Emerging Evidence on COVID-19

Evidence Brief of Multisystem Inflammatory Syndrome in Adults (MIS-A)

Introduction

What are the epidemiological and clinical characteristics of multisystem inflammatory syndrome in adults (MIS-A)?

Numerous cases of Multisystem Inflammatory Syndrome in Children (MIS-C) have been described worldwide since the beginning of the COVID-19 pandemic. More recently, clinical features similar to MIS-C have been described in adults. A definition for Multisystem Inflammatory Syndrome in Adults (MIS-A) does not exist; therefore, case selection has been based on the definition of MIS-C excluding the age criteria.

There are at least four definitions of MIS-C. The World Health Organisation (WHO) (1) definition of MIS-C includes children and adolescents below the age of 19, a positive COVID-19 test or likely contact with COVID-19 positive individuals and several signs and symptoms, which include fever lasting for more than 3 days and two of the following:

- Rash
- Bilateral non-purulent conjunctivitis
- Signs of muco-cutaneous inflammation signs (in the mouth or on the hands or feet)
- Hypotension or shock
- Myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including echocardiogram findings or elevated Troponin/NT-proBNP)
- Coagulopathy (increased prothrombin time, activated partial thromboplastin time, elevated D-Dimers)
- Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

There must be laboratory evidence of inflammation, such as an elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or procalcitonin, and other obvious microbial causes of inflammation such as bacterial sepsis, staphylococcal or streptococcal shock syndromes must be excluded as a plausible diagnosis.

The Centers for Disease Control (CDC) (2) Health Advisory defines an MIS-C case as an individual below the age of 21 presenting with fever lasting for more than 24 hours and laboratory evidence of inflammation such as an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin. The patient must also have an evidence of clinically severe illness requiring hospitalization, with multisystem organ involvement and no alternative plausible diagnoses. The patient must be positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or must have been exposed to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

According to the Royal College of Paediatrics and Child Health (RCPCH) (3) a case MIS-C is a child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with persistent fever over 38.5 °C, most of the time, oxygen requirement, hypotension, and other additional features. The laboratory tests must show abnormal fibrinogen, absence of potential causative organisms (other than SARS-CoV-2), high CRP, high D-Dimers, high ferritin, hypoalbuminaemia, and/or lymphopenia. This may include children fulfilling full or partial criteria for Kawasaki disease. Any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus must be excluded. The SARS-CoV-2 PCR testing may be positive or negative.

Finally, the Canadian Pediatric Society (CPS) (4) defines MIS-C as the presence of high and persistent fever (≥3 days) unexplained by other causes. Fever together with laboratory evidence of marked systemic inflammation and temporal association with COVID-19 having been present in the community should raise the index of suspicion for MIS-C. The clinical presentations described to date have included fever with hyperinflammation; a Kawasaki-like syndrome; and shock or toxic shock-like states, with signs of hypotension and poor perfusion related to severe myocardial dysfunction. GI distress, that may or may not occur with neurological signs such as neck stiffness, altered mental status, or lethargy.

This review describes the first reported cases of MIS-A in order to identify common features of the disease and raise the awareness of clinicians regarding the appropriate management of cases. It summarizes literature until November 13, 2020.

Key Points

Demographic characteristics, COVID status, and comorbidities

- All nine MIS-A cases described were relatively young adults, with a median age of 31 years and IQR [25-45]. Six cases (67%) were male (5-10) and three cases (33%) were female (11-13). Six out of nine studies reported ethnicity. Three cases (33%) had African origins (5,7,12), two cases (22%) were of Hispanic origin (10,13) one (11%) was Caucasian (9). In the three remaining cases (33%) ethnicity was not reported.
- All nine cases underwent a RT-PCR test. Five cases (56%) had negative RT-PCR results, but positive serology tests (5-7,9,13). One case (11%) had a negative PCR result with a history of a positive RT-PCR result a few days earlier (12). Results of RT-PCR swab test and serology were both positive in one case (11%)(11). The two remaining cases (22%) had a positive RT-PCR test but did not undergo serology test (8,10).These findings suggested that MIS-A generally occurred (n=6; 67%) during viral clearance.
- Seven out of nine studies reported on comorbidity. Two cases (22%) had both hypertension and obesity (5,12) of which one of them also had diabetes (12). Five cases (56%) had no known comorbidity (8,10,13) and in two (22%) the comorbidity status was not reported.

Clinical and laboratory findings

- All cases had fever; seven cases had fever for 5-7 days prior to hospital admission; two cases did not report on the duration of fever (4,11).
- The majority of cases (n=8; 89%) had digestive symptoms upon admission. The most common digestive symptom was diarrhea (n=6; 67%) followed by vomiting (n=4; 44%), rash (n=4; 44%) and neck pain (n=4; 44%) with or without lymphadenopathy. One case (11%) had bilaterally enlarged parotid glands.
- All cases had multi-organ involvement. Cardiovascular system involvement was the most common (n=7; 78%)(5,6,8-11,13), represented via echocardiography by acute myocardial dysfunction with left ventricular systolic dysfunction and pericardial effusion (n=4, 44%), ventricular fibrillation, dilated inferior vena cava (n=2; 22%) with overloaded right ventricular pressure and mild enlargement of the main pulmonary artery and hyperkinetic left ventricle (n=1; 11%).
- All cases had elevated inflammatory markers. The most common elevated inflammatory marker was C-reactive-protein CRP (n=8; 89%) (5,6,8-11), followed by D-dimers (n=6; 67%) (6,8,10-13) and troponin (n=6; 67%) (5-10). Lymphopenia was also common (n=6; 67%) (7-11).

Treatment and outcome

- Intravenous immunoglobulin (n=3; 33%) (7,10,11), prednisolone (n=3; 33%) (7,8,13) and aspirin (n=3; 33%) (6,11,13) were the most common treatments given. Immunoglobulin was not given in one case because the patient responded well to aspirin. In another case, prednisolone was not given because the patient had a concomitant tracheal aspiration positive for *Enterobacter aerogenes* that was then treated with Trimethoprim Sulfamethoxazole (5). One patient did not receive any specific treatment; as she died while being evaluated for admission and could not be resuscitated (12).
- Seven cases (77%) survived hospitalization. Three cases (33%) had severe symptoms, requiring admission to the ICU but recovered (5,6,11). Two cases (22%) presented with hypotension and tachycardia upon admission but did not require admission to intensive care unit (ICU) and recovered (9,10,13). One case (11%) presented with vasoplegic shock upon admission, had a length of stay (LOS) in hospital of 8 days and recovered under treatment (9). One case (11%) did not demonstrate shock-like signs and recovered under treatment (8). One case died in hospital (11%). The case that died had been previously hospitalized for COVID-19 and discharged 12 days earlier, upon readmission she presented with rapid onset of fever and developed hemodynamic instability and ventricular fibrillation and could not be resuscitated. The outcome of one patient (11%) was not reported (7).

Overview of the Evidence

Nine case reports of MIS-A were identified in the literature. Five cases were identified in the United-States, two in France and two in the United Kingdom. The case descriptions revealed similarities in clinical features such as occurrence after viral clearance, fever, digestive symptoms, cardiac involvement and elevated inflammatory markers. All cases where hospitalized, two required admission to the ICU and one died. The most common treatments were intravenous immunoglobulin, prednisolone and aspirin. The findings suggest early recognition of MIS-A may improve outcome.

Limitations

Only case reports were identified in this review. Although case reports can help in the identification of new trends or diseases, they have a number of limitations. They are difficult to compare since cases have different backgrounds and are not representative of a population. Therefore these findings are very preliminary; as more studies become available we will learn more about the common epidemiological and clinical characteristics of this condition.

Data gaps

It appears MIS-A is a rare complication of COVID-19 disease. Studies to date include a total of 9 MIS-A cases and were limited to three countries, United-States, France and the United-Kingdom. There is no definition of MIS-A; using the MIS-C case definition (minus age) has challenges as there are at least 4 definitions and in the cases reviewed, how they met the case definition was not always clear. For example, the authors did not always specify how they excluded all other potential causes of the multi system inflammatory syndrome and the duration of fever or presence of comorbidities were not always reported. More systematic description of ethnicity and Severity of the disease is needed. For example, when hypotension was identified, the presence or not of shock-like syndrome was not always specified.

A case definition for MIS-A is needed to help standardize reporting. Future studies of MIS-A are also indicated to learn more about this disease and the effectiveness of treatment.

Table: Summary of case reports on Multisystem Inflammatory Syndrome in Adults (MIS-A) (n=9)

STUDY	METHOD	KEY OUTCOMES
Case reports (n=9)		
Boudhabhay (2020) (5) Case report France 16 Sept 2020*	A case of MIS-A was described, including clinical and laboratory characteristics, treatment and outcome. The case met only RCPCH definition, since the duration of the fever was not specified.	*Demographic characteristics and past medical history* • The patient was a 46 years old male of African descent. • History of hypertension and obesity *MIS-A characteristics* Fever and other signs and symptoms • Admitted for hypertensive emergency (189/123 mmHg) and fever (duration not reported). Evidence of coagulopathy and renal involvement • Acute kidney injury (AKI): Serum creatinine (sCr) level was 169µmol/L associated with 1g per day proteinuria, aseptic pyuria, no hematuria and low natriuresis (< 20mmol/L) • Renal biopsy light microscopy revealed typical lesions of thrombotic micro angiopathy TMA including fibrin thrombi within glomeruli and myxoid intimal alterations of arterioles and small-to-medium sized renal arteries • On day four the patient presented evanescent facial erythema and developed acute myocardial dysfunction with reduced left ventricular ejection fraction to 40%, pericardial effusion. On day five the patient presented a neurological impairment. Abnormal supratentorial periventricular MRI signals responsible for a restriction of the diffusion due to an acute vasculitis. PCR and serology for SARS-CoV-2 • RT-PCR negative, IgM negative and IgG positive (no previous COVID-19 symptoms were reported) Inflammatory markers • C-Reactive protein (CRP) level was 312 mg/L • Thrombocytopenia: neutrophil count was 18.7 G/L • High sensitive Troponin (hsTroponin) elevation

		Treatment • No immunosuppressive treatment was introduced because of concomitant tracheal aspiration positive for *Enterobacter aerogenes* treated with trimethoprim sulfamethoxazole. • Dobutamine and renal replacement therapy (RRT). • Specific complement inhibition with Eculizumab therapy (900mg) *Severity and outcome* • On day 5 hospitalization neurological impairment appeared with coma leading to intubation and mechanical ventilation. • The patient was discharged after 30 days in hospital.
Chowdhary (2020) (6) Case report United Kingdom Sept 2020*	A case of MIS-A was described, including clinical and laboratory characteristics, treatment and outcome. The case met RCPCH, CDC, CPS and WHO definitions.	*Demographic characteristics and past medical history* • 26 years old male • Ethnicity was not reported. • The presence or absence of comorbidity was not reported. • Exposure to SARS-CoV-2 was reported. *MIS-A characteristics* Fever and other signs and symptoms • Patient was admitted after five days of fever • Dry cough, myalgia, diarrhoea, vomiting, and abdominal pain • Patient was hypotensive and hypoxic upon admission One or more organ involved (pulmonary, cardiac, digestive) • Computed tomography (CT) showed bilateral pulmonary basal ground-glass changes and bowel oedema • Initial transthoracic echocardiography demonstrated severe left ventricular (LV) systolic dysfunction with pericardial effusion. • CT of the abdomen demonstrating mesenteric lymphadenopathy and small bowel oedema PCR and serology for SARS-CoV-2 • RT-PCR negative, IgG and IgM positive serology Inflammatory markers • C-reactive protein (CRP) 419 mg/L • Ferritin 3275 lg/L (<322 µg/L)

		• Procalcitonin 164 lg/L (<50 µg/L) • Troponin I 2030 ng/L (<57 ng/L) • D-dimer 2722 ng/mL (<220 ng/mL) Treatment • Vasopressor therapy, high-dose aspirin, and broad-spectrum antibiotics in intensive care • Immunomodulatory therapy was not given due to the good response to aspirin. *Severity and outcome* • The case was admitted to ICU and recovered over 10 days.
Fox (2020) (12) Case report United States July 2020*	A case of MIS-A was described, including clinical and laboratory characteristics, treatment and outcome. The case met only RCPCH definition, since the duration of the fever was not specified.	*Demographic characteristics and past medical history* • The patient was a 31 years old African American female. • Comorbidities: hypertension with lisinopril, diabetes with poor adherence to metformin and glizide, and obesity (BMI=36.1 kg/m^2) • She had been discharged 12 days earlier after a hospitalization for COVID-19 disease with a positive RT-PCR. *MIS-A characteristics* • Admitted for sudden fever 39.8 ºC (duration not specified), tachycardia 120 beats/min, left-sided neck pain, nausea and vomiting Inflammatory markers • D-dimer level of 2.48 nmol/L • C-reactive protein levels 165 mg/L then 580 mg/L • Ferritin level, 114.2 µg/L • Lactic acid level, 3.1 mmol/L • Lymphopenia One or more organ involved (pulmonary, cardiac, parotids, renal) • Computed tomography scan of her neck showed bilaterally enlarged parotid glands and swelling in the posterior nasopharynx to oropharynx. • Computed tomography scan of her chest showed interval improvement of bibasilar ground-glass opacities, with cervical and anterior mediastinal lymphadenopathy

		• Creatinine level 202.44 µmol/L; glomerular filtration rate 32 mL/min/1.73 m^2 PCR and serology for SARS-CoV-2 • RT-PCR was positive 12 days prior to re-admission MISC-A, RT-PCR was negative at re-admission and serology was not performed *Treatment, severity and outcome* • Patient developed hemodynamic instability and ventricular fibrillation during evaluation for hospital admission and died.
Jones (2020)(7) Case report United Kingdom The date the study was conducted was not reported Sept 2020*	A case of MIS-A was described, including clinical and laboratory characteristics, treatment and outcome. The case met RCPCH, CDC, CPS and WHO definitions.	*Demographic characteristics and past medical history* • The case was a 21 years old male of African descent. • The presence or absence of comorbidity was not reported. *MIS-A characteristics* Fever and other signs or symptoms • 6 days of fever • Admitted for abdominal pain associated with constipation, anorexia • Transient maculopapular palmar rash 4 days into illness • Non-exudative conjunctivitis, • Cervical lymphadenopathy, • Cracked lips, and prominent lingual papillae PCR and serology for SARS-CoV-2 • RT-PCR negative and serology was strongly positive, suggesting recent exposure to SARS-CoV-2 One organ or more involved • Rash • Conjunctivitis • Cervical lymphadenopathy • Cracked lips, and prominent lingual papillae Inflammatory markers • Lymphopenia • Elevated inflammatory and elevated troponin T • Other infective and inflammatory conditions were excluded

		Treatment • Intravenous immunoglobulin • Methylprednisolone *Severity and outcome* • The patient was discharged after a length of stay in hospital of 8 days.

Kofman(2020) (11)
 	
Case report
 	
United States
 	
The date the study was conducted was not reported
 	
Sept 2020*
	A case of MIS-A was described, including clinical and laboratory characteristics, treatment and outcome.
	
	The case met RCPCH, CDC, CPS and WHO definitions.
		Demographic characteristics and past medical history
		• The case was a 25 years old female.
		• Ethnicity was not reported.
		• She was non-smoker, not a drug user, no medications, no known allergies.
		• She had taken ibuprofen and acetaminophen over the prior week for symptomatic relief.
		
		MIS-A characteristics
		Fever and other signs and symptoms
		• One week of low grade fever, weakness, dyspnea, fatigue
		• Also developed mild cough, sore throat, vomiting, diarrhea, and lymph node swelling
		• Upon admission
		  ○ She was afebrile, with mild hypotension (blood pressure 98/56 mmHg)
		  ○ Oxygen saturation was normal on room air.
		  ○ She appeared ill, with tender cervical lymphadenopathy
		  ○ Significant conjunctival injection without perilimbal sparing; injected, erythematous, and cracked lips
		  ○ Tenderness to palpation in the left lower abdominal quadrant
		
		One or more organ involved (renal, cardiac, digestive, ocular)
		• Acute kidney injury: Creatinine 7.74 mg/dL (Normal: 0.5 -1.2 mg/dL) and leukocytosis
		• Point-of-care echocardiogram revealed a dilated inferior vena cava andoverloaded right ventricular pressure
		• CT angiogram of the chest showed mild enlargement of the main pulmonary artery
		• CT abdomen/pelvis demonstrated mild peripancreatic fat stranding, felt to possibly represent acute uncomplicated

		pancreatitis, as well as nonspecific bilateral perinephric fat stranding • Conjunctivitis PCR and serology for SARS-CoV-2 • Positive RT-PCR and IgG serology Inflammatory markers • C-reactive protein 90 mg/L (Normal: 0-10 mg/L) • D-dimer 960 mg/L (Normal : 0-574 mg/L) • Ferritin 798 ng/ml (Normal : 11-307 ng/ml) • Lymphocytes 3% (Normal: 19-53) Treatment: • Aggressive fluid resuscitation and vasopressor • Intravenous immunoglobulin (IVIG), 2 g/kg split equally between hospital days 2 and 3 • Aspirin 325 mg daily for 7 days • Patient was offered remdesivir under an Emergency Use Authorization (EUA) basis, but declined • At discharge she was prescribed a 7-day course of apixaban for COVID-19-associated coagulopathy per Emory University Hospital COVID-19 treatment guidelines Severity and outcome • The patient was admitted to ICU twice during her hospital stay and was discharged day 5.
Lidder (2020) (8) Case report United States May 2020	A case of MIS-A was described, including clinical and laboratory characteristics, treatment and outcome. The case met RCPCH, CDC, CPS and WHO definitions.	*Demographic characteristics and past medical history* • The case was a 45 years old male with no comorbidities. • Ethnicity was not reported. *MIS-A characteristics* Fever and other signs and symptoms • He had fever for 5 days, sore throat, diarrhea, eye redness, eyelid swelling, and a diffuse rash including bilateral upper and lower eyelids. One or more organ involved (renal, cardiac, digestive, ophthalmological)

		• A transthoracic echocardiogram demonstrated global hypokinesis and a reduced ejection fraction of 40%.
		• CT imaging showed unilateral cervical lymphadenopathy with a lymph node measuring 1.8 cm.
		• Photophobia and swollen eyelids. No vision changes including blurry vision and eye pain.
		• Uncorrected near visual acuity was 20/20 bilaterally
		  ○ Bilateral superficial punctate keratitis, symmetric anterior chamber (AC) inflammation with 10–15 cells per high power field, and normal intraocular pressure. Dilated fundus exam was notable only for one small peripheral cotton wool spot in each eye.
		• Punch biopsy of his erythema multiforme-like rash
		  ○ Showed sparse superficial perivascular infiltrate of lymphocytes with neutrophils and scattered eosinophils, suggestive of toxic shock syndrome.
		
		Excluding other cause
		• Testing for myositis and HIV was negative.
		• An exhaustive rheumatologic workup including ANA, RF, anti-CCP, anti-Smith, anti-dsDNA, p-ANCA/MPO, c-ANCA/PR3 was also negative.
		• Blood cultures were negative.
		
		PCR and serology for SARS-CoV-2
		• Positive RT-PCR
		
		Inflammatory markers
		• Lymphopenia
		• Ferritin, CRP, ESR, D-dimer and troponin were elevated
		
		Treatment:
		• Ophthalmic lubricating therapy in addition to prednisolone acetate 1% eye drops four times daily for his photophobia in the setting of AC inflammation
		• IVIG and an IL-6 inhibitor (tocilizumab) in addition to using a topical triamcinolone ointment for his diffuse rash

		Severity and outcome • The length of stay in hospital was not reported but the patient did not demonstrate shock-like signs.

Moghadam (2020) (9)
 	
Case report
 	
France
 	
The date the study was conducted was not reported
 	
July 2020*
	A case of MIS-A was described, including clinical and laboratory characteristics, treatment and outcome.
	
	The case met RCPCH, CDC and WHO definitions.
		Demographic characteristics and past medical history
		• The case was a 21 years old Caucasian male.
		• The presence or absence of comorbidity was not reported.
		
		MIS-A characteristics
		Fever and other signs and symptoms
		• He had fever and non-bloody watery diarrhea lasting for 7 days.
		• Asymptomatic rash over his trunk and palms, consisting of erythematous round-shaped macules with a darker and raised rim, 1-3 cm in diameter
		• Bilateral conjunctivitis
		• Blood pressure 80/40 mmHg
		• Respiratory rate was 38 breaths/min, and oxygen saturation was 97% on ambient air
		
		One or more organ involved (cardiac, digestive, pleural)
		• Electrocardiogram showed diffuse negative T waves, and echocardiography displayed hyperkinetic left ventricle with normal ejection fraction, normal right cavities, and dilated non-compressible inferior vena cava.
		• Thoraco-abdominal computed tomography (CT) scan did show
		  ○ Signs of congestive heart failure
		  ○ Bilateral pleural effusion
		  ○ Wall thickening of the right colon
		• Respiratory function deterioration
		
		PCR and serology for SARS-CoV-2
		• Negative RT-PCR and IgG positive serology
		
		Inflammatory markers
		• Lymphocytes of 900/mm3
		• C-reactive protein 365 mg/L
		• Procalcitonin was 3.4 ng/mL
		• Ferritin was 1282 mg/L (normal <30)
		• Lactate 2.4 mmol/L (normal <1.6)

		• Troponin level was 550 ng/L (normal <34) • Cutaneous biopsy showed a slightly inflammatory infiltrate in upper dermis, and direct cutaneous immunofluorescence was negative. Exclusion of other causes • Patient denied any drug intake • He did not smoke tobacco, or use illicit drugs • Extensive infectious inquiry and search for antinuclear antibodies were negative • The rash was particular and diagnosis of erythema multiforma and subacute lupus erythematosus were ruled out. Treatment: • Volume resuscitation • Noradrenaline • Antibiotics (ie, ceftriaxone and amikacin) • High-flow nasal oxygenation Severity and outcome • The length of stay in ICU was 8 days.
Sokolovsky(2020) (13) Case report United States The date the study was conducted was not reported June 2020*	A case of MIS-A was described, including clinical and laboratory characteristics, treatment and outcome. The case met RCPCH, CDC, CPS and WHO definitions.	*Demographic characteristics and past medical history* • The case was a 36 years old Hispanic female. • She had no known comorbidity. *MIS-A characteristics* Fever and other signs and symptoms • One week of fever, abdominal pain, vomiting, and diarrhea • Two days of a diffuse rash and arthralgias • Tachycardia, tachypnea, hypotensive • Classic phenotype of complete Kawasaki's Disease: bilateral nonexudative conjunctivitis mucositis wit cracked lips, edema of the bilateral hands and feet; a diffuse maculopapular rash and cervical lymphadenopathy One or more organ involved (cardiac, digestive) • CT angiogram of the chest: normal lung parenchyma and a trace right pleural effusion

		• CT abdomen/pelvis illustrated mild circumferential gallbladder wall thickening and a small area of colitis • Echocardiogram after treatment with ○ IVIG revealed an EF of 65% with moderate tricuspid valve regurgitation. Subsequent CTA coronaries was normal except for a trace pericardial effusion. PCR and serology for SARS-CoV-2 • Negative RT-PCR and IgG positive serology Inflammatory markers • CRP: 30 mg/dL (0.0–0.9) • D-dimer: 652 ng/mL (<318) Exclusion of other cause • Anti-dsDNA, anti-smith, anti-RNP, SSB, RF, CCP, ANCA, ASO, and anti-Jo-1 antibodies were negative • HIV and hepatitis panels were negative Treatment: • Fluid resuscitation for shock • A single dose of aspirin 650 mg • IVIG 2 g/kg • Methylprednisolone 2 mg/kg for 5 days followed by a prednisone taper Severity and outcome • She stayed at least 6 days in hospital.
Shaigany (2020) (10) Case report United States The date the study was conducted was not reported	A case of MIS-A was described, including clinical and laboratory characteristics, treatment and outcome. The case met RCPCH, CDC,	*Demographic characteristics and past medical history* • The case was a 45 years old Hispanic male. • He had no known comorbidity. *MIS-A characteristics* Fever and other signs and symptoms • Six days of fever, sore throat, diarrhoea, bilateral lower extremity pain, conjunctivitis, and diffuse exanthema • Exposure to SARS-CoV-2 infection 2 weeks earlier • Respiratory rate was 25–33 breaths per min • Hypotension (systolic blood pressure 80–90 mm Hg)

July 2020	CPS and WHO definitions.	• Tachycardia with episodes of atrial fibrillation with rapid ventricular response
		• Bilateral, nonexudative 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
		
		One or more organ involved (renal, cardiac, digestive, ophthalmological)
		• CT of the neck revealed inflammation and oedema involving the bilateral lower eyelid and pre-septal space, as well as sub-occipital reactive lymphadenopathy.
		• Electrocardiogram demonstrated:
		  ○ ST elevations in the anterolateral leads,
		  ○ Global hypokinesis of the left ventricular wall with a mild to moderately reduced ejection fraction of 40%
		• 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.
		
		PCR and serology for SARS-CoV-2
		• Positive RT-PCR
		
		Inflammatory markers
		• Lymphopenia (0–700 lymphocytes per µL)
		• 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
		• Interleukin-6 (IL-6) 117 pg/mL
		• Troponin 8·05 g/mL)

		Exclusion of other causes • HIV-1 and HIV-2 antibodies were negative • Bacterial blood cultures were negative Treatment: • Therapeutic dose low molecular weight heparin • Intravenous immunoglobulin (2 g/kg) over 2 days • A single intravenous dose of the IL-6 inhibitor tocilizumab (400 mg) Severity and outcome • The patient was 8 days in hospital and did not require vasopressor support or intensive care unit level of care.

*The date was based on the publication date as the date the case occurred was not reported

Methods:

A daily scan of the literature (published and pre-published) is conducted by the Emerging Science Group, PHAC. The scan has compiled COVID-19 literature since the beginning of the outbreak and is updated daily. Searches to retrieve relevant COVID-19 literature are conducted in Pubmed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN, Research Square and cross-referenced with the COVID-19 information centers run by Lancet, BMJ, Elsevier, Nature and Wiley. The daily summary and full scan results are maintained in a refworks database and an excel list that can be searched. Targeted keyword searching is conducted within these databases to identify relevant citations on COVID-19 and SARS-COV-2. Search terms used included: "MIS-A", "Kawasaki", "multisystem inflame", "multi-system inflam", "inflammatory multisystem", "inflammatory multi-system", and "inflammatory disease" , "Kawasaki-like", "COVID-19 linked disease. This review contains research published up to November 13, 2020.
Each potentially relevant reference was examined to confirm it had relevant data and relevant data is extracted into the review.

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