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ORIGINAL ARTICLE

Multisystem inflammatory syndrome (MIS-C) in a child after SARS-CoV-2 infection

Ana Cleide Silva Souza [1], Jamile Souza Fernandes[1], Ricardo Torres Negraes[2], Luciana S. Nina de Azevedo[3]

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COVID-19,
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Abstract

Objectives: The multisystem inflammatory syndrome is a potentially fatal complication of coronavirus 2 (SARS-CoV-2). Since April 2020, information on a Kawasakis-like disease and inflammatory response in children, associated with severe acute respiratory syndrome SARS-CoV-2, has been related. It has been still unclear the risk factors, pathogenesis, prognosis, and therapy specific to this condition, known as multisystemic inflammatory syndrome in children (MIS-C). MIS-C usually affects children older than 5 years, predominantly of African descent, and has a higher incidence of cardiac changes (myocardite, valvulite, pericardite, and coronary abnormalities). Therefore, early recognition is crucial, although no standardized treatment guidelines have been agreed. The aim of this study is to report the management and evolution of a seriously ill child admitted to the intensive care unit (ICU) with cardiogenic shock secondary to acute myocarditis and suspected SARS-CoV-2 infection. **Case Report:** Child, 9 years old, with SARS-CoV-2 infection, presenting initial Kawasaki disease and abrupt progression to vasoplegic shock, myocarditis, and hyperinflammation syndrome, evidenced by high levels of troponin I, ferritin, C-reactive protein (CRP), D-dimer, and hypoalbuminemia (table 1). Evolved with an excellent outcome although the need of support at pediatric intensive care unit. **Comments:** Patients with a multisystem inflammatory response associated with previous SARS-CoV-2 infection need special and early attention regarding diagnosis and medical assistance, as for the rapid evolution of the disease as for its severity and extent.

[1] Cosme e Damião Children's Hospital, Pediatrics Department - Porto Velho - Rondônia - Brazil.
[2] Cosme e Damião Children's Hospital, Pediatric Hematology - Porto Velho - Rondônia - Brazil.
[3] Cosme e Damião Children's Hospital, Pediatric Cardiology - Porto Velho - Rondônia - Brazil.

Correspondence to:
Ana Cleide Silva Souza.
Hospital Infantil Cosme e Damião. Rua Benedito de Souza Brito, nº 4045, Industrial. Porto Velho, RO, Brazil. CEP: 76821-260. E-mail: anacleides@hotmail.com

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Table 1. Laboratory test results from hospital to ICU admission.

Laboratory tests	D1	D3	D4	D5	D6	Reference value.[19]
Hemoglobin	9,4	8,9	9,5	12,1	11,6	12,5-14,5 g/dL
Hematocrit	28,2	26,6	26,6	33,4	32,9	36-45%
Leukocytes	13.300	12.180	13.480	17.680	17.990	3.500-10.000/mm^3
Platelets	117.000	128.000	174.000	203.000	268.000	100.000-424.000/mm^3
ESR*	15					3-13mm
Ferritin		233			380,2	7,0-140 ng/dL
LDH*		175			243	115-25 UI/L
D-dimer			5.600	5.198	3.186	<500 ng/dL
Fibrinogen			281			100-400 mg/dL
Troponin		0,02		0,02	0,02	<2,0 ng/L
CPK*		35			14	30-300 U/L
CK-MB*					15,5	<25 U/L
Creatinine	0,89	0,62	0,56	0,55	0,47	0,32-0,64 mg/dL
Urea	46,1	33	28	17,6	16,7	8-36 mg/dL
Chlorine	99	104		98,3	100,9	98-112 mmol/L
Phosphor	3,3	3		3,7	3,3	4,5-5,5 mg/dL
Sodium	130	140	136	134	132	135-145 mmol/L
Calcium	8,1	7,56	7,51	7,4	7,63	8,8-10,8 mg/dL
Magnesium	1,4	2,1	2,5	1,9	1,5	1,6-2,4 mg/dL
Potassium	3,8	3,86	3,52	3,3	3,86	3,5-5,1 mmol/L
Albumin	2,7	2,08		2		2,9-4,7 g/dL
Uric acid	3,5	6				0,5-5,0 mg/dL
CRP*	6	115	90,4	45,7	26	<6,0 mg/dL
Lactate		10,4		11	21	0,5-2,0 mmol/L
PT/INR*		1,29				10-14”/0,8-1
APTT*		29,3				24-40”

*D: day; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; CK-MB: creatinine kinase MB fraction; CRP: C-reactive protein; PT: prothrombin time; INR: international normalized ratio; APTT: activated partial thromboplastin time. All tests were performed based on manufacturer protocols. We opted to define reference values based on age and sex.

INTRODUCTION

The first case of a child aged six months with Kawasaki disease (KD) and COVID-19 was reported in the United States on April 7, 2020. Since then, reports from several other countries have described cases of the same association of conditions.[1,2] The condition named multisystem inflammatory syndrome in children (MIS-C) has been described to occur concomitantly with COVID-19, as some children with MIS-C have also been diagnosed with SARS-CoV-2 infection based on polymerase chain reaction (PCR) or serology tests.[1,2]

MIS-C shares clinical and workup characteristics with several conditions, including Kawasaki disease, toxic shock syndrome, bacterial sepsis, and macrophage-activation syndrome.[2] Although children and adolescents with COVID-19 develop mostly asymptomatic disease, they are not free from having severe clinical complications.[3]

KD is a primary acute systemic vasculitis of medium-size vessels and the main cause of acquired heart disease in children in developed nations.[2,3] Clinical signs of the disease include fever for at least five days in association with at least four of the five criteria defined by the American Heart Association (AHA), as follows: changes in the lips and oral cavity; conjunctival hyperemia; extremity changes; polymorphous exanthem; and usually unilateral cervical lymphadenopathy ≥1.5cm.[4,5]

Severe cases of KD may present as toxic shock syndrome, defined as sustained systolic hypotension or clinical signs of poor perfusion, a potentially fatal complication that may be followed by multiple organ dysfunction syndrome.[6]

The definition of MIS-C given by organizations such as the Royal College of Paediatrics and Child Health, the Centers for Disease Control and Prevention, and the World Health Organization is based on six key elements: age of 0-19 years;

persistent fever; laboratory evidence of inflammation; signs or symptoms of organ dysfunction; absence of an alternative diagnosis; and temporal relationship with COVID-19 or exposure to the pathogen causing the disease (Chart 1).[7-10]

Laboratory evidence of increased levels of inflammation and coagulation disorder markers such as the D-dimer and of markers of heart disease such as troponin-T and BNP (B-type natriuretic peptide) suggest the presence of cardiac function involvement, shock, or both.[10] Among the acute manifestations of the disease, pericardial effusion and myocarditis with altered left ventricular ejection fraction are the most common findings seen in echocardiography.

The choice of therapy for MIS-C is based on the spectrum of the disease, on whether it meets the criteria for KD or atypical KD, or if it includes coronary artery alterations. Patients are prescribed high dose intravenous immunoglobulin (IVIG) 2g/kg and aspirin for its anti-platelet effects.[1,10] Anticoagulation might be needed if D-dimer levels increase due to hypercoagulability and thrombus formation, as often seen in adults with COVID-19.[10,11] Cardiogenic shock and myocardial involvement may result in death. Continuous cardiac monitoring, serial measurement of cardiac markers, and echocardiography (focusing on heart and coronary artery function) are also important.[10]

This article reports the management and progress of a severely ill child admitted to an ICU with cardiogenic shock secondary to acute myocarditis suspected for SARS-CoV-2 infection.

CASE REPORT

A 9-year-old girl arrived at our center with persistent high fever (40°C), odynophagia; she was in poor general condition. The patient was brought to our service after experiencing symptoms for four days. The patient was diagnosed with bacterial tonsillitis and was started on amoxicillin. She had non-purulent conjunctivitis, bilateral cervical adenopathy, edema in her face and extremities, diffuse cutaneous rash, and had difficulty walking for leg myalgia. On Day 6 from symptom onset, she was brought again to our service and was admitted with a diagnosis of KD. In the interview, we found she had diarrhea and anosmia for 30 days, lasting for seven days, and that her family members had flu-like symptoms. At the time, she was prescribed social isolation and was not tested for COVID-19.

During physical examination on admission the patient was afebrile, with facies of acute suffering; she was in fair general condition, prostrated, pale, hydrated, anicteric, acyanotic, eupneic, with good peripheral perfusion, and had diffuse cutaneous rash. She was irritated, conscious, responsive, and had a Glasgow Coma Scale score of 15, without signs of motor deficit or meningeal irritation. The patient had bilateral conjunctivitis and periorbital edema; and a palpable bilateral fibroelastic cervical adenopathy not adhered to deeper tissues measuring approximately 3 cm. Cardiorespiratory and abdominal examination did not result in noteworthy findings. She had edema on the dorsum her hands and feet.

She tested positive for COVID-19 (IgM and IgG). Echocardiography revealed mild pericardial effusion (PE) and mild tricuspid regurgitation (TR); she had a pulmonary artery systolic pressure (PASP) of 20 mmHg and mild mitral regurgitation (MR).

The patient met five of the six diagnostic criteria for KD and was started on single-dose IVIG and ASA for its anti-inflammatory properties on the first day of admission. The fever spikes stopped and her general condition improved. However, the patient still had tachycardia at rest and mild tachypnea. An new echocardiogram revealed dilated heart chambers, marked TR with a PASP of 40 mmHg, mild left ventricular systolic dysfunction – ejection fraction (EF) of 47%, a left coronary artery (LCA) with a diameter of 2.4 mm, and a right coronary artery (RCA) with a diameter of 2 mm (reference

Chart 1. Definition of MIS-C according to the World Health Organization.

Definition of MIS-C according to the World Health Organization	
Mandatory criteria	- Age 0-19 years
	- Fever for 3 days
	- Laboratory evidence of inflammation (ESR or CRP or Procalcitonin)
At least two of the following	- Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral cavity, hands or feet);
	- Hypotension or shock;
	- Features od cardiac dysfunction (myocarditis, pericarditis, valvulitis, or coronary dysfunction) - in echocardiogram or Troponin or NT-pro-BNP;
	- Evidence of coagulopathy (PT, APTT, and D-dimer);
	- Gastrointestinal symptoms.
Including these factors	- No other obvious cause of inflammation, including bacterial sepsis or toxic shock syndrome;
	- Evidence of COVID-19 or likely contact with individuals with COVID-19.

*ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NT-pro-BNP: N-terminal pro–B-type natriuretic peptide; PT: prothrombin time; APTT: activated partial thromboplastin time.

values: LCA 2.4 mm/RCA 2.1mm). Since she had myocarditis, the patient was referred to the intensive care unit (ICU). She was prescribed milrinone, ceftriaxone, and furosemide. The patient was hemodynamically stable, but presented borderline blood pressure levels, which prompted the prescription of continuous adrenaline infusion and Clexane. The third echocardiogram showed that the EF had improved to 58% as the patient was administered a vasoactive drug; she also had mild PE, an RCA with a diameter of 2 mm, and an LCA with a diameter of 3 mm (normal Z-score).

Additional tests showed unaltered myocardial necrosis markers and altered D-dimer and fibrinogen levels (table 2). The elevated D-dimer level led to changes in the dose of Clexane. Echocardiography revealed the following EF: 69%; moderate TR; PASP: 35 mmHg; mild MR; and mild PE. At this time, the patient was only on milrinone.

The improvements seen in clinical signs, cardiac function, blood pressure levels, and hemodynamic stability led to the removal of the patient from the ICU after five days of IVIG. She was referred to the pediatric ward until she met the criteria for discharge, which happened after 12 days of hospitalization. The patient would then be followed at the cardiology ward.

During follow-up, an electrocardiogram showed evidence of early repolarization; myocardial perfusion scintigraphy showed no signs of ischemia, preserved left ventricular function, and an EF of 76%.

This article describes the case of a previously healthy child with MIS-C and SARS-CoV-2 infection. Despite needing intensive care, the patient progressed well.

DISCUSSION

The clinical manifestations observed in the patient described in this article were similar to the findings seen in individuals with Kawasaki disease shock syndrome (KDSS), which stems from myocardial dysfunction and decreased peripheral vascular resistance and usually requires resuscitation with intravenous fluids and infusion of inotropic and vasoactive agents in an ICU setting. However, it may mimic toxic shock syndrome and warrant the systematic administration of antibiotics, as seen in this article and in the literature.[12,13]

Table 2. Laboratory test results during stay at pediatric ward.

Laboratory tests	D6	D7	D8	D9	D11	Reference value[19]
Hemoglobin	11,6		11,6	11,6	12,2	12,5-14,5 g/dL
Hematocrit	32,9		35,6	40,1	39,5	36-45%
Leukocytes	17.990		14.460	13.610	8.900	3.500-10.000/mm^3
Platelets	268.000		370.000	501.000	529.000	100.000-424.000/mm^3
ESR*	380,2		287,7		190	7,0-140 ng/dL
Ferritin	243					115-25 UI/L
LDH*	3.186	2.872	2.341	1.566		<500 ng/dL
D-dimer	0,02		0,01			<2,0 ng/L
Fibrinogen	14		18	10		30-300 U/L
Troponin	15,5	14	8	15,1		<25 U/L
CPK*		2,86				3,5-4,7 g/dL
CK-MB*	0,47	0,51	0,39		0,47	0,32-0,64 mg/dL
Creatinine	16,7	11,4	18,5		33,8	8-36 mg/dL
Urea	100,9	99,3	104,7			98-112 mmol/L
Chlorine	3,3	4,19	3,4	5	4,6	4,5-5,5 mg/dL
Phosphor	132	130	135	136	134	135-145 mmol/L
Sodium	7,63	8	8,01	8,93	8,3	8,8-10,8 mg/dL
Calcium	1,5	1,52	2,1	2,6	1,8	1,6-2,4 mg/dL
Magnesium	3,86	4,11	4,72	5,36	5,1	3,5-5,1 mmol/L
Potassium		2,86	2,89	3,32		2,9-4,7 g/dL
Albumin	26	15,31	11,6	7	<6,0	<6,0 mg/dL
Uric acid	21	9	14			0,5-2,0 mmol/L
CRP*				1,17		10-14”/0,8-1
Lactate				32,2	41	24-40”

*D: day; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; CK-MB: creatinine kinase MB fraction; CRP: C-reactive protein; PT: prothrombin time; INR: international normalized ratio; APTT: activated partial thromboplastin time. All tests were performed based on manufacturer protocols. We opted to define reference values based on age and sex.

The pathophysiology of KDSS remains unclear. High levels of proinflammatory cytokines may contribute with the distributive component. KDSS has been associated with high levels of IL-6, C-reactive protein (CRP) and procalcitonin. Our patient had high CRP levels, as in the data presented in a case series.[12]

In a prospective observational study, Toubiana *et al*. looked into the possible time-related associations with COVID-19 in a group of 21 hospitalized children and adolescents with signs of KD and found that the mean time between the onset of symptoms of COVID-19 and KD was 45 days (18-79 days) and the mean age at the presentation of symptoms was 7.9 years (3.7-16.6 years); ten patients had pericardial effusion (48%).[12]

Grimaud *et al.*[15] published a study describing the cases of 20 severely ill children suspected for COVID-10 admitted at an intensive care unit for cardiogenic shock secondary to acute myocarditis. The authors showed that, in addition to acute myocardial systolic dysfunction, all children had hypotension and 15 had clinical signs of vasoplegia; all were prescribed IVIG for the first two days of hospitalization and were discharged with fully recovered systolic function and significant decreases in inflammation biomarkers after treatment.

Whittaker *et al*. published evidence of the existence of three patterns of involvement in hospitalized children with MIS-C. The first group of children had persisting fever and high inflammatory marker levels, but no signs of KD, shock, or organ failure. The second group met the diagnostic criteria for KD. The third group had shock and clinical, echocardiogram, and laboratory evidence of myocardial injury.[12]

The data presented in this article are consistent with the findings reported in other studies, thus building the case for a condition that occurs after infection by SARS-CoV-2.[14,15]

Studies showing clinical evidence from children are still scarce. Cardiac manifestations such as myocardial and coronary artery involvement occur repeatedly and must be recognized and managed. Clinical follow-up is of the essence, since outcomes are unclear and patients are at risk of presenting cardiac involvement. A consolidated approach must be developed to recognize the progression and stages of MIS-C.

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