/L
Ferritin	237 ng/mL	11–306 ng/mL
Lactic acid	0.9 mmol/L	0.3–1.9 mmol/L
Prothrombin time/ International normalized ratio	11.3 s/1.0	9.6–12.4 s/2–3.5
Activated partial thromboplastin time	31.2 s	23–32 s
Antithrombin III activity	86%	80%–135%
Fibrinogen	**810** mg/dL	150–440 mg/dL
D-dimer	**1.92** mg/L	<0.5 mg/L
Soluble interleukin 2 receptor	**1499.5** pg/mL	175.3–858.2 pg/mL
Urinalysis	Notable for: slightly cloudy, 3+protein, 2+ketones, 1+blood, rare bacteria†	–

Abnormal findings in bold font.
*Lowest value.
†Patient was menstruating
WCC, white cell count.

dose 20 days later. Six weeks prior to her presentation, the patient's two younger siblings developed febrile illnesses of unclear aetiology that lasted 36 hours and self-resolved. They were seen at an urgent care facility at that time and had negative SARS-CoV-2 PCR testing. They did not have COVID-19 antibody testing performed at that time or subsequently. No one else in the home was sick and the final diagnosis of the siblings at the urgent care facility was an unspecified viral illness. At that time, the patient developed dysuria and haematuria without vaginal discharge, spotting or abdominal pain and was prescribed nitrofurantoin at an urgent care facility for treatment of a urinary tract infection. She had no fever or other symptoms at that time and her symptoms resolved shortly thereafter with antibiotics. The patient had no known contact with COVID-19 positive individuals and no travel, animal or other environmental exposures.

Vital signs in the emergency department were notable for: temperature 39.6°C, heart rate 121 beats/min, blood pressure 122/70 mm Hg and oxygen saturation 100% in room air. Anthropometrics included: weight 77 kg, height 165.1 cm and body mass index 28.3 kg/m^2. The patient was ill appearing with persistent tachycardia despite normal saline boluses (2 L in total) and maintenance fluids. Her blood pressure remained normal. Her initial examination was otherwise unremarkable apart from bilateral non-exudative conjunctivitis.

INVESTIGATIONS

See table 1 for pertinent laboratory values from the patient's admission, which were notable for absolute lymphocytopenia and elevated inflammatory markers, troponin, fibrinogen, D-dimer and soluble IL-2 receptor. Complete metabolic panel and complete blood count (CBC) with differential were unremarkable. Infectious workup including SARS-CoV-2 PCR, qualitative nucleic acid testing for influenza A/B, respiratory syncytial virus, and human metapneumovirus, as well as Lyme antibody were all negative. Blood and urine cultures were without growth. She had a normal chest x-ray; ECG showed normal sinus rhythm with rsR' pattern which was considered a likely normal variant in the setting of normal QRS duration and no significant increase in voltages. Echocardiogram showed normal biventricular function, valvular function and coronary artery dimensions. The patient was admitted to the paediatric intensive care unit for telemetry monitoring. Paediatric infectious diseases and immunology and cardiology services were consulted. Her troponin, initially elevated at 0.23 ng/mL, subsequently normalised by day 1 of hospitalisation.

DIFFERENTIAL DIAGNOSIS

The patient fulfilled clinical and laboratory criteria for MIS-C including ≥24 hours of fever, evidence of systemic inflammation with at least two organ systems involved (gastrointestinal, haematological, dermatological/mucocutaneous, neurocognitive and cardiac) and illness requiring hospitalisation. She had a positive COVID-19 IgG (Beckman Coulter Access SARS-CoV-2 IgG), although this could certainly have been secondary to receipt of vaccine. Stool studies were not performed as her diarrhoea resolved. The patient did not fulfil criteria for KD, acute COVID-19, bacterial sepsis or toxic shock syndrome. As above, viral aetiologies were explored but molecular testing for additional viruses (such as enterovirus/rhinovirus, adenovirus and parainfluenza) was not sent as extended viral testing at our centre has a multiday turnaround time. Given expanded viral testing was not sent, it remains possible that another viral aetiology, not specified, could have caused this patient's presentation. Viral aetiologies known to cause multisystem involvement are listed in box 1. This patient was immunocompetent and was not expected to present with serious illness secondary to these other viruses, however, it remains possible that another viral illness was present. She had no evidence of excessive immune activation (such as haemophagocytic lymphohistiocytosis or macrophage activation syndrome) or rheumatological disease such as systemic lupus erythematosus or vasculitis. In the absence of an alternative plausible diagnosis, the decision was made to treat her for MIS-C.

TREATMENT

Treatment for MIS-C was initiated with intravenous immune globulin 2 g/kg ×1 dose, as well as medium dose aspirin 650 mg every 6 hours for anti-inflammatory effect,[15] and methylprednisolone 1 mg/kg every 12 hours. She was also given enoxaparin secondary to concern for risk of coagulopathy as she was taking combined oral contraceptives. By 24 hours after treatment initiation, the patient defervesced and reported that all of her symptoms had resolved. Her physical examination was normal including resolution of conjunctivitis. She was discharged 48 hours from admission in good condition on aspirin 81 mg daily and oral prednisone taper over 3 weeks.

OUTCOME AND FOLLOW-UP

At the time of outpatient follow-up 2 weeks from hospital discharge, the patient reported she was back to her baseline.

Box 1 Differential diagnosis of viral aetiologies presenting with multisystem involvement and/or myocarditis[27 28]

Adenovirus.
Coxsackie virus.
Cytomegalovirus.
Enterovirus.
Epstein-Barr virus.
Parvovirus.

Follow-up echocardiogram remained normal. Labs showed slight increase in white cell count to 11×10^9/L and neutrophilia (absolute neutrophil count 8.99×10^9/L), likely secondary to neutrophil demargination related to corticosteroid therapy. C reactive protein (CRP) had normalised to <1.0 mg/L. Given the previously noted IgG titre may have been from vaccination, antinucleocapsid IgG testing (Abbott ARCHITECT SARS-CoV-2 IgG) was performed (this testing was not available at the time of hospitalisation). Testing was negative, suggesting she had not had prior COVID-19 disease. Due to the onset of a multisystem inflammatory process potentially consistent with MIS-C occurring 12 weeks postvaccination, this case was reported to the Massachusetts Department of Public Health and the US Vaccine Adverse Event Reporting System.

DISCUSSION

COVID-19 infection is associated with multiple acute and post-infectious complications. Vaccination against COVID-19 is a powerful tool to decrease morbidity and mortality globally. As with any vaccination, adverse events have been identified, including reactogenicity symptoms which occur frequently but are generally quite mild. More serious vaccine-related adverse effects including anaphylaxis, immune thrombocytopenia and venous thrombosis have been infrequently reported.[16] Myocarditis and myopericarditis are now a known rare and serious adverse event of the SARS-CoV-2 mRNA vaccines.[17–20] The incidence of these complications is significantly lower than that occurring after natural infection, and thus, the benefits of vaccination outweigh the known risks in this regard.[21]

Salzman *et al* recently described three adult patients in the USA with MIS following SARS-CoV-2 mRNA vaccination, but all of these patients were found to have recent SARS-CoV-2 infection confirmed by molecular testing.[22] As noted above, Nune *et al* recently reported the case of a 44-year-old woman thought to have multisystem inflammatory syndrome after COVID-19 mRNA vaccine.[14] This patient presented a few days after vaccination with fever, diarrhoea, abdominal pain, rash, subcutaneous oedema, pulmonary embolism and acute kidney injury. Repeated molecular testing for SARS-CoV-2 was negative. She showed no response to broad-spectrum antibiotics but recovered rapidly after treatment with methylprednisolone. In this case, multiple investigations for infectious and inflammatory aetiologies were performed, however, there was no other plausible diagnosis to explain the patient's illness. Yousaf *et al* recently reported 21 individuals ages 21 and younger with MIS-C following SARS-CoV-2 mRNA vaccination, 6 of whom had no prior evidence of COVID-19 infection.[23]

Our patient presented with her illness 12 weeks after vaccination. This is greater than the original definition of MIS-C per CDC criteria, but it is within the range per WHO and the Brighton Collaborative Case Definition.[10 13] MIS-C cases with longer latency periods up to 16 weeks have been reported in the literature and it is possible that the original time frame of 4–6 weeks is too strict to encompass all cases of MIS-C.[23 24]

Our patient had negative testing for more common acute respiratory illnesses but did not receive additional viral testing. Her constellation of symptoms in the setting of immune competence, ill appearance and CRP >200 mg/L seemed less consistent with a viral illness. Nonetheless, multisystem involvement and/or myocarditis has been described secondary to other viruses (see box 1) and it remains possible that one such aetiology could have caused this patient's presentation. She was not tested for other tickborne disease apart from Lyme disease, however her symptoms along with a normal CBC except for isolated lymphopenia, as well as her rapid improvement without antimicrobial therapy, was not consistent with these diagnoses. Her gastrointestinal symptoms included 4 episodes of non-bloody diarrhoea which were transient and promptly resolved; therefore, stool cultures and testing could not be performed. In addition, her presentation is less likely attributable to an underlying autoimmune or autoinflammatory process given her lack of history of such a process, her negative family history, as well as her prompt response to treatment without recurrence of symptoms at the time of this publication.

Regarding the patient's COVID-19 antibody testing, it is important to note that the antinucleocapsid testing sent (Abbott ARCHITECT SARS-CoV-2 IgG) has a sensitivity and specificity approaching 100% for detecting evidence of prior infection per manufacturer's package insert.[25] Therefore, the likelihood of a false negative result in our patient is extremely low. In comparison, anti-spike IgG, which in this case likely represents vaccination, has a sensitivity of 96.8% and specificity of 99.6%.[25 26]

The antinucleocapsid antibody assay was not available at the time of this patient's acute presentation. Given that the treatment for MIS-C includes treatment with pooled antibodies, a positive antinucleocapsid antibody titre drawn after acute management, while still quite sensitive, may not be specific for detecting evidence of prior infection. Therefore, in future instances, it is of critical importance to consider antibody testing prior to treatment with IVIG, with measurement of virus-specific antibodies such as antinucleocapsid antibodies in vaccinated persons. In addition, as the clinical criteria for MIS-C can in many instances overlap with that of other autoimmune or autoinflammatory conditions, the widespread availability of antinucleocapsid antibody testing with timely results would be useful in the acute evaluation of vaccinated patients in these populations.

As noted above, the pathophysiology of MIS-C is distinct from that occurring with acute COVID-19 although this is still being clarified. Mechanisms proposed for postvaccine phenomena, primarily mRNA vaccine-associated myocarditis, include hypersensitivity reaction, immune cross-reactivity, genetic or sex-related factors.[19] It is possible that the aetiology of postvaccination MIS-C in patients without prior COVID-19 infection may be due to an underlying inflammatory condition that has not been previously identified.[23]

Understanding of the variety of phenotypes is still evolving and there is not currently one universal presentation of MIS-C.[4 8] Fortunately, the proposed occurrence of MIS-C in the context of vaccination without preceding acute COVID-19 infection can be considered mild with respect to the spectrum of MIS-C severity given lack of cardiac sequelae and rapid response to immunomodulation. If MIS-C can occur secondary to vaccination as opposed to natural infection, the phenotype may very well be expected to be mild, although further data is needed to confirm.

Importantly, serious adverse effects of COVID-19 vaccination are rare in the context of widespread vaccination, and thus far data indicate that the benefits of vaccination against COVID-19 far outweigh

Patient's perspective

When I first started feeling any symptoms that I may have been sick it was rather rapid. I woke up in the middle of the night with a throbbing headache. At the time I didn't take any pain relievers but tried to get back to bed. I didn't get much sleep and woke up with the same throbbing feeling in my head. I took my temperature and it was reading around 102 degrees. I did have finals that day so all I did to alleviate my symptoms was take Tylenol and Motrin on a ladder sequence. This fever persisted for days and was rising in temp even though I was taking medication. I did not have the headache anymore once I started taking meds. I had many of the associated signs with fever such as chills, and then sweating. I talked to my PCP and was told to see urgent care when my temp hit 104. It only hit 104 when left untreated and lingered for days. I went to urgent care and got no answers but was told I had bit of blood in my urine even though I was menstruating. I then went home and the next day my fever was still high, so I went to the hospital. This morning was the only time I threw up-due to what I believe was stress to go to the hospital since I had this happen various times before.

On arrival at the hospital, I really struggled being alone without my parents. I felt really scared because no one knew what was going on and, in the ER, I had tested negative for pretty much everything. I was then sent to the ICU and my mom was allowed with me. I stayed there until they concluded MISC. I was then sent to the paediatrics floor to get my IVIG. I felt really worried the entire time and my heart rate would not want to go down. Once I started IVIG I immediately felt better but just wanted to leave the hospital. I still am confused at my diagnosis and how I got this. The team was excellent, and I feel a lot better now. I do get anxious when I feel out of breath and I pay extra close attention to my HR but I was really fortunate.

the risks. Clinicians should continue to follow guidelines with respect to vaccine administration. As vaccination campaigns proceed globally, ongoing surveillance will be necessary to assess whether more cases of MIS-C without evidence of preceding COVID-19 infection occur in vaccinated persons. Clinicians should be aware of this possibility and report any potential adverse events related to vaccination.

Learning points

- Multisystem inflammatory syndrome in children (MIS-C) is a postinfectious inflammatory condition typically occurring several weeks to months following SARS-CoV-2 infection, but to our knowledge has not previously been reported following vaccination in the absence of prior SARS-CoV-2 infection.
- MIS-C related to COVID-19 vaccination may represent a milder phenotype compared with MIS-C secondary to natural infection.
- SARS-CoV-2-specific antibody testing should be sent in vaccinated persons presenting with clinical criteria consistent with MIS-C. Differential diagnoses including viral syndromes leading to multisystem involvement should be explored as potential aetiologies.
- Antinucleocapsid antibody testing is highly sensitive and specific for detecting evidence of preceding COVID-19 infection and is not altered by vaccination status.
- Although vaccination against COVID-19 is critical to decrease morbidity and mortality worldwide, adverse effects in children may include MIS-C. Continued reporting and tracking of vaccine outcomes and reactions are key to determining trends.

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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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