Case report

COVID-19 related multisystem inflammatory syndrome in children (MIS-C): a case series from a tertiary care hospital in Sri Lanka

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Abstract

Although it has clinical features that overlap with Kawasaki disease (KD) and toxic shock syndrome (TSS), an intense inflammatory storm distinguishes multisystem inflammatory syndrome in children (MIS-C) from KD and TSS. We report four children with laboratory evidence of severe acute respiratory syndrome - coronavirus - 2 (SARS-CoV-2) infection presenting with persistent fever, mucocutaneous signs, and raised inflammatory markers associated with remarkable multi-organ involvement, particularly that of the gastrointestinal and cardiovascular systems. All of them responded well to immunosuppressive therapy, including intravenous immunoglobulin and methylprednisolone. The distinguishing clinical characteristics found in MIS-C include the age of the child, gastrointestinal symptoms, and hypotension without coronary involvement. Immediate medical care is needed for a better outcome, and most children need management in an intensive care unit.

Keywords: Multisystem inflammatory syndrome in children, COVID-19, Kawasaki disease, Toxic shock syndrome, Severe acute respiratory syndrome coronavirus 2

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Introduction

In April 2020, investigators from United Kingdom (UK) noted an unprecedented cluster of eight children with hyperinflammatory shock, showing features that overlap with atypical Kawasaki disease (KD), Kawasaki disease shock syndrome, or toxic shock syndrome (TSS) (1). Later, this disorder was termed multisystem inflammatory syndrome in children (MIS-C) by the United States Centres for Disease Control and Prevention (CDC) and the World Health Organization (WHO). MIS-C patients typically present with persistent fever, mucocutaneous signs, and raised inflammatory markers (2,3). However, remarkable multi-organ involvement, particularly in the gastrointestinal (GI) and cardiovascular systems, have been identified. Although SARS-COV-2 was initially thought to have a milder impact on children, it is no longer considered as such due to MIS-C (4). We describe the clinical features, laboratory findings, and management of four children with MIS-C treated in Colombo North Teaching Hospital, Ragama.

Case 01

A one-year-old girl was admitted to the ward with fever for 6 days associated with vomiting, loose stools, irritability, and reduced appetite. She was febrile (104°F) with bilateral conjunctivitis, red lips, erythematous papular rash over the chest, and tachycardia (heart rate 138/min). Other vital signs were normal. On investigation, she had lymphocytopenia, thrombocytopenia, hyponatremia, hypoalbuminemia, elevated levels of c-reactive protein (CRP), lactate dehydrogenase (LDH), serum ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and D-dimers (Table 1). Intravenous (IV) vancomycin and ceftriaxone were started empirically for septicaemia. As fever and mucocutaneous manifestations persisted with elevated CRP, a diagnosis of MIS-C was considered. Even though initial SARS-CoV-2 Polymerase Chain Reaction (PCR) testing and SARS-CoV-2 rapid antigen test (RAT) were negative, SARS-CoV-2 antibody became positive (antibody titre >10). Echocardiography was normal with no coronary artery abnormalities. She was treated with IV immunoglobulin (IVIG) 2 g/kg infusion over 48 hours with IV methylprednisolone 30 mg/kg for 3 days and low dose aspirin (Table 2). She fully recovered after 11 days.

Case 02

A 13-year-old boy was admitted to the ward with fever for four days associated with vomiting, headache, dizziness, arthralgia, myalgia, abdominal pain, and reduced appetite. He was ill-looking, febrile, and had fissured lips and bilateral conjunctivitis. On admission, he had hypotension (blood pressure 80/50 mmHg) with tachycardia (heart rate 132/ min) with low volume pulse, tachypnoea and significant right hypochondrial tenderness. Neutrophilic leucocytosis, lymphocytopenia, anaemia, thrombocytopenia, hyponatremia, hypoalbuminemia with a high erythrocyte sedimentation rate (ESR) and CRP were noted (Table 1). Intravenous (IV) 0.9% saline bolus was administered followed by an infusion of inotropes.

Despite being SARS-CoV-2 PCR and SARS-CoV-2 RAT negative, SARS-CoV-2 antibody was detected in him (antibody titre >10). IV ceftriaxone and IV flucloxacillin were administered empirically and continued for ten days. He received IVIG 2 g/kg over 48 hours, IV methylprednisolone 30 mg/kg/day for 3 days, and low dose aspirin (Table 2). He required intensive care for 5 days due to persistent hypotension after which he recovered completely.

Case 03

A 3-year-old girl was admitted to the ward with fever for 5 days associated with loose stools, irritability, and reduced appetite. She was febrile (105°F) and ill-looking with periorbital swelling and bilateral conjunctivitis with tachycardia (heart rate 160/min). Other vital signs were normal. Neutrophilic leucocytosis, anaemia, hyponatremia, hypoalbuminemia, elevated CRP, and ESR were noted (Table 1). IV meropenem and oral azithromycin were started empirically. Persistent symptoms with high CRP suggested MIS-C. SARS-CoV-2 PCR testing was positive. Her echocardiogram was normal. She was given IVIG 2 g/kg infusion over 48 hours with IV methylprednisolone 2 mg/kg bd for 3 days and low dose aspirin. Later she developed persistent hypotension and required intensive care where adrenalin infusion and prophylactic enoxaparin were started (Table 2). She fully recovered after 4 days.

Case 04

A 13-year-old boy was admitted to the ward with fever for three days associated with vomiting, headache, arthralgia, myalgia, abdominal pain, and reduced appetite. He was febrile (103.4°F) and ill-looking with periorbital swelling, conjunctivitis, cracked red lips, left side renal angle tenderness, neck stiffness, tachycardia (heart rate 122/min) and hypotension. Neutrophilic leucocytosis, lymphocytopenia, thrombocytopenia, hyponatremia, hypoalbuminemia, elevated CRP, ESR, ALT, AST, and prothrombin time were noted (Table 1). IV cefotaxime and benzathine penicillin were started on suspicion of leptospirosis. As fever, mucocutaneous manifestations, and hypotension persisted with elevated CRP, severe MIS-C was considered. SARS-CoV-2 PCR was positive.

He required intensive care admission due to persistent hypotension and oliguria. His echocardiogram was normal. He was treated with IVIG 2 g/kg over 48 hours, IV methylprednisolone 2 mg/kg twice daily for 5 days, and low dose aspirin. He also required intensive care with intravenous adrenaline (Table 2) and fully recovered after 4 days.

Table 1: Clinical features and investigations of four children with MIS-C

	Case 01	Case 02	Case 03	Case 04
Age (years)	1	13	3	13
Sex	Female	Male	Female	Male
Presenting symptoms				
Fever	6 days	4 days	5 days	3 days
Irritability/ altered mentation	+	+	+	-
Vomiting	+	+	-	+
Diarrhoea	+	-	+	+
Abdominal pain	-	+	-	+
Myalgia	-	+	-	+
Arthralgia	-	+	-	+
Headache	-	+	-	+
Signs				
Rash	+	-	-	-
Conjunctivitis	+	+	+	+
Periorbital oedema	-	-	+	+
Fissured lips/strawberry tongue	+	+	-	+
Lymphadenopathy	-	-	-	-
Extremity oedema	-	-	-	-
hypotension	-	+	+	+
Kernig sign	-	-	-	-
Neck stiffness	-	-	-	+
Investigations				
SARS-CoV-2 PCR	Negative	Negative	Positive	Positive
SARS-CoV-2 RAT	Negative	Negative	Negative	Negative
SARS-CoV-2 antibody (Ig M/ IgG)	Positive	Positive	Not done	Not done
Total white cell count (/mm^3)	6.73×10^3	22.6×10^3	15.68×10^3	12.1×10^3
Neutrophils (/µL)	4.76×10^3	21.9×10^3	12.97×10^3	10.6×10^3
Lymphocytes (/µL	1.45×10^3	0.6×10^3	1.85×10^3	1.2×10^3
Haemoglobin (g/dL)	11.8	10.8	9.1	11.2
Platelet (/µL)	85	167	189	150
CRP (mg/dl)	205	237	318	285
ESR (mm/ 1^{st} hour)	20	42	126	25
Alanine transaminase (U/L)	158	58	16	41
Albumin (g/dL)	3.3	3.3	2.7	2.0
Serum sodium (mmol/L)	132	127	133	127

+ present; - absent; SARS-CoV-2= Severe Acute Respiratory System Coronavirus-2; Y= years.

Table 2: A summary of the management of four children with MIS-C

Therapy	Case 01	Case 02	Case 03	Case 04
IV immunoglobulin (2 **g/kg over 48 hours)**	+	+	+	
Methylprednisolone	30 mg/kg daily 5 days	30 mg/kg daily 3 days	2 mg/kg bd 3 days	2 mg/kg bd 5 days
Aspirin	+	+	+	+
Enoxaparin	-	-	+	-
Adrenalin	-	+	+	+

+ treatment is given; - treatment is not given; bd= twice daily; IV= intravenous; kg= kilograms; mg= milligrams

Discussion

The first wave of SARS-CoV-2 was reported in January 2020 in Sri Lanka with the majority of infected children being asymptomatic (5,6). Most of the cases of MIS-C in Sri Lanka were diagnosed during the second wave in October 2020 following the recognition of MIS-C in April 2020 in the UK.

MIS-C is a rare complication associated with COVID-19. Persistent fever without a clear clinical source is the mainstay of the diagnosis of MIS-C. Six out of 6 WHO criteria must be met for diagnosis of MISC (3). Therefore, any child with suspected MIS-C should also be evaluated for infectious and non-infectious aetiologies.

All children in our case series had fever and conjunctivitis during the course of illness. Majority had irritability, tongue/lip involvement, vomiting, and diarrhoea with half of them having abdominal pain, arthralgia, myalgia, and headache. Upon investigation all of them had high ESR and CRP. However, SARS-CoV-2 PCR or IgG/IgM positivity was seen only in a half. Leucocytosis, thrombocytopenia, anaemia, hypoalbuminemia, and elevated transaminases were seen only in a minority. All of them were treated with IVIG, IV methylprednisolone and aspirin and only some required enoxaparin and adrenalin.

Though MIS-C along with KD and TSS, shares fever, rash, conjunctivitis, and mucocutaneous involvement with elevated inflammatory markers, a higher inflammatory storm with gastrointestinal symptoms and hypotension without coronary artery involvement sets MIS-C apart (4). Our case series supports this, as all the cases had gastrointestinal symptoms and 2 out of 4 cases had hypotension on presentation. The overlapping features and similar therapeutic options between these syndromes suggest that they may share similar pathophysiology as almost all the patients responded to IVIG, aspirin, and glucocorticoids.

In summary, MIS-C is a severe form of systemic inflammatory disorder characterized by extreme inflammation, fever, gastrointestinal symptoms, conjunctivitis, rash, and hypotension. Many progress rapidly into shock and cardiorespiratory failure. Immediate medical care is needed for a better outcome and most children will need management in an intensive care unit. The treatment consists of administration of IVIG, steroids, aspirin, and the involvement of a multidisciplinary team of healthcare providers. Even though all children recovered completely from the acute stage, the potential long-term sequelae of MIS-C will only be revealed in time to come.

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