



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

An adult with Kawasaki-like multisystem inflammatory syndrome associated with COVID-19

Multisystem inflammatory syndrome in children (MIS-C) is a newly described condition associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure that is reminiscent of both Kawasaki disease and toxic shock syndrome. A recent surge in this disease has prompted health advisories by the US Centers for Disease Control and Prevention (CDC),¹ the Royal College of Paediatrics and Child Health,² and WHO.³ As SARS-CoV-2 spreads and awareness of MIS-C grows, the number of reported cases continues to increase. As of June 30, 2020, 230 paediatric MIS-C cases and two deaths have been reported in New York state, USA.

Here we describe the case of an adult male who presented to NYU Langone Health in New York City, NY, USA, with a Kawasaki-like multisystem inflammatory syndrome in the setting of SARS-CoV-2 infection, similar to what has been reported in children. Although we caution readers from making broad conclusions from this single case, we report this presentation to heighten awareness of the possibility of a COVID-19-associated Kawasaki-like multisystem inflammatory condition in adults.

The patient is an Hispanic man, aged 45 years, without any past medical history (body-mass index 26.6 kg/m²) who presented to the emergency department with 6 days of fever, sore throat, diarrhoea, bilateral lower extremity pain, conjunctivitis, and diffuse exanthem after having cared for his wife with SARS-CoV-2 infection 2 weeks earlier. The patient denied respiratory symptoms on presentation, although his respiratory rate was elevated (25–33 breaths per min), and he had

not taken any medications before symptom onset. A SARS-CoV-2-specific RT-PCR was positive, and chest x-ray showed diffuse interstitial haziness typical of COVID-19. Vital signs throughout admission were notable for persistent fever despite antipyretics (maximum temperature 39.4°C), hypotension (systolic blood pressure 80–90 mm Hg), tachycardia with episodes of atrial fibrillation with rapid ventricular response, and minimal oxygen requirements (1–2 L/min by nasal cannula). Physical examination revealed bilateral, non-exudative conjunctival injection, tender left neck swelling with palpable lymphadenopathy, periorbital oedema with overlying erythema, lip cheilitis, and targetoid erythematous papules and plaques with central duskiness involving the back, palms, neck, scalp, anterior trunk, and upper thighs. Images were obtained with patient consent and are shown in the appendix.

Complete blood counts showed leukocytosis (11 600–16 500 white blood cells per μ L), with lymphopenia (0–700 lymphocytes per μ L), neutrophilia (10 100–15 000 neutrophils per μ L), atypical lymphocytosis (2% atypical lymphocytes), and increased band neutrophils (2–16% band cells), whereas comprehensive metabolic panels showed hyponatraemia (serum sodium 124–135 mmol/L) and elevated hepatic enzymes (aspartate aminotransferase [AST] 96–198 U/L; alanine aminotransferase 78–133 U/L). Notably, his platelet counts were normal. Inflammatory markers were elevated, including an erythrocyte sedimentation rate of 120 mm/hr, ferritin of 21 196 ng/mL, C-reactive protein of 546.7 mg/L, D-dimer of 2977 ng/mL, procalcitonin of 31.79 ng/mL, and interleukin-6 (IL-6) of 117 pg/mL. Troponin was elevated (peak 8.05 g/mL), as was B-type natriuretic peptide (170 pg/mL). HIV-1 and HIV-2 antibodies and bacterial blood cultures were negative.

Contrast-enhanced CT of the neck revealed inflammation and oedema involving the bilateral lower eyelid and pre-septal space, as well as suboccipital reactive lymphadenopathy (largest lymph node measuring 1.8 cm). Electrocardiogram demonstrated ST elevations in the anterolateral leads, triggering left heart cardiac catheterisation, which showed angiographically normal arteries. A subsequent transthoracic echocardiogram displayed global hypokinesis of the left ventricular wall with a mild to moderately reduced ejection fraction of 40%. A slit lamp examination of both eyes confirmed diffuse conjunctivitis with chemosis, as well as the presence of inflammatory cells within the anterior chamber, indicative of uveitis. A 4-mm punch biopsy of the skin was performed on a papule on the back, with histology revealing rare intraepithelial collections of neutrophils with necrotic keratinocytes and a sparse interstitial, mixed-cell dermal infiltrate with vacuolar interface changes.

Given the patient's constellation of signs (fever for more than 5 days, erythema multiforme-like rash, bilateral non-exudative conjunctivitis, erythema or cracking of the lips, unilateral cervical lymphadenopathy measuring more than 1.5 cm in diameter), he met American Heart Association (AHA) criteria for Kawasaki disease,⁴ and he was diagnosed with Kawasaki-like multisystem inflammatory syndrome associated with COVID-19. The patient underwent therapy with therapeutic dose low molecular weight heparin, intravenous immunoglobulin (2 g/kg) over 2 days, and a single intravenous dose of the IL-6 inhibitor tocilizumab (400 mg). He was also enrolled in two randomised controlled trials (NCT04369742, NCT04364737) for COVID-19 treatment. He did not require vasopressor support or an intensive care unit level of care and was maintained on minimal oxygen requirements. Following intravenous



Published Online
July 10, 2020
[https://doi.org/10.1016/S0140-6736\(20\)31526-9](https://doi.org/10.1016/S0140-6736(20)31526-9)

For NY state data on Childhood Inflammatory Disease Related to COVID-19 see

<https://coronavirus.health.ny.gov/childhood-inflammatory-disease-related-covid-19>

See Online for appendix

Submissions should be made via our electronic submission system at <http://ees.elsevier.com/thelancet/>

immunoglobulin and tocilizumab administration, he showed clinical improvement with defervescence, resolution of tachycardia and tachypnoea, improvement in rash, cheilitis, and conjunctivitis, and down-trending inflammatory markers. He was discharged 9 days after hospital admission. Upon outpatient follow-up, he had complete resolution of his diffuse cutaneous eruption and conjunctivitis as well as a normal repeat echocardiogram.

Our patient's clinical presentation and course share a striking resemblance to the newly characterised MIS-C.⁵⁻⁹ With the exception of his age, our patient meets the current case definition for MIS-C according to both the CDC¹ and WHO.³ Although it is postulated that children experience a Kawasaki-like MIS-C as a post-infectious phenomenon, it remains unclear whether our patient had an asymptomatic SARS-CoV-2 infection in the preceding weeks, with a persistent positive RT-PCR result, or whether his hyperinflammatory disorder occurred as a direct manifestation of acute infection. If the latter is true, it is notable that he did not experience the hypoxic respiratory failure most frequently associated with moderate to severe COVID-19, despite his abnormal chest x-ray findings.

Emerging reports have revealed a pattern of clinical differences distinguishing MIS-C from classic Kawasaki disease.⁵⁻⁹ Notably, although our patient's presentation met AHA criteria for Kawasaki disease, he also exhibited many MIS-C-related features such as a predominance of gastrointestinal symptoms, generalised extremity pain, and prominent cardiac dysfunction, and his cardiac findings (elevated cardiac enzymes and left ventricular hypokinesis with a reduction in ejection fraction) resemble findings of myocarditis recently described in MIS-C.¹⁰ Furthermore, our patient's palmar lesions are distinct from the acral erythema and swelling with subsequent desquamation typically

seen in Kawasaki disease, and his diffuse conjunctivitis was not limbic-sparing. Biochemically, he demonstrated markedly elevated C-reactive protein, neutrophilia, and lymphopenia, which are more consistent with MIS-C than with classic Kawasaki disease.^{7,8}

Although the cause of Kawasaki disease remains unknown, the most widely accepted theory is an aberrant immune response to an infectious trigger. Emerging reports depict the phenotype of MIS-C as a combination of Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome (or haemophagocytic lymphohistiocytosis),⁵⁻⁹ all syndromes of dysregulated immune responses. Our patient's presentation also included features typical of these different multisystem inflammatory syndromes. Many of his laboratory findings were consistent with haemophagocytic lymphohistiocytosis (markedly elevated ferritin, elevated triglyceride and AST), although he did not have organomegaly and cytopenias typically observed with this syndrome.¹¹ His skin biopsy findings had features typical for Kawasaki disease (non-specific sparse inflammatory infiltrate) and features suggestive of toxic shock syndrome (few intraepidermal neutrophils with necrotic keratinocytes), providing histological support for a distinct inflammatory syndrome. MIS-C has several features resembling Kawasaki disease, but it is important to distinguish MIS-C from classic Kawasaki disease. Diagnostic distinction from classic Kawasaki disease might have meaningful implications: whereas treatments targeting IL-6 are currently being investigated among therapeutic options for COVID-19-associated hyperinflammation, the IL-6 inhibitor tocilizumab might provoke the development of coronary artery aneurysms in patients with classic Kawasaki disease.¹²

Given the recent recognition and evolving understanding of MIS-C, standardised treatment guidelines have yet to be established. It is unclear

to what degree our patient responded to intravenous immunoglobulin versus tocilizumab, and as treatment algorithms are designed for MIS-C, it will be important to monitor patients receiving tocilizumab for potential development of coronary artery aneurysms.

We highlight this case to draw attention to the presence of a Kawasaki-like multisystem hyperinflammatory syndrome in an adult with SARS-CoV-2 infection and note clinical improvement following administration of anticoagulation, intravenous immunoglobulin, and tocilizumab. We emphasise the importance of multidisciplinary care and recognition of the possibility of this syndrome across specialties, as provision of care for our patient necessitated coordinated efforts between specialists in emergency medicine, internal medicine, infectious diseases, cardiology, rheumatology, dermatology, and ophthalmology. Although this patient's Kawasaki-like presentation bears a strong resemblance to MIS-C, as recently described in paediatric cohorts, we acknowledge that this isolated case may represent a spurious finding rather than an instance of a larger disease pattern. Nevertheless, we present this case to raise awareness of a potential MIS-C-like condition in adults. Further investigation is warranted to better elucidate the possibility of an MIS-C analogue syndrome in adults as we continue to expand our understanding of SARS-CoV-2-related syndromes.

SS and MG contributed equally. We declare no competing interests.

Sheila Shaigany, Marlis Gnirke, Allison Guttmann, Hong Chong, Shane Meehan, Vanessa Raabe, Eddie Louie, Bruce Solitar, *Alisa Femia
alisa.femia@nyumc.org

Ronald O Perelman Department of Dermatology (SS, SM, AF), Ronald O Perelman Department of Emergency Medicine (MG, HC, BS), Division of Rheumatology, Department of Medicine (AG), and Division of Infectious Diseases & Immunology, Department of Medicine (VR, EL), New York University Grossman School of Medicine, New York, NY 10016, USA

- 1 Centers for Disease Control and Prevention Health Alert Network. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). May 14, 2020. <https://emergency.cdc.gov/han/2020/han00432.asp> (accessed June 12, 2020).
- 2 Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. May 1, 2020. <https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf> (accessed May 6, 2020).
- 3 WHO. Multisystem inflammatory syndrome in children and adolescents with COVID-19. May 15, 2020. <https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19> (accessed June 12, 2020).
- 4 McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017; **135**: e927–99.
- 5 Riphagen, S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; **395**: 1607–08.
- 6 Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. *J Pediatric Infect Dis Soc* 2020; published online May 28. <https://doi.org/10.1093/jpids/piaa069>.
- 7 Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020; **395**: 1771–78.
- 8 Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020; published online June 8, 2020. <https://doi.org/10.1001/jama.2020.10369>.
- 9 Punapattanapong S, Brooks EB. New spectrum of COVID-19 manifestations in children: Kawasaki-like syndrome and hyperinflammatory response. *Cleve Clin J Med* 2020; published online June 3. <https://doi.org/10.3949/ccjm.87a.ccc039>.
- 10 Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation* 2020; published online May 17. <https://doi.org/10.1161/circulationaha.120.048360>.
- 11 Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033–34.
- 12 Nozawa T, Imagawa T, Ito S. Coronary-artery aneurysm in tocilizumab-treated children with Kawasaki's disease. *N Engl J Med* 2017; **377**: 1894–96.