

CASE REPORT

Distinguishing Multisystem Inflammatory Syndrome in Children (MIS-C) From Kawasaki Disease: A Case Report

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a relatively rare complication of Covid-19 infection occurring in children and adolescents. Some of its clinical presentations overlap with those of Kawasaki disease (KD). We report the case of a six-year-old girl who presented with a six-day history of fever, bilateral conjunctivitis, oral mucosal changes, generalised body rash and cervical lymphadenopathy, all of which are common presentations for both MIS-C and KD. There was, however, a history of Covid-19 infection one month prior, and her Covid-19 antibodies were positive. Laboratory investigations revealed elevated inflammatory markers, including C-reactive protein, ferritin, procalcitonin and interleukin-6, as well as an elevated troponin level. These findings, in combination with the clinical history, were consistent with MIS-C. Intravenous immunoglobulin and corticosteroids were administered, leading to clinical improvement. This case highlights the common and divergent features of MIS-C and KD and the importance of recognising these features for effective treatment and improved outcomes.

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INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a rare hyperinflammatory condition in paediatric patients that develops following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and affects various organ systems [1]. It often develops 2-6 weeks after Covid-19 infection or exposure [1, 2]. The disease can lead to serious complications, such as multiorgan failure and cardiogenic shock [1]. Endothelial dysfunction and the resulting cytokine storm have been suggested as mechanisms for end-organ damage [1]. One study indicates that the SARS-CoV-2 spike protein might directly stimulate the immune system, acting as a superantigen [1].

The clinical presentation of MIS-C closely resembles Kawasaki disease (KD) to the extent that it was initially termed Kawasaki-like disease [3]. Approximately 30% of children with MIS-C meet the criteria for complete KD, making differentiation between the two conditions

challenging [2, 3]. In addition to fever, other common overlapping clinical features include conjunctival injection, generalised body rash, oral mucosal changes, and cervical lymphadenopathy [2, 3]. Although these similarities suggest that the diseases belong to the same spectrum of inflammatory disorders, many consider them to be two distinct diseases based on their epidemiology, pathophysiology, and other clinical and laboratory findings [2, 3]. This case highlights the common and divergent features of MIS-C and KD, as well as their diagnostic criteria.

CASE REPORT

A six-year-old girl was referred from a primary health clinic following six days of fever accompanied by a generalised body rash, right neck swelling, sore throat and reduced oral intake. She had no gastrointestinal symptoms such as vomiting, diarrhoea or abdominal pain. The patient did not experience any breathing difficulties or neurological symptoms. Apart from a history of category 2A Covid-19 infection 30 days prior, during which she was home quarantined, she had no other significant medical history.

On examination, the patient was tachycardic but

normotensive. She had bilateral non-purulent conjunctival redness, injected lips and a red tongue. Cervical lymphadenopathy and generalised maculopapular rashes were observed over the abdomen and bilateral lower limbs, along with hepatomegaly.

Laboratory investigations on admission revealed elevated inflammatory markers, including C-reactive protein (CRP), ferritin, procalcitonin and interleukin-6 (IL-6), as well as an elevated lactate dehydrogenase (LDH) (Table

1). Given the differential diagnoses of MIS-C and KD, troponin I was measured and was found to be raised. Otherwise, there were no significant abnormalities in the full blood count (FBC), renal profile (RP), and liver function test (LFT). The patient's Covid-19 antibody serology was positive with a negative Covid-19 RTK antigen. Her electrocardiogram (ECG) was normal, and the echocardiography showed good contractility, with no evidence of pericardial effusion, no dilatation of chambers and no coronary artery dilatation.

Table 1: Laboratory investigation results

Investigations	Day 1 of admission	Day 3 of admission	Day 6 of admission	Reference Interval
Full blood count (FBC)				
Haemoglobin	13.9	11.3	13.4	11.5-15.5 g/dL
White cell count	5.64	4.61	8.91	5-13 10 ³ /uL
Neutrophils	3.87	2.73	6.35	1.0-8.0 10 ³ /uL
Lymphocytes	1.38	1.57	1.96	1.0-5.0 10 ³ /uL
Platelet	168	265	522	170-450 10 ³ /uL
Renal profile (RP):				
Sodium	135	137	137	135-150 mmol/L
Potassium	3.8	3.8	4.3	3.5-5.0 mmol/L
Urea	3.2	2.3	4.3	1.7-8.3 mmol/L
Creatinine	35	32	36	53-106 umol/L
Liver function test (LFT)				
Albumin	41.4	29.8	36.7	35.0-50.0 g/L
Total protein	71.0	82.9	82.6	66.0-87.0 g/L
Total bilirubin	9.2	5.2	4.4	5.0-21.0 umol/L
Alkaline phosphatase (ALP)	161	122	128	53-141 U/L
Alanine aminotransferase (ALT)	12.6	9.2	21.5	0.0-43.0 U/L
Aspartate aminotransferase (AST)	36	26	39	3-40 U/L
Creatine kinase	144	34	-	25-200 U/L
Lactate dehydrogenase (LDH)	359	264	-	140-271 U/L
C-reactive protein (CRP)	11.00	5.17	0.85	0.00-0.50 mg/dL
Ferritin	1288.1	836.0	335.9	23.9-336.2 ug/L
Procalcitonin	4.94	-	-	Risk of severe sepsis and/or septic shock. <0.50 ng/mL: Low 0.50-2.00 ng/mL: Moderate >2.00 ng/mL: High
Troponin-I	96.9	-	-	Female: ≤11.6 pg/mL
Interleukin-6 (IL-6)	-	107.97	-	< 6.4 pg/mL
D-dimer	3.61	1.53	0.95	<0.5 ug/mL
Fibrinogen	575	444	-	174.4-495.0 mg/dL
Blood culture and sensitivity	No growth	-	-	
Covid-19 RTK Ag	Negative	-	-	
Covid-19 antibody spike protein	>25.50 (Positive)	-	-	U/mL

Covid-19, Coronavirus disease 2019; RTK Ag, Rapid Test Kit Antigen

The patient received intravenous immunoglobulin (IVIG) and corticosteroid therapy. Prophylactic anticoagulant and antiplatelet medications, i.e., subcutaneous enoxaparin and oral aspirin, were commenced. The patient demonstrated clinical improvement with declining trends in the inflammatory markers. She was discharged on the seventh day of admission. A repeat echocardiography performed four weeks later revealed no coronary dilatation post-syndrome.

DISCUSSION

MIS-C was first described in April 2020 in the United Kingdom, and since then, similar cases have been reported elsewhere [1]. In the US, the reported incidence

of MIS-C is approximately 2 per 100,000 individuals under the age of 21 years, compared to 25 per 100,000 individuals under the age of 5 years for KD [3]. In Malaysia, the MIS-C Malaysia Study Group reported 174 MIS-C cases from June 2020 to December 2021, with 57% of them aged between 5 and 11 years old [4]. KD generally affects children younger than 5 years old, with the highest prevalence seen in Japanese and Asian descendants [2, 3]. In contrast, MIS-C tends to occur in children older than 5 years and is more commonly seen in Hispanic and African American children [2].

As mentioned, some of the signs and symptoms of MIS-C overlap with those of KD, as demonstrated in this case. Fever, maculopapular rash, cervical lymphadenopathy

and bilateral non-exudative conjunctivitis, which are hallmarks of KD, are also commonly present in MIS-C [2, 3]. However, children with MIS-C typically (60-100%) present with gastrointestinal symptoms such as abdominal pain, vomiting and diarrhoea, which are not common with KD [2, 3], although these symptoms were absent in this patient. Cardiac involvement is also seen in both conditions. KD is the most common cause of acquired cardiac disease in developed countries, with coronary artery aneurysm being the main complication [2, 3]. Although the mechanism for the development of the aneurysm is unknown, it is thought to be due to immune complexes triggering inflammation [2]. In MIS-C, the cardiac manifestations include left ventricular dysfunction, myocarditis, and coronary artery dilatation. Myocarditis can also be a complication of KD, albeit uncommon [3]. In this patient, troponin I was elevated on admission, suggesting myocardial injury, but no repeat samples were taken. However, the patient's ECG and echocardiography revealed no abnormalities during admission and four weeks later. The common ECG abnormalities seen in MIS-C are repolarisation abnormalities, ischaemic changes, and first-degree atrioventricular block. [1] Besides an elevated troponin, an elevated brain natriuretic peptide (BNP) is also commonly seen in MIS-C, although it was never measured in this patient [2]. A hypercoagulable state is also more common in MIS-C than KD, leading

to complications of deep venous thrombosis and pulmonary embolism [1, 2]. D-dimer is often elevated in patients with MIS-C compared to those with KD, as demonstrated in this case [2]. Other presentations of MIS-C include neurocognitive symptoms such as headache and lethargy, respiratory symptoms and myalgias [1]. In the MIS-C Malaysia Study Group, all affected children had fever for more than four days, with asthenia, left ventricle dysfunction (100%), bulbar conjunctivitis (89%), gastrointestinal involvement (nausea, vomiting) (83%), shock (68%), cervical and mesenteric lymphadenopathies (60%), skin rash (57%), and red and cracked lips (54%) [4].

Regarding laboratory investigations, both KD and MIS-C have raised CRP and ESR, as well as other inflammatory markers such as ferritin, D-dimer, and IL-6; however, higher levels are seen in MIS-C, as in this patient [1]. Lymphocyte and platelet counts are often low in MIS-C, whereas in KD, leukocytosis and thrombocytosis are more common [1]. Normochromic normocytic anaemia is also an additional feature seen in KD [1]. This patient, however, had neither abnormality. Other abnormalities seen in MIS-C include raised liver enzymes, elevated LDH, and hypertriglyceridaemia [1]. Table II compares the common features of KD and MIS-C with the findings from the patient described in this case report.

Table II: Comparison between the common features of KD and MIS-C

Feature	KD	MIS-C	Patient
Cause	Unknown; suspected to be triggered by an infectious agent.	Associated with recent COVID-19 infection.	COVID-19 infection 30 days prior to the current presentation.
Age Group	Primarily affects children under 5 years old.	More commonly affects children (> 7 years old) and adolescents.	6 years old
Duration of Fever	Usually lasts more than 5 days.	Fever \geq 24 hours	Six days fever
Symptoms	– Rash, bilateral conjunctivitis, cervical lymphadenopathy, oral mucosal changes (cracked red lips, strawberry red tongue). – GIT symptoms are uncommon.	– Rash, bilateral conjunctivitis, cervical lymphadenopathy have been reported (30% of children with MIS-C meet the criteria for KD). – Commonly associated with GIT symptoms. – Others: neurocognitive and respiratory symptoms.	– Rash, bilateral conjunctivitis, injected lips, red tongue, cervical lymphadenopathy. – No GIT symptoms, neurocognitive and respiratory symptoms.
Cardiac complications	Risk of coronary artery aneurysms or myocarditis.	Risk of left ventricular dysfunction, myocarditis, and coronary artery dilatations.	No cardiac complications
Laboratory Findings	– Elevated inflammatory markers (e.g., CRP, ESR, ferritin, D-dimer). – Anaemia, leukocytosis and thrombocytosis.	– Higher levels of inflammatory markers (e.g., CRP, ESR, ferritin, D-dimer). – Lymphopenia, or thrombocytopenia. – Elevated troponin and BNP levels.	– Elevated inflammatory markers (CRP, ESR, ferritin, PCT, D-dimer and IL-6). – No lymphopenia, or thrombocytopenia – Elevated troponin.

BNP: brain natriuretic peptide; CRP: C-reactive protein; IL-6: interleukin-6; PCT: procalcitonin; GIT: Gastrointestinal

Generally, it takes two to six weeks from the active infection to the onset of MIS-C symptoms in children with a known history of Covid-19 infection [1-3]. In the majority of cases, the duration between acute infection and onset of MIS-C symptoms is unknown because most children with acute infection remain asymptomatic. In contrast, the exact cause of KD is unknown but is

postulated to be due to a prior viral infection that results in acute vasculitis [2].

There are several diagnostic criteria for MIS-C, such as those from the Centers for Disease Control and Prevention (CDC) in 2020, as well as criteria from the World Health Organization (WHO) [1]. The MIS-C

case definition was revised by the Council of State and Territorial Epidemiologists (CSTE) in 2023 [5]. The 2023 definition aimed to improve the identification of MIS-C and to help discriminate between KD and MIS-C [5]. The new definition requires both clinical and laboratory criteria to be met for a confirmed case of MIS-C, while a probable case is defined by meeting clinical and epidemiological criteria [5]. This 2023 case definition differs from the original 2020 by including a specific cut-off for CRP at ≥ 3.0 mg/dL as evidence of inflammation, as well as eliminating respiratory, renal and neurological systems as part of the multisystem organ involvement, and incorporating KD as an alternative diagnosis of MIS-C [5]. In the 2020 MIS-C definition, children who met the criteria for both MIS-C and KD were considered to have MIS-C [5].

This child met all the case definitions of MIS-C, including those of the recent 2023 MIS-C case definition. She is in the expected age group (six years old), had a six-day fever, with evidence of systemic inflammation indicated by an elevated CRP level of ≥ 3.0 mg/dL, and exhibited two systemic involvements (mucocutaneous, by the presence of body rashes, bilateral non-purulent conjunctivitis, injected lips and red tongue; and cardiac involvement as evidenced by elevated troponin). In addition, there was a history of recent Covid-19 infection, as evidenced by her clinical history and positive Covid-19 serology.

There is no standardised protocol for the treatment of MIS-C due to it being a relatively new disease [2]. However, IVIG and corticosteroids have been shown to improve short-term cardiovascular outcomes compared to IVIG alone [5]. Anti-coagulation is also recommended due to the proinflammatory state [1]. In contrast, the treatment of KD is well-established and also involves administration of IVIG as well as aspirin. However, corticosteroids are often reserved only for those with high-risk features such as coronary artery changes or refractory fever [5].

CONCLUSION

This case highlights the need for heightened clinical awareness of the potential overlap between the presentations of KD and MIS-C. Nevertheless, understanding the differences in their clinical history, presentation, and changes in laboratory markers helps

in differentiating the two diseases and guiding their management.

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