Short Report

Multisystem inflammatory syndrome in children: A Sri Lankan case series

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Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) / Coronavirus Disease 2019 (COVID-19) pandemic poses numerous challenges to the medical community around the world[1]. The classical respiratory symptoms associated with SARS-CoV-2 include rhinorrhoea, sore throat, cough and shortness of beath[2,3]. However, diagnosing some rare manifestations of SARS-CoV-2 is challenging. Multisystem Inflammatory Syndrome in Children (MIS-C) is one such complication, where a delayed diagnosis could be fatal. Although MIS-C was first described in the UK in April 2020, the disease has not been reported from Sri Lanka until recently[4]. We report three unrelated patients with MIS-C in whom the diagnosis of SARS-CoV-2 was made after developing MIS-C.

Case 1

A 9-year-old boy presented with high fever with chills for seven days, arthralgia, myalgia, headache, and reduced urine output. On the day of admission, he complained of severe abdominal pain. There was no history of muddy exposure, outside food ingestion or recent travel history. Contact history of SARS-CoV-2 was not disclosed, and the SARS-CoV-2 rapid antigen test (RAT) was negative. On examination, the child was febrile with a temperature of 39.5°C and irritable. He had bilateral conjunctival suffusion, cracked lips, muscle tenderness, tenderness over temporomandibular joints, neck stiffness and a positive Kernig sign. He had tachycardia (heart rate 110/min), but his blood pressure (BP) was normal (92/50 mmHg) on admission. His C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated (Table 1). Standard agglutination test for typhoid, leptospira IgM antibodies and rickettsial antibodies were negative. He was initially managed as acute bacterial meningitis with intravenous (IV) cefotaxime. Due to poor response to IV antibiotics after 48 hours and the appearance of features of Kawasaki disease (KD) such as non-purulent conjunctivitis and cracked lips, MIS-C was suspected. SARS-CoV-2 Polymerase Chain Reaction (PCR) of the child, mother and father were positive, and the SARS-CoV-2 antibody of the child was positive (antibody titre >10). Echocardiography showed an ejection fraction of 55% (normal >60%) and left ventricular dysfunction with no coronary artery abnormalities. The child was given IV immunoglobulin (IVIG) 2g/kg infusion over 8 hours. He developed hypotension (BP 78/34 mmHg) while in the ward, for which he was commenced on IV adrenaline infusion and transferred to the paediatric intensive care unit (PICU). In the PICU, the child required IV milrinone infusion along with adrenaline. He recovered fully after five days in the PICU and remained well after one month.

Case 2

A 4-year-old boy presented with fever for five days, abdominal pain, watery loose stools and vomiting for two days. He developed conjunctival redness and periorbital oedema on day five of the illness. There was no past or contact history of SARS-CoV-2 infection, muddy exposure, or travel. On examination, he was febrile (temperature 39.8°C), tachycardic (heart rate 120/min) and ill-looking and had conjunctival suffusion, periorbital oedema, neck stiffness and mild right hypochondrial tenderness. The mucous membranes were normal, and there were no rashes, hepatosplenomegaly or lymphadenopathy. Investigations revealed normocytic anaemia, low normal platelet count and

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elevated CRP (Table 1). Due to conjunctival suffusion and poor response to IV antibiotics which were started due to possible bacterial acute gastroenteritis, MIS-C was suspected. SARS-CoV-2 PCR of the child and mother and SARS-CoV-2 antibody test of the child were positive (antibody titre >10) on day seven of the illness. SARS-CoV-2 RAT was negative. Echocardiography showed good ventricular function and no coronary abnormalities. The child was given IVIG 2g/kg infusion over 8 hours. Due to hypotension (blood pressure- 76/38 mmHg), the child was transferred to the PICU on the following day and was given an IV adrenaline infusion. The child had an uneventful recovery after 4-5 days in the PICU and remained well after one month.

Case 3

An 11-year-old boy presented with fever with chills, headache, arthralgia, myalgia, severe abdominal pain, vomiting, irritability and a skin rash for four days. There was no history of muddy exposure, outside food ingestion or recent travel history. On examination, he was ill, irritable and febrile (temperature 39°C). He had conjunctival suffusion and an urticarial rash involving the chest, axilla, genitalia, palms and soles (Figures 1 and 2). The mucous membranes were normal, and there was no hepatosplenomegaly or lymphadenopathy. His full blood count revealed thrombocytopenia, and his CRP was 226mg/L (Table 1). SARS-CoV-2 PCR of the child and his mother and SARS-CoV-2 antibody of the child were positive (antibody titre >10). Echocardiogram was normal. He developed hypotension (blood pressure 80/40 mmHg) and was commenced on IV adrenaline infusion. The child was treated with IVIG 2g/kg infusion over 8 hours. He continued to have fever after IVIG and was transferred to the PICU. At the PICU, the child required a second dose of IVIG and IV methylprednisolone 2mg/kg/day for 5 days, for which he showed improvement.

Table 1. A summary of clinical and laboratory features of three cases of MIS-C

	Case 1	**Case 2**	**Case 3**
Symptoms			
Fever	7 days	5 days	4 days
Abdominal pain	+	+	+
Irritability	+	+	+
Arthralgia	+	-	+
Myalgia	+	-	+
Headache	+	-	+
Diarrhoea	-	+	-
Vomiting	-	+	+
Signs			
Conjunctival suffusions	+	+	+
Cracked lips	+	-	-
Generalised rash	-	-	Urticarial
Cervical lymphadenopathy	-	-	-
Extremity changes	-	-	-
Neck stiffness	+	+	-
Kernig sign	+	-	-
Hypotension	+	+	+
Periorbital oedema	-	+	-
Investigations			
Haemoglobin (g/dL)	11.1	8.4	12.9
Total white cell count (/mm^3)	8.7×10^3	7.4×10^3	5.9×10^3
Neutrophils (%)	84%	77%	83%
Lymphocytes (%)	11%	19%	8%
Platelet count (/mm^3)	211	153	76
C-reactive protein (mg/L)	116	125	226
Alanine transaminase (IU/L)	13	50	54
Serum sodium (mmol/L)	135	126	127
Troponin I	Negative	Negative	Negative
SARS-CoV-2 Rapid Antigen Test	Negative	Negative	Negative
SARS-CoV-2 polymerase chain reaction	Positive	Positive	Positive
SARS-CoV-2 antibody (Day of illness)	Positive (Day 10)	Positive (Day 7)	Positive (Day 5)

SARS-CoV-2: Severe Acute Respiratory System Coronavirus-2

Figure 1: ***Photograph demonstrating non-purulent conjunctivitis***
Permission given by parents to publish photograph

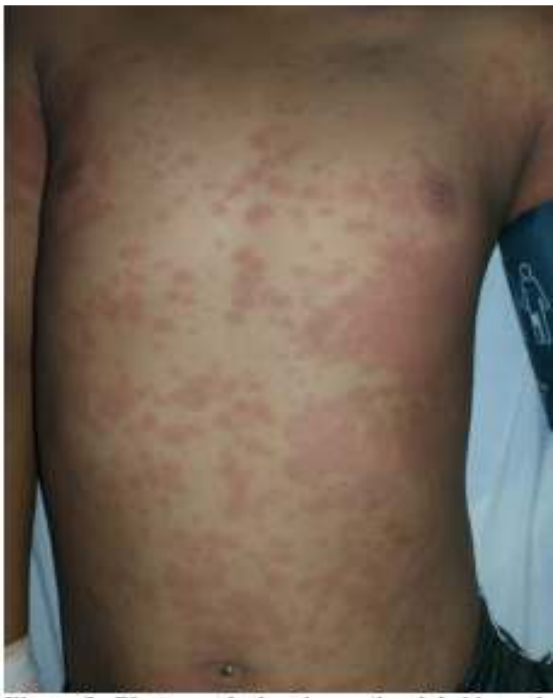

Figure 2: ***Photograph showing urticarial skin rash***

Discussion

MIS-C is a rare complication of SARS-CoV-2 infection. It was initially thought to be a part of incomplete KD; however, currently, it is considered a separate disease[1,2]. MIS-C typically develops 4-8 weeks following infection with SARS-CoV-2, where immune dysregulation has been suggested as the possible mechanism. Of the children with confirmed MIS-C, 90% are positive for SARS-CoV-2 antibodies, and 30% are positive for SARS-CoV-2 PCR[1].

MIS-C shows a wide range of clinical features that include fever, features of KD and hypotension. There is considerable phenotypic overlap of MIS-C with KD[1,2]. Approximately 40-50% of children with MIS-C also fulfil criteria for complete or incomplete KD[4,5]. The diagnosis of complete KD is made if four out of five principal criteria - conjunctival injection, erythema of oral mucosa, extremity oedema, polymorphic skin rash, and unilateral cervical lymphadenopathy - occur with fever which lasts for more than 5 days. Incomplete KD is diagnosed when only two or three principal criteria are present with fever and raised CRP or ESR along with dilated coronary arteries in echocardiography or presence of three or more of the additional laboratory criteria; i.e. anaemia, leucocytosis, thrombocytosis, hypalbuminaemia, pyuria, and raised alanine transaminase.

The features that help to differentiate MIS-C from KD include higher age at presentation (usually >5 years), presence of gastrointestinal symptoms (abdominal pain in particular), hypotension and myocardial dysfunction without coronary artery involvement, very high inflammatory markers (CRP and ESR) and thrombocytopenia. All three patients had fever, severe abdominal pain, conjunctival suffusion, and hypotension without coronary involvement, suggesting that these features could be considered as common clinical manifestations of MIS-C at least in this part of the world.

The other feature highlighted in these case reports is the lack of recent or direct contact history of SARS-CoV-2 and negative SARS-CoV-2 RAT. It indicates that a high degree of suspicion is required when making the diagnosis, especially when the above clinical features occur in combination. Also, our case series emphasises the need for early use of IVIG in MIS-C that could be lifesaving. All three patients recovered completely with IVIG therapy. Although IVIG and methylprednisolone are considered as therapeutic options for MIS-C, universal guidelines have not yet been developed. Therefore, this case series will further strengthen the evidence for early use of IVIG in MIS-C.

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