Multisystem Inflammatory Syndrome Following SARS-CoV-2 Vaccination in Two Children

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This report presents 2 pediatric cases of multisystem inflammatory syndrome in children and adults (MIS-C/A) post severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination (MIS-V). Both children presented with MIS-V within 6 weeks of receiving their first and only dose of Pfizer-BioNTech's SARS-CoV-2 vaccine. The first patient had symptoms of MIS-C/A with peri-myocarditis and shock, and the second 1 had classic Kawasaki disease features. Both responded well to intravenous immunoglobulins and/or systemic corticosteroids. Both children were positive only for SARS-2-CoV antispike (S) (and not for antinucleocapsid [NC]) antibodies consistent with a postvaccine, and not a postinfection, event. Surveillance for rare adverse events following immunization should continue, especially now that SARS-CoV-2 vaccination is approved in the 5 to 11 year age group that has had the highest risk of developing MIS-C post SARS-CoV-2 infection. Our patients did not receive any further SARS-CoV-2 vaccines. Our report highlights the importance of measuring differentiating antibodies (anti-S and anti-NC) that can be used within a specific timeframe to help determine if a patient has MIS-V post vaccine (only anti-S present), or MIS-C/A post SARS-CoV-2 infection (both anti-S and anti-NC present).

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus disease 2019 (COVID-19), started worldwide in December 2020.[1] Multisystem inflammatory syndrome in children and adults (MIS-C/A) is a post-SARS-CoV-2 infection syndrome with an estimated incidence of 1 in 3000 to 4000 (ages <21 years).[2–5] The World Health Organization and the United States Centers for Disease Control and Prevention have issued guidelines for MIS-C/A surveillance and diagnosis.[6,7] The Brighton Collaboration provides diagnostic criteria for MIS-C/A and MIS post SARS-CoV-2 vaccination (MIS-V).[7] Published cases exist of MIS-C/A in vaccinated patients.[8–18] Initial cases of MIS-V (without previous SARS-CoV-2 infection) have been reported.[8,19–32] We describe 2 MIS-V cases in Canadian children. Parental consent was obtained to publish these findings.

CASE 1

Five weeks after his first (and only) Pfizer-BioNTech SARS-CoV-2 vaccine (left deltoid), a healthy 12-year-old boy presented to our emergency department with 3 days of low grade fever and painful left axillary lymphadenopathy and redness (pruritic nonscarlatiniform contiguous erythema). An ultrasound confirmed nonsuppurative adenitis (multiple enlarged lymph nodes, some 2 cm in diameter, with surrounding soft tissue inflammation). He was prescribed cephalexin for cellulitis. He returned

abstract

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These are 2 cases of multisystem inflammatory syndrome following severe acute respiratory syndrome coronavirus 2 vaccination in children. Differentiating serology helps to distinguish multisystem inflammatory syndrome in children and adults from multisystem inflammatory syndrome post coronavirus disease 2019 vaccine.

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2 days later with fever (39.4°C) and extension of an erythematous rash to the anterolateral left thorax, and a new pruritic macular rash behind both knees and thighs. He had bilateral conjunctivitis, dry cough, and nonbilious vomiting without abdominal pain.

He denied recent viral illnesses or previous COVID-19, known contacts with individuals with SARS-CoV-2 infection, skin trauma, or foreign travel. Cephalexin was the only recent medication taken.

He was admitted and treated with intravenous vancomycin and cefazolin after obtaining blood and urine cultures. He developed hypotension (systolic blood pressure 70 mm Hg unresponsive to intravenous fluids) and was transferred to the PICU without requiring inotropic support. Two nasopharyngeal (NP) SARS-CoV-2 real time polymerase chain reaction nucleic acid amplification tests (RT-PCR-NAAT) were negative.

Within 24 hours, he developed a generalized rash, cracked lips, and strawberry tongue. Investigations revealed marked lymphopenia, elevated C-reactive protein (CRP), and very elevated troponins (Table 1). Cefazolin was discontinued and ceftriaxone was begun after drawing another blood culture, and subsequent microbiological testing was done (Table 2). The electrocardiogram (ECG) suggested pericarditis (generalized T-wave abnormalities), but an echocardiogram was normal. A small pleural effusion was seen on chest x-ray (CXR).

He was diagnosed with MIS-C (Brighton Collaboration level 1 criteria). Other diagnoses considered included Kawasaki disease (KD), toxic shock syndrome, *Mycoplasma pneumoniae* induced rash and mucositis or Stevens-Johnson Syndrome, post viral (non-SARS-CoV-2) peri-myocarditis, adenoviral infection, and MIS-V (Table 2).

He received intravenous immunoglobulins (IVIg), methylprednisolone, and acetylsalicylic acid (ASA). Blood cultures were negative. He did not meet criteria for a diagnosis of toxic shock syndrome. Antibiotic therapy was changed to azithromycin and was discontinued after a diagnosis of *Mycoplasma pneumoniae* induced rash and mucositis and Stevens-Johnson Syndrome was excluded (Table 2).

Within 24 hours, his clinical state and troponin levels rapidly improved. Serial ECGs, echocardiograms, and CXRs were normal. He went home in stable condition 2 weeks after admission. Troponins normalized and he remained well at 6 weeks post discharge, at which time ASA was stopped.

SARS-CoV-2 serological testing (drawn before IVIg administration) sent to the Manitoba Cadham Provincial Laboratory showed presence of antispike (S) (DiaSorin LIAISON SARS-CoV-2 S1 and S2 IgG assay) and absence of antinucleocapsid (NC) antibodies (Abbott ARCHITECT SARS-CoV-2 IgG assay).

CASE 2

A 14-year-old male presented to our hospital 2 weeks after case 1 with 2 days of abdominal distress (pain and vomiting), and 1 day of fever, truncal rash, and sore throat. Twelve days before the hospital visit, he had nasal congestion and got tested at a community testing center with a NP SARS-CoV-2 RT-PCR-NAAT (negative). He had no history of SARS-CoV-2 infection or known contacts with individuals with SARS-CoV-2 infection. He received his first (and only) dose of Pfizer-BioNTech's SARS-CoV-2 vaccine 4 weeks before his hospital visit. In the emergency department, he was diagnosed with scarlet fever and discharged on amoxicillin. A bacterial throat swab was not done but NP SARS-CoV-2 RT-PCR-NAAT was negative. He returned the following evening for generalized rash, extremity swelling, and worsening abdominal distress. Investigations revealed lymphopenia (1.2 [normal (N): 1.30–5.20] X 10^9/L]), elevated CRP (44 [N: 0.00–5.00] mg/L), and cholestatic hepatitis (Alanine aminotransferase: 190 [N: 0–18] U/L,

TABLE 1 Results for Laboratory Investigations Over Time (Case 1)

	Patient 1				
Test, Units (Normal Reference)	Admission to Wards	Admission to PICU	1 Day After IVIg and Methylprednisolone	At Hospital Discharge	Outpatient (Weeks After Hospitalization Discharge)
Troponin-1 high sensitivity (ng/L) (≤17.5)	11 368.2	6656.2	1430.3	106.6	9.0 (1)
Absolute lymphocyte count (X10/L)^9 (1.30–5.20)	1.23	0.52	0.79	4.96	2.67 (6)
Platelet count (X10/L)^9 (140–450)	235	232	265	769	325 (6)
Ferritin (μg/L) (6.0–110.0)	166.9	137.0	134.9	—	25.5 (6)
C-reactive protein (mg/L) (0.00–5.00)	103.5	128.7	201.5	13.7	0.3 (2)

Em-dashes indicate test was not performed.

TABLE 2 Microbiological Investigations for Both Cases

Test Performed	Result (Unit)	
	Patient 1	Patient 2
Blood bacterial cultures	No growth (2 after cephalexin; 1 after vancomycin and ceftriaxone)	No growth (2 before amoxicillin; 1 after)
Urine bacterial culture	No growth (after cephalexin)	No growth (no antibiotics)
Nasal SARS-CoV-2 RT-PCR[a]	Negative	Negative (×2)
Nasal BioFire PCR NAAT[b]: adenovirus, coronaviridae (229E, HKU1, NL63, OC43, SARS-CoV-2, human metapneumovirus, human rhinovirus or enterovirus, influenza (A, B), parainfluenza virus (1, 2, 3, 4), respiratory syncytial virus, *Bordetella pertussis*, *Bordetella parapertussis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*).	Negative	Negative
Nasal multiplex PCR respiratory virus panel[c]: adenovirus, coronaviridae (229E, OC43), human metapneumovirus, human rhinovirus or enterovirus, influenza (A, B), parainfluenza virus (1, 2, 3), respiratory syncytial virus.	Negative	—
Bacterial throat culture (while on vancomycin and ceftriaxone)	No β hemolytic streptococci isolated	—
Mycoplasma pneumoniae naso-oropharyngeal PCR	Negative (before azithromycin)	—
Adenovirus, enterovirus, parvovirus B19 blood PCR	Negative	—
Methicillin-resistant *Staphylococcus aureus* nasal PCR	Negative (before vancomycin)	—
Serology testing (Epstein-Barr virus IgG, IgM)	Negative	Negative
Cytomegalovirus (IgG, IgM)	Positive, negative	—
Parvovirus B19 IgM	Negative	—
HIV 1, 2 (antigen or antibody)	Negative	—
Syphilis EIA	Negative	—
Mononucleosis heterophile antibody	Negative	Negative
Leptospira IgG	Negative	—
Hepatitis A total antibody	—	Negative
Hepatitis B surface antibody or antigen	—	Immune or negative
Antistreptolysin O titer (IU/mL)	—	Negative
SARS-CoV-2 (anti-spike IgG, anti-NC IgG)	Positive, negative	Positive, negative

Serology tests were performed before administration of IVIg; —, test not performed.
[a] Cepheid Xpert Xpress SARS-CoV-2.
[b] BioFire Respiratory 2.1 (RP2.1) Panel (bioMérieux, Saint-Laurent, Quebec, Canada).
[c] An internally-validated RT-PCR test based on an assay described elsewhere [33,51].

γ glutamyl transferase : 268 [N: 0–40] U/L, direct bilirubin 13.1 [N: 1.7–8.6] μmol/L). Initial microbiological investigations were negative (Table 2) and an abdominal ultrasound was unremarkable. A diagnosis of "viral illness" was made and amoxicillin was discontinued.

Three days later, he returned with nonpurulent conjunctivitis, pruritus, and skin desquamation. He was well, but met 5 of 6 diagnostic criteria for KD, had marked lymphopenia (0.27×10^9/L), inflammation (CRP: 45 mg/L, erythrocyte sedimentation rate: 42 [N: 0–10] mm/hr, Ferritin: 127 [N: 6.0–110.0] μg/L), and improved hepatic panel tests (alanine aminotransferase 78 U/L, γ glutamyl transferase 158 U/L, direct bilirubin 3.9 μmol/L). A laboratory-developed multiplex RT-PCR respiratory virus assay[33] and a repeat NP SARS-CoV-2 RT-PCR-NAAT were negative. CXR, ECG, and echocardiogram were normal. Brighton Collaboration level 1 criteria for MIS-C were met. SARS-CoV-2 serology (drawn before IVIg administration using the same assay as case 1) detected anti-S but not anti-NC antibodies.

He was admitted and treated with IVIg and ASA. He quickly became afebrile and was discharged from the hospital 3 days later. On follow-up a week after discharge, mild dilatation of the right distal coronary artery was noted, which normalized 4 weeks later along with the remaining blood work. ASA was stopped after 6 weeks of treatment.

We concluded that both patients had MIS-V. Both will receive longitudinal subspecialty follow-up and will be exempted from further SARS-CoV-2 vaccination. Notably, patient 2 developed COVID-19 7 months after his MIS-V diagnosis but had mild symptoms (fever, sore throat, nasal congestion), and recovered.

DISCUSSION

MIS-C/A is a post-SARS-CoV-2 infection syndrome but its etiopathogenesis remains uncertain.[2,3,6,7] It has been suggested that the SARS-CoV-2 spike protein acts as a superantigen to promote a cytokine storm that manifests with the signs and symptoms of MIS-C/A.[34] With this in mind, surveillance for MIS-V has been ongoing with the Brighton Collaboration guidelines. Although these guidelines provide a recognition tool, they do not suggest

differentiating serology (antispike and NC antibodies) as a way to distinguish MIS-C/A and MIS-V.[7] Recently, differentiating serology has been suggested to help distinguish cases of MIS secondary to SARS-CoV-2 infection from cases of MIS secondary to vaccination in SARS-CoV-2 naïve individuals.[8,18,22,26,29,31]

Infection with SARS-CoV-2 leads to the formation of anti-S and anti-NC (among other) antibodies, but vaccination does not lead to anti-NC antibody production.[35–40] Diagnostic serology using different assays has shown variable results (sensitivity and specificity) in patients with SARS-CoV-2 infection.[35–43] Depending on the assay used, anti-NC antibody levels in adults decline at a much more rapid rate than anti-S antibody levels, so that the opportunity to establish an association of MIS-C/A to a preceding and previously undiagnosed SARS-CoV-2 infection diminishes over time.[39,41] In 1 small study, younger adults with milder symptoms of SARS-CoV-2 infection, and children regardless of symptom severity (including MIS-C), had low or even undetectable levels of anti-NC antibody (ThermoFisher Scientific assay).[35] However, studies that have used other assays have reported robust and lasting levels of anti-S and anti-NC antibodies in children more than 6 months post infection, and in all patients with MIS-C.[36–38] Our MIS-V patients were tested using an assay that has been shown to be quite sensitive in detecting anti-NC antibodies in adults 6 weeks after SARS-CoV-2 infection and in a large pediatric seroprevalence study where 50% were asymptomatic (indicating previous or unknown infection).[41–43] False negative anti-NC tests in 2 MIS-C/A patients is unlikely. Of note, no children (aged 5–19 years) in a recent United States seroprevalence study seroreverted from positive to negative anti-NC status during 6 months of testing.[38]

Rarely, peri-myocarditis occurs within a week post mRNA-based SARS-CoV-2 vaccination. This is more frequently observed in young adolescent and adult males and most often after the second dose.[44,45] Additionally, MIS-C/A generally occurs 2 to 6 weeks after SARS-CoV-2 infection.[2,3,6,7] Both patients presented with symptoms of MIS 2 to 6 weeks after being exposed to the SARS-CoV-2 spike protein from only 1 dose of the SARS-CoV-2 vaccine (similar timeline to how MIS-C/A presents after SARS-CoV-2 infection).

The diagnosis of MIS-V was entertained by the consultant services upon PICU admission (patient 1), and other diseases (including COVID-19) were ruled out (Table 2). Both patients presented at a time when school had been out for the summer for over a month and when there was no community surge of SARS-CoV-2 infections. Per the Brighton criteria, MIS-V should occur within 12 weeks of SARS-CoV-2 vaccination. We concluded, based on the local epidemiologic context and the differentiating serology results, that a postinfectious association was unlikely. Our 2 pediatric cases add to an expanding case series of MIS-V.[8,19–32] Other reported MIS-V cases are questionable in light of prior SARS-CoV-2 infections.[8–18]

Both of our cases reported could simply be caused by KD unrelated to SARS-CoV-2. However, their older age and marked lymphopenia are atypical for KD. The likelihood that our patients had bacterial sepsis is low but cannot be completely excluded given that both patients were being treated with antibiotics when cultures were obtained.

Interestingly, patient 1 developed late painful lymphadenopathy and expanding skin erythema ipsilateral to vaccine administration as a harbinger for MIS-V. This is similar to a case described by Nune et al.[19] Benign lymphadenopathy and even erythema are transiently seen early post SARS-CoV-2 vaccination.[46,47] Therefore a delayed (>3 weeks) reaction may suggest a novel clinical sign that heralds MIS-V for some.

In mid-autumn 2021, SARS-CoV-2 vaccination started in Canada and the United States for children aged 5 to 11 years – the group at highest risk for MIS-C. One could hypothesize that this age group would have similarly been at the highest risk of developing MIS-V if vaccine spike protein stimulates an abnormal cytokine response similar to what is observed in MIS-C, a rare event after natural SARS-CoV-2 infection. However, it is important to emphasize that vaccination with mRNA anti-SARS-CoV-2 vaccines decreases the risk of MIS-C following SARS-CoV-2 infection by over 90%.[48,49] We emphasize that MIS-V is an extremely rare adverse event of SARS-CoV-2 vaccination (estimated <1 per million from US surveillance), and has been reported infrequently despite the administration of >11 billion SARS-CoV-2 vaccinations worldwide[1,8,50]).

We extol the benefits of SARS-CoV-2 vaccination as the best means of preventing infection and safely achieving SARS-CoV-2 immunity. Nonetheless, surveillance and reporting of vaccine adverse events will inform us of rare emerging situations. Moreover, although recommendations for SARS-CoV-2 vaccination post MIS-C and peri-myocarditis exist, they are needed for individuals who may experience MIS-V. We recommend serological tests for both the anti-S and anti-NC antibodies to exclude recent SARS-CoV-2 infection in vaccinated

individuals who present with MIS-C/A symptoms. Finally, better understanding of pediatric SARS-CoV-2 serology is needed moving forward.

ABBREVIATIONS

ASA: acetylsalicylic acid
COVID-19: coronavirus disease 2019
CRP: C-reactive protein
CXR: chest x-ray
ECG: electrocardiogram
IVIg: intravenous immunoglobulins
KD: Kawasaki disease
MIS-C/A: multisystem inflammatory syndrome in children and adults
MIS-V: multisystem inflammatory syndrome post COVID-19 vaccine
NC: nucleocapsid
NP: nasopharyngeal
RT-PCR-NAAT: real time – polymerase chain reaction – nucleic acid amplification technique or test
S: spike
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
SJS: Stevens-Johnson syndrome
TSS: toxic shock syndrome

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