Multisystem inflammatory syndrome in an adult after SARS-CoV-2 infection

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A 60-year-old man presented to the emergency department with a 5-day history of mild shortness of breath, profound fatigue, anorexia and fever of up to 40°C. He also reported a lymph node enlargement over the left side of his neck, which had resolved 2 days before presentation. Four weeks earlier, he had tested positive for SARS-CoV-2 infection, confirmed by polymerase chain reaction (PCR) testing. He had no known comorbidities and had not received vaccination against SARS-CoV-2.

The patient's heart rate was 150 beats/min, with new-onset atrial fibrillation. His blood pressure was 106/67 mm Hg and his oxygen saturation on room air was normal. His respiratory examination showed good air entry bilaterally, without crepitus, crackles or wheezing on auscultation. He had bilateral nonpurulent conjunctivitis (Figure 1A), erythema and enlargement of his tongue (Figure 1B), bilateral pitting edema, and erythema of the distal portion of his toes bilaterally (Figure 1C). Lesions were not associated with any vesicles, erosive features, crusting, fissures, warmth, swelling or tenderness. A chest radiograph showed right lower lobe opacification. An electrocardiogram showed atrial fibrillation with rapid ventricular response, as well as nonspecific diffuse ST-T wave abnormality (Figure 2). Computed tomography (CT) of the patient's chest with contrast was negative for pulmonary embolism, but showed right heart enlargement and early pulmonary edema.

KEY POINTS

- Multisystem inflammatory syndrome is an uncommon but severe complication primarily described in children and adolescents after infection with SARS-CoV-2; it can also occur in older individuals.
- After recovery from SARS-CoV-2 infection, clinicians should suspect multisystem inflammatory syndrome in adults when a patient has prolonged fever, with multiorgan involvement.
- Elevated inflammatory markers support the diagnosis.
- Prompt initiation of therapy with immunomodulatory treatment can prevent severe outcomes.

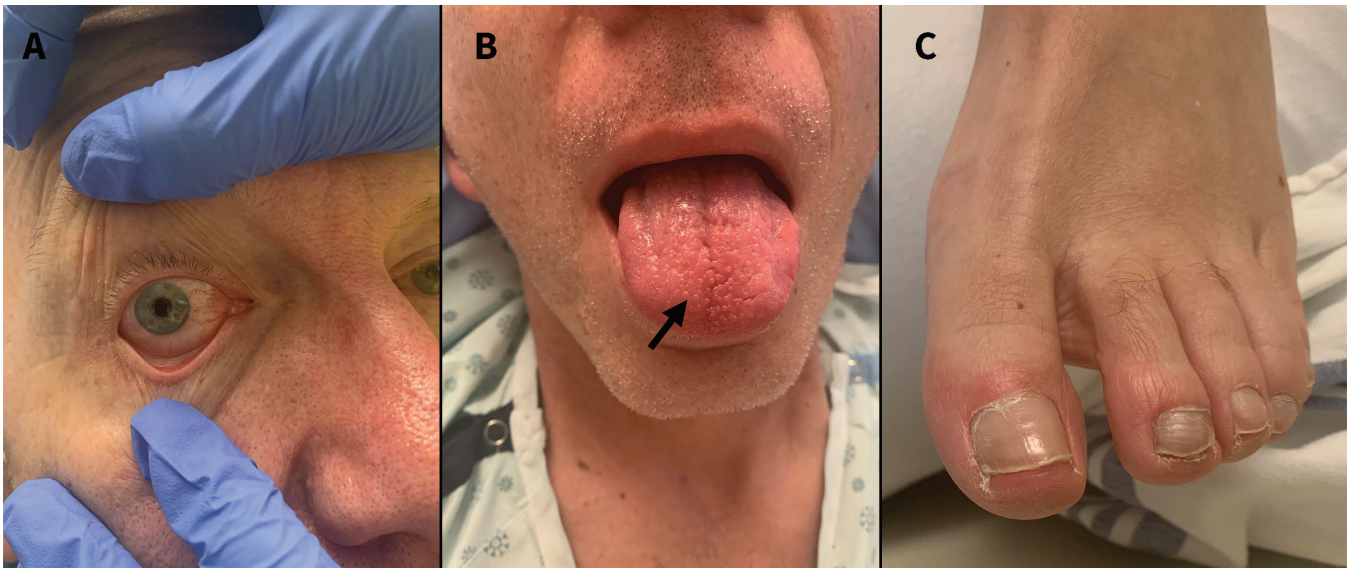

Figure 1: (A) Nonpurulent bilateral conjunctivitis in a 60-year-old man (only right eye shown). (B) Glossitis manifesting as nontender diffuse erythema and symmetric enlargement of the tongue. Small enanthem of the anterior third of the dorsum of the tongue (small erythematous bumps [arrow]) with hyperplastic fungiform and filiform papillae. (C) Left toes showing nonblanching maculopapular erythema. All images were taken before treatment was started.

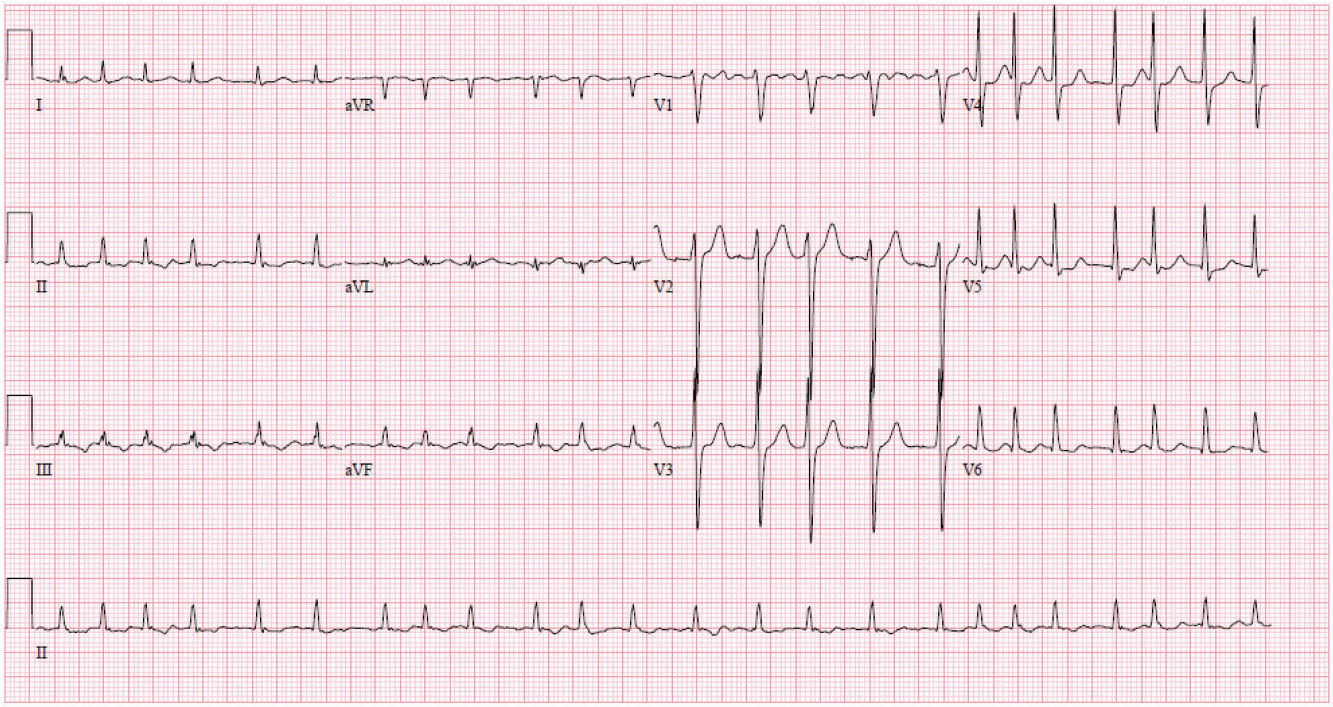

Figure 2: Electrocardiogram showing ventricular rate of 143 beats/min, atrial fibrillation with rapid ventricular response and diffuse nonspecific ST-T wave abnormality.

The patient was admitted and started on empirical piperacillin–tazobactam for possible bacterial pneumonia as a superinfection of his previous SARS-CoV-2 infection. Initial laboratory workup was notable for elevated C-reactive protein, D dimer, ferritin and leukocytosis with neutrophilia (Table 1[1]), indicating acute inflammation. His troponin level was elevated, and he had a substantially elevated pro–brain-type natriuretic peptide level. Blood cultures, urine culture and a respiratory viral panel were drawn and later returned negative. The patient also tested negative for HIV and hepatitis C and was immune to hepatitis B. An autoimmune workup collected before initiation of therapy was negative. COVID-19 immunoglobulin G serology was positive. A transthoracic echocardiogram, done after initiation of corticosteroids, showed normal sinus rhythm and normal right and left ventricular systolic and diastolic function with mild to moderate mitral regurgitation. There were no previous echocardiogram studies with which to compare these findings.

Given the patient's recent history of SARS-CoV-2 infection, fevers without localizing symptoms, oral mucosal changes, cervical lymphadenopathy, conjunctivitis and lower extremity changes, we suspected inflammatory post–COVID-19 syndrome. The presentation was similar to reported cases of an uncommon but severe complication in children and adolescents infected with SARS-CoV-2, called multisystem inflammatory syndrome in children (MIS-C), as well as to Kawasaki-like illness (Table 2[2–4]). Both the pediatric and adult rheumatology teams involved in the patient's care agreed that he met the preliminary Centers for Disease Control and Prevention (CDC) criteria for multisystem inflammatory syndrome in adults (MIS-A) and the criteria for complete Kawasaki disease, and he had multiple features consistent with MIS-C.

We started the patient on acetylsalicylic acid (ASA) and methylprednisolone and discontinued antibiotics. The next day, he received intravenous (IV) immunoglobulin. Within 24 hours of beginning treatment, he reported substantial improvement in his level of energy, shortness of breath and anorexia, with documented resolution of fever, improved conjunctivitis (Figure 3A), and decreased erythema of his tongue (Figure 3B), as well as reduction in inflammatory markers (Table 1). Repeat electrocardiogram was normal (Figure 4). The patient was discharged home 5 days after admission. Fourteen days after discharge, and again at a 6-week follow-up, he continued to improve clinically and biochemically (Table 1).

Discussion

Since the beginning of the SARS-CoV-2 pandemic, new information has been emerging on the trajectory of the disease. Examples of complications include venous thromboembolism, cardiovascular disease, acute kidney or liver injury, neurologic symptoms and post–COVID-19 syndrome.[5] Multisystem inflammatory syndrome in children was first described in April 2020 as a hyperinflammatory syndrome with features resembling Kawasaki disease.[2,3,6] As of May 3, 2021, 3742 children in the United States had been formally diagnosed with MIS-C according to the criteria outlined in Table 2, with 35 related deaths.[7]

In October 2020, the CDC published a review of 27 adult cases that fit the description of a multisystem inflammatory syndrome.[4] The preliminary case definition of MIS-A is shown in Table 2, and cases described to date have been in patients younger than 50 years. As we continue to learn about MIS-A, however, it is prudent not to assume any age limitation when considering the diagnosis, as our case suggests.[4,8–10]

Table 1: Laboratory data for 60-year-old man with multisystem inflammatory syndrome after SARS-CoV-2 infection*

Laboratory value	On admission	Day 1 after steroids	Day 2 after steroids, day 1 IVIG	Day 3 steroids, day 2 IVIG, discharge day	6 wk after discharge	12 wk after discharge	16 wk after discharge	Reference range
Hematology and chemistry								
C-reactive protein (mg/L)	**274.7**		**71.6**	**35.1**	< 0.6	< 0.6	1.5	0.0–8.0
Ferritin (ug/L)	**888**		**731**	**715**	154	82	58	300–500
D dimer (mg/LFEU)	**2.14**		**1.07**	**1.01**	**0.81**	**0.61**	**0.58**	< 0.50
INR	**1.3**			**1.3**				0.9–1.1
Leukocytes (10^9/L)	**16.2**	**15.0**	**18.6**	8.0	4.1	4.3	4.1	4.0–11.0
Neutrophils (10^9/L)	**14.0**	**13.3**	**16.7**	6.2	1.9	2.0		2.0–8.0
Platelet count (10^9/L)	248	375	**505**	**464**	202	218	179	150–400
Lymphocytes (10^9/L)	0.9	0.8	**0.6**	0.9	1.8	1.8		0.7–3.5
Hemoglobin (g/L)	**133**	**125**	**120**	**116**	154	151	156	137–180
Mean corpuscular vol. (fL)	93	92	93	93	96	96		82–100
Triglycerides (mmol/L)			2.11		1.65	1.50	1.67	0.00–1.70
ALT (U/L)	**41**				14	9	8	8–40
Creatinine level (μmol/L)	97	78	84	82	78	73	74	50–120
Troponin (ng/L)	**38**							0–13
NT-pro BNT (ng/L)	**2840**				70	63	< 50	0–300
Lactate (mmol/L)	2.2							0.5–2.2
Creatine kinase (U/L)	29							0–195
Lipase (U/L)	17							0–80
Lactate dehydrogenase (U/L)	199							100–235
Alkaline phosphatase (U/L)	128							30–145
Bilirubin total (μmol/L)	15							0–24
Glucose (random) (mmol/L)	7.1							3.3–11.0
Urine analysis								
Leukocytes	**Trace**							Negative
Nitrites	Negative							Negative
Protein	Negative							Negative
Glucose	Negative							Negative
Ketones	Negative							Negative
Blood	**Trace**							Negative
Leukocytes	**6–10**							0–5/hpf
Epithelial cells	**Moderate**							/hpf¶
Hyaline cast	**5–10**							/lpf¶
Microbiology data								
Blood cultures	Negative × 2							Negative
Urine culture	Negative							Negative
COVID-19 NAT†	**Negative and positive****	**Negative**						Negative
COVID-19 serology‡	**Positive**							Negative
Respiratory infection panel§	Negative							Negative
HIV serology	Negative							Negative
Hepatitis C antibody	Negative							Negative

Note: ALT = alanine aminotransferase, FEU = fibrinogen-equivalent units, hpf = high power field, INR = international normalized ratio, IVIG = intravenous immunoglobulin, lpf = low power field, NAT = nucleic acid amplification, NT pro-BNP = N-terminal pro–brain-type natriuretic peptide.
*Bolded values show abnormal results.
†All COVID-19 NAT were on nasopharyngeal swabs.
‡Immunoglobulin G serology testing.
§Respiratory infection panel tests for influenza (A and B), parainfluenza virus (1, 2, 3, 4), human coronaviruses (229E, NL63, OC43, HKU1), metapneumovirus, enterovirus, rhinovirus and adenovirus.
¶No reference range, as normally not seen.
**The patient had testing done as an outpatient on the day of admission (negative results) and then again when he went to the emergency department (positive results). For the positive nasopharyngeal swab, the cycle threshold value was 36 (very high), and insufficient for sequencing the spike protein and whole-genome sequencing. A higher cycle threshold value correlates with lower viral load[1] and the repeat nasopharyngeal swab the next day came back negative. This likely suggests that the positive result was from residual RNA from the previous SARS-CoV-2 infection 4 weeks earlier, rather than reinfection or persistent infection.

Table 2: CDC criteria for multisystem inflammatory syndrome in adults and children with SARS-CoV-2 infection and Kawasaki disease[2–4]

Characteristic	Multisystem inflammatory syndrome in adults	Multisystem inflammatory syndrome in children	Kawasaki disease
Case definition	Hospital admission of a patient aged ≥ 21 yr without evidence of severe respiratory illness and no alternative plausible diagnosis and involvement of 1 or more extrapulmonary organ systems: • Hypotension or shock • Cardiac dysfunction • Arterial or venous thromboembolism • Acute liver injury and laboratory evidence of acute inflammation	Patient aged < 21 yr with fevers > 38.0°C for ≥ 24 h, or report of subjective fever lasting ≥ 24 h with laboratory evidence of clinically severe illness requiring hospital admission with multisystem (≥ 2) organ involvement: • Cardiac • Renal • Respiratory • Hematologic • Gastrointestinal • Dermatologic • Neurologic	Complete Kawasaki disease: Fevers ≥ 5 d AND ≥ 4 principal clinical features • Extremity changes* • Rash† • Conjunctivitis‡ • Oral changes§ • Cervical lymphadenopathy (at least 1.5 cm in diameter, usually unilateral) Suspected incomplete Kawasaki disease: Fevers ≥ 5 d AND 2–3 compatible clinical criteria, or infants with fevers ≥ 7 d without other explanation.
Supportive investigations and laboratory finding	Elevated CRP, ferritin, D dimer or IL-6	Elevated CRP, ESR, fibrinogen, procalcitonin, D dimer, ferritin, lactate dehydrogenase or IL-6, elevated neutrophils, reduced lymphocytes and low albumin	CRP ≥ 3.0 mg/dL (or) ESR ≥ 40 mm/hr AND 1) Positive echocardiogram: From AHA criteria,[2] echocardiography is considered positive if any of 3 conditions are met: • Z score of left anterior descending coronary artery or right coronary artery ≥ 2.5; coronary artery aneurysm is observed; or ≥ 3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion • or Z scores in left anterior descending coronary artery • or right coronary artery of 2–2.5 OR 2) ≥ 3 supportive laboratory findings (anemia for age, platelet count ≥ 450 000 after 7th day of fevers, albumin ≤ 3.0 g/dL, elevated alanine aminotransferase, leukocytes ≥ 15 000/mm^3, or urine with ≥ 10 leukocyte/hpf)
SARS-CoV-2	Positive for current or previous SARS-CoV-2 infection (nucleic acid, antigen, or antibody) during admission or in the previous 12 wk	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test, or exposure to a suspected or confirmed COVID-19 case within 4 wk before onset of symptoms	NA

Note: AHA = American Heart Association, CDC = Centers for Disease Control and Prevention, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, hpf = high power field, IL-6 = interleukin 6, NA = not applicable, RT-PCR = reverse transcription–polymerase chain reaction.
*Erythema and edema of the hands and feet in acute phase or periungual desquamation in subacute phase, or both.
†Maculopapular, diffuse erythroderma or erythema multiforme-like.
‡Bilateral bulbar conjunctival injection without exudate.
§Erythema and cracking of lips, strawberry tongue, or erythema of oral and pharyngeal mucosa.

Many questions about MIS-A remain unanswered. Our patient did not present with the more commonly reported symptoms of stroke, shock or cardiac dysfunction requiring management in the intensive care unit.[4] This may be explained by our patient having a milder spectrum illness or by the prompt diagnosis and interventions he received. Several features of our patient's presentation raised early concern for MIS-A or a Kawasaki-like illness. Our patient met the diagnostic criteria for complete Kawasaki disease (5 d of fever and 4 out of 5 clinical features: extremity changes, conjunctivitis, oral changes and cervical lymphadenopathy; our patient did not have a rash) and MIS-C (except for age). However, evidence of recent SARS-CoV-2 infection and the age of the patient made MIS-A more likely as the cause.

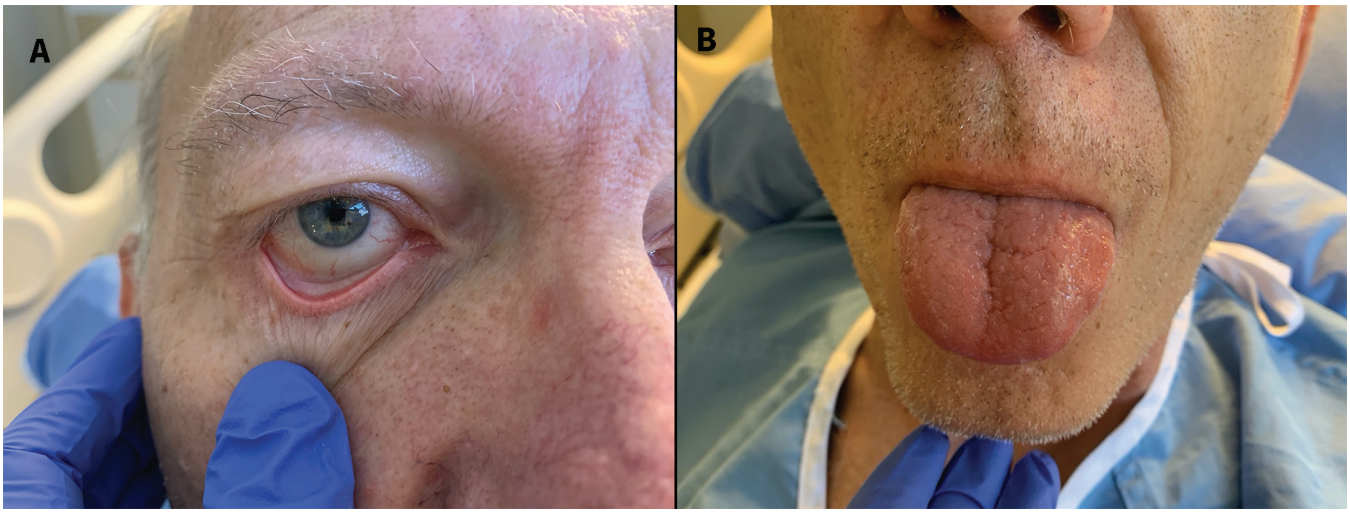

Figure 3: Near-complete resolution of the patient's conjunctivitis (A) and improvement in glossitis, and near-complete resolution of enanthem of the tongue (B) on day 1 after initiation of high-dose steroids.

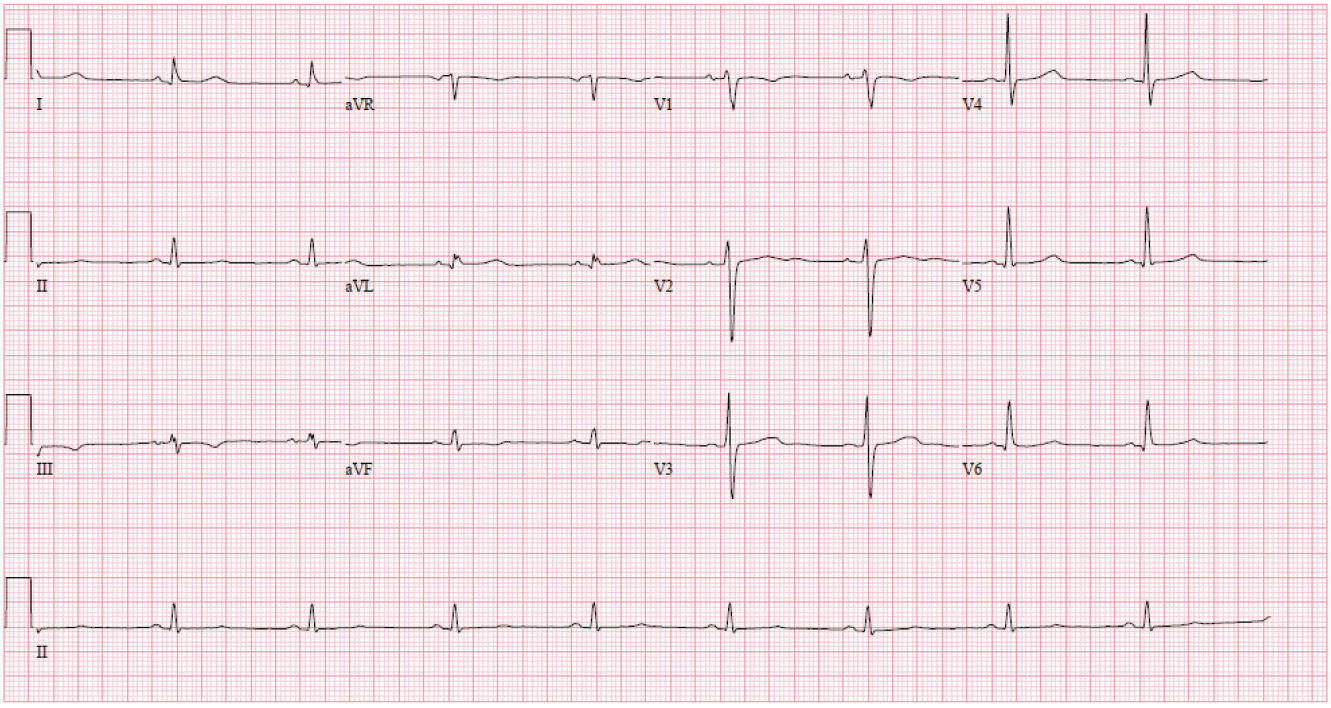

Figure 4: Sinus bradycardia of 54 beats/min and otherwise normal electrocardiogram with resolution of atrial fibrillation and ST-T changes prior to discharge.

The American College of Rheumatology published a review comparing and contrasting features between MIS-C and Kawasaki disease, and it reported that about 25%–50% of patients who fulfilled criteria for MIS-C also met the full diagnostic criteria for Kawasaki disease.[11] Two differences between the conditions were ethnic distribution (highest among people of Japanese descent in patients with Kawasaki disease) and age distribution (usually younger than 5 yr for Kawasaki disease, and a broader range, from 3 months to 21 yr, for MIS-C).[2,11,12]

Standardized treatment for MIS-A is yet to be established. Our patient improved with 3 days of methylprednisolone 125 mg/d, then an oral prednisone taper of 50 mg/d for 3 days, followed by a tapering dose decreasing by 10 mg/d every 3 days until he was weaned off steroids (for a total oral course of 15 d). He received IV immunoglobulin 1 g/kg/d for 2 days and oral ASA 325 mg/d until clinical resolution, as evidenced by absence of fevers and normal C-reactive protein. This treatment was based on expert opinion and up-to-date evidence on Kawasaki disease and MIS-C.[2,6,8,11–13] The American College of Rheumatology recommends a step-wise approach to immunomodulatory treatment in MIS-C with IV immunoglobulin or glucocorticoids considered as first-tier agents,[11] and the American Heart Association recommends high-dose

immunoglobulin (2 g/kg) as a single IV dose for treatment of Kawasaki disease.[2] Although the patient did not have clinically significant thrombocytosis, we prescribed a short course of high-dose ASA to prevent thrombosis and coronary artery aneurysms.[11]

The optimal follow-up for MIS-A is currently unknown, but experts support monitoring for coronary artery dilatation and aneurysm, as with MIS-C- or Kawasaki-like illness.[2,11] Unlike in children, for whom echocardiography is the imaging choice for coronary artery diameter, the visualization of coronary arteries becomes progressively more difficult as body size increases, making CT coronary angiography preferred for surveillance in adults.[2] Our patient's coronary angiogram showed triple-vessel coronary artery disease without clinically important stenosis and no coronary aneurysms or findings suggestive of coronary artery vasculitis. At time of writing, a repeat CT to visualize coronary artery calibre is still pending for 6 months after discharge.

Unlike for MIS-C, there is currently no requirement to report cases of MIS-A to provincial or state authorities, but this should be encouraged to facilitate research and improve patient outcomes.[6]

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