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COVID-19 Related Multisystem Inflammatory Syndrome in Children: A Case Series from a Tertiary Hospital in Riyadh, Saudi Arabia

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Abstract

Introduction: We report an eight-case series of coronavirus disease 2019 (COVID-19)-related multisystem inflammatory syndrome in children (MIS-C). **Methods:** Children who tested positive for COVID-19, met the MIS-C criteria of the World Health Organization (WHO), and were hospitalized at a tertiary hospital in Riyadh from September to December 2021 were identified and their clinical data reviewed. **Results:** The age at diagnosis is between 4 to 13 years old. Fever, decreased oral intake, gastroenteritis, and abdominal pain were the most common symptoms. All cases showed hyperinflammation with high C-reactive protein, erythrocyte sedimentation rate, ferritin levels, and deranged coagulation profiles. Most of the cases had elevated B-type natriuretic peptide (75%) and troponin (100%) levels. However, two cases had cardiovascular involvement. Two patients presented with acute respiratory distress syndrome and required mechanical ventilation. The mean hospital stay was 13.1 days, with seven patients initially requiring intensive care management for ionotropic support. Most cases required broad-spectrum antibiotics, intravenous steroids, intravenous immunoglobulin, and aspirin. All patients recovered and were discharged from the hospital in good clinical condition. **Conclusion:** Children with COVID-19 are at risk of developing MIS-C. Practitioners must have a high index of suspicion for its diagnosis and should start treatment as soon as possible to prevent unfavorable outcomes.

Keywords

COVID-19, MIS-C, SARS-Cov2, Pediatric, Emergency

1. Introduction

The global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, which causes coronavirus disease 2019 (COVID-19), has spread rapidly. The pandemic began in 2020, with the first case reported in Saudi Arabia on March 2, 2020 [1]. Children with COVID-19 normally have moderate symptoms in contrast to adults, who frequently exhibit severe interstitial pneumonia and hyperactivation of the inflammatory cascade [2]. However, in rare cases, children can be severely affected, with severe clinical manifestations differing from that in severe cases in adults.

In April 2020, initial reports from the United Kingdom (UK) documented eight pediatric cases with incomplete Kawasaki disease (KD)-like presentations [3]. Since then, similar reports of affected children have emerged from other parts of the world [4] [5]. This condition has been termed multisystem inflammatory syndrome in children (MIS-C) related to COVID-19.

The case definition of the MISC-C related to COVID-19 was formulated by the Center for Disease Control (CDC) [6] and World Health Organization (WHO) [5] as a fever, two-system involvement, increased inflammatory markers, and COVID-19 infection confirmed by polymerase chain reaction (PCR) or exposure to infected cases in the previous 4 weeks.

There have been very few reports of MIS-C in Asia, with most cases reported in North America and Europe [5] [7] [8] [9]. Large case studies carried out in the United States (US) and the UK have shown that the risks for acquiring MIS-C may differ by gender, age, and ethnicity, while primarily affecting males belonging to black and Hispanic communities [7] [8]. Moreover, some cases have been reported in Middle Eastern countries, such as Saudi Arabia, Qatar, the United Arab Emirates (UAE), and Jordan [10]-[15].

In this study, we report eight cases as part of the global effort to establish a clear picture of this syndrome to enable further development of evidence-based clinical guidelines to detect and treat affected children early and properly.

2. Method

The Security Forces Hospital is one of the tertiary care hospitals in Riyadh, Saudi Arabia. We carried out a descriptive analysis that summarized the clinical presentation, complications, and outcomes of patients who met the case definition for MIS-C from September to December 2021.

We collected 8 cases were hospitalized at a tertiary hospital in Riyadh, Saudi Arabia. Children who tested positive for COVID-19 by PCR or antibody serology and who met the WHO MIS-C criteria were identified in the electronic medical records. Medical microbiologists and pediatric emergency medicine physicians reviewed their charts. Data were collected and de-identified in a standard format. For continuous variables, descriptive statistical analyses were performed and the results presented as means, or as numbers and percentages for nominal and categorical variables.

3. Results

We assessed eight cases of MIS-C, all of which were treated at our hospital and met the WHO guidelines. Most patients were female, with a mean age of 9 years at diagnosis (62.5%) (Table 1). Most patients had previously been in good health (75%). Seven patients were first admitted to the pediatric intensive care unit (PICU). The most prevalent presenting symptoms in MIS-C patients at our hospital were fever (100%), reduced oral intake (100%), gastroenteritis with diarrhea and vomiting (87.5%), and abdominal pain (62.5%) (Table 1). There was a low prevalence of upper respiratory infection (URI) symptoms, with two patients reporting cough and conjunctivitis.

Of the eight patients, five received positive PCR results for COVID-19 (62.5%). The remaining three had previously tested negative by PCR but tested positive for COVID-19 by antibody serology (Table 2). All patients underwent comprehensive laboratory testing upon admission or when MISC was suspected (Table 2).

Three patients were lymphopenic for their age, and most of the patients had high total white blood cell (WBC) counts (>11 × 10^3 /L; 75%). Six patients had thrombocytosis. All MIS-C patients displayed hyperinflammation, abnormal coagulation profiles, and elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin levels. (Table 2) The most frequent abnormalities on chest radiography are bilateral perihilar infiltrates and peribronchial thickening. One patient underwent abdominal ultrasonography followed by abdominal computed tomography (CT), which revealed mesenteric lymph nodes

Table 1. Patient characteristics and clinical presentation.

	Demographic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Summery
	Age (Yars)	4	9	9	13	9	10	6	12	9
	Gender	Male	Female	Male	Female	Female	Male	Female	Female	Female, 63%
	Chronic diseases	No	No	No	No	No	No	Yes	Yes	Healthy, 75%
Clinical Presentation	Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
	Rash	Yes	Yes	No	No	Yes	No	No	No	38%
	Tachycardia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
	Tachypnea	No	No	Yes	Yes	No	Yes	No	Yes	50%
	Hypotension	Yes	No	Yes	Yes	Yes	No	Yes	Yes	75%
	Abdominal Pain	Yes	No	No	Yes	Yes	No	Yes	Yes	63%
	Diarrhea	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	88%
	Vomiting	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	88%
	Decreased Oral Intake	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
	Cough	No	No	Yes	No	No	Yes	No	No	25%
	Conjunctivitis	Yes	Yes	No	No	No	No	No	No	25%

Table 2. Patients laboratory results.

Laboratory		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Summery
COVID-19	PCR*	Positive	Positive	Negative	Negative	Positive	Positive	Negative	Positive	62.5%
	Antibody Serology	Not Done	Not Done	Positive	Positive	Not Done	Not Done	Positive	Not Done	3/3 Positive 100%
Hematology	WBC*	Normal	Normal	High	High	High	High	High	High	75% Above Normal Range (4 - 11 (10^3/L))
	Hemoglobin	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	100% Normal Range (11 - 15 G/Dl)
	Lymphocyte	Normal	Normal	Low	Normal	Low	Low	Normal	Normal	38% Below Normal Range (1.3 - 8 (10^9/L))
	Neutrophil	Normal	Normal	High	High	High	High	High	High	75% Above Normal Range (30%–70%)
	Platelets	Normal	Normal	High	High	High	High	High	High	75% Above Normal Range (150 - 450 (10^3/Ul))
Inflammatory Markers	ESR*	High	High	High	High	High	High	High	High	100% Above Normal Range (0 - 20 Mm/H)
	CRP*	High	High	High	High	High	High	High	High	100% Above Normal Range (<5 Mg/L)
	Ferritin	High	High	High	High	High	High	High	High	100% Above Normal Range (22 - 275 Ug/L)
Coagulation	Prothrombin Time	High	High	Not Done	Not Done	Not Done	High	Not Done	High	4/4, 100% Above Normal Range (11 - 15 Sec)
	D-Dimer	High	High	High	High	High	High	High	High	100% Above Normal Range (0 - 0.5 Ug/Ml)
	Fibrinogen	High	High	High	High	High	High	High	High	100% Above Normal Range (1.91 - 4.14 G/L)
Cardiac Enzymes	Troponin (Ng/L)	High	High	High	High	High	High	High	High	100% Above Normal Range (<34.20 Ng/L)
	ProBNP*	High	High	High	High	Normal	High	Normal	High	75% Above Normal Range (<73 Ng/L)
Renal	Creatinine	Normal	High	High	High	Normal	Normal	Normal	Normal	38% Above Normal Range (40 - 72 Umol/L)
	Urea	Normal	High	High	High	Normal	Normal	Normal	Normal	38% Above Normal Range (2.50 - 6 Mmol/L)

*COVID-19: cornoa virus 2019, PCR: polymerase chain reaction, WBC: white blood cells, CRP: c-reactive protein, ESR: Erythrocyte sedimentation, proBNP: ProB-Type Natriuretic Peptide.

with prominent appendices (Case 5). In another case, ultrasonography revealed hepatomegaly associated with elevated liver function enzymes, which subsided after two weeks of follow-up (Case 7). All patients underwent echocardiography at the time of diagnosis with a minimum four-week follow-up, and patients with

abnormal results underwent echocardiography at 8 weeks or earlier (Table 3).

Two patients in the study group had cardiovascular involvement inform of dilated left ventricle, depressed left ventricle, and Mitral Valve Regurgitation (25%). Two patients had ejection fractions (EF) < 55%, indicating ventricular dysfunction. Five patients had inotropic support either to maintain blood pressure not responding to fluids or cardiac contractility. However, High B-type natriuretic peptide (proBNP) and troponin levels were detected in 75% and 100% of the patients (Table 2).

Acute respiratory distress syndrome (ARDS) was evident in two cases (cases 6 and 8; Table 3) and required mechanical ventilation. In both cases, the hospital stay was extended and exceeded 10 days. One patient (case 6) who had trouble walking and speech abnormalities underwent physiotherapy, occupational therapy, and speech therapy followed by brain MRI and the results were unremarkable.

Table 3. Patients' clinical outcome and treatment.

Clinical Outcome		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Summery
Hospital Length Of Stay (Days)		11	13	9	20	10	22	6	14	13.12
ICU Stay (Days)		5	0	3	12	4	6	3	11	5.5
Mechanical Ventilation		Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	88%
Shock		Yes	No	Yes	Yes	Yes	No	Yes	Yes	75%
Abnormal Echocardiogram		No	No	Yes	Yes	No	No	No	No	25%
Abnormal ECG*		No	No	Yes	Yes	No	No	No	No	25%
Ejection Fraction		65%	70%	48%	40%	70%	65%	65%	67%	25% Below The Normal Range (>55%)
Dilated Left Ventricle		No	No	Yes	No	No	No	No	No	13%
Depressed Left Ventricle		No	No	No	Yes	No	No	No	No	13%
Mitral Valve Regurgitation		No	No	Yes	No	No	No	No	No	13%
Abnormal CXR*		No	No	Yes	No	Yes	Yes	No	Yes	50% Abnormal
Abnormal US Abdomen*		No	Not Done	Not Done	Not Done	Yes	Not Done	Yes	Not Done	2/3, 66.6% Abnormal
Abnormal CT Abdomen*		Not Done	Not Done	Not Done	Not Done	Yes	Not Done	Not Done	Not Done	1/1, 100% Abnormal
Treatment	IVIG*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
	Corticosteroids	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
	Antibiotics	Yes	Yes	Yes	Yes	Yes	Yes	None	Yes	88%
	Antivirals	None	None	Yes	None	Yes	Yes	None	Yes	50%
	Inotropes	Yes	None	Yes	Yes	Yes	None	None	Yes	63%
	Aspirin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%

*ICU: intensive care unit, ECG: electrocardiogram, CXR: chest x-ray, US: ultrasound, CT: computed tomography, IVIG: intravenous immunoglobulins.

After 2 weeks of follow-up, these difficulties resolved, and the patient was in good health.

The average length of hospital stay for the MIS-C patients in this study was 13.1 days. Of these, 87.5% were initially admitted to the PICU, where they required intubation, and ionotropic support was initially needed for five patients (62.5%).

Broad-spectrum antibiotics, intravenous (IV) steroids, IV immunoglobulin, and aspirin were administered to the majority of patients as per the Saudi Ministry of Health Protocol for MIS-C (**Table 3**). All the patients received aspirin throughout their hospital stay and after being discharged to prevent coronary thrombosis. All our patients achieved full recovery and left the hospital in good clinical condition.

4. Discussion

This report presents the cases of eight children who visited our hospital with MIS-C associated with COVID-19. KD and toxic shock syndrome (TSS) have similar characteristics, but are also distinct from one another [11]. This case series offers details on the disease epidemiology at a single tertiary hospital.

A history of COVID-19 exposure or infection based on PCR results led to an early suspicion of MIS-C for most patients. Antibody serology testing was helpful in determining the COVID-19 infection status in three cases where PCR results were previously negative. Overall, most of our patients had positive COVID-19 PCR results (62.5%), which was similar to the ≥50% positive COVID-19 PCR results reported in other studies [14] [16] [17]. The remaining three patients who tested positive for SARS-CoV-2 antibodies by serological testing at the time of presentation supported the postinfectious nature of the disease [18].

The clinical presentations in most MIS-C patients in this case series were consistent with other findings, with fever and gastrointestinal problems being the most common early symptoms [10] [12] [13] [14] [15] [17] [19]. As per our observations, respiratory symptoms were less common in this series, with only two patients who developed a cough and five more that required intubation for ionotropic support in the absence of severe lung disease. Although some studies have indicated that a larger percentage of people require respiratory assistance during their illness, our results were consistent with earlier studies of pediatric cases [12] [16] [19] [20]. The patients' signs and symptoms in our case series contrasted with a previously published study on children in Latin American communities, which found a higher prevalence of upper and lower respiratory tract infections and a lower percentage of gastrointestinal symptoms among MIS-C patients [21].

Recent publications have confirmed certain cardiac involvement in patients with MIS-C, emphasizing its similarities with KD. This highlights the need for cardiac evaluation using echocardiography at the time of diagnosis and at frequent intervals in accordance with KD treatment [7] [22]. It has been shown that

up to 56% of patients with MIS-C have decreased ventricular function, with EF being the most prevalent cardiac abnormality found in these individuals, at 55% [19] [22]; however, KD has a lower proclivity for substantial ventricular dysfunction [14]. Although most patients in our case series required inotropic support either to maintain blood pressure not responding to fluids or cardiac contractility, only two had transient left ventricular dysfunction that recovered quickly, in contrasts with patients with KD who rarely present with hemodynamic instability. Similar results have been reported in Qatar and Saudi Arabia [7] [13] [14].

Elevated troponin levels have previously been linked to poor outcomes in patients with COVID-19 and may indicate the degree of systemic inflammation and myocardial damage [23]. The troponin, proBNP, and D-dimer levels were elevated in our case series (**Table 2**). According to one study, coronary artery involvement occurs in up to 15% of MIS-C cases, with only a few individuals developing large aneurysms [17] [20] [22] [24]. Although the real rate of such involvement is unknown, it appears to be similar to that of KD, in which it occurs in around 25% and 4% of untreated and treated individuals, respectively [25].

In our case series, there were no reports of aneurysms detected by echocardiography. Elevated levels of inflammatory markers and signs of coagulopathy are typical laboratory findings with significance in the clinical diagnosis of MIS-C. The relationship between the two factors in MIS-C patients, however, remains unknown. It has been proposed that a "cytokine storm," which is an increased production of inflammatory cytokines, particularly interleukin (IL)-6, may activate the coagulation cascade in COVID-19 patients [26] [27].

In our study, patients with MIS-C had coagulation dysfunction in the form of significantly increased D-dimer and fibrinogen levels and irregular PT. IL-6 levels, on the other hand, were not available. One study found a favorable connection between IL-6 and fibrinogen levels in individuals with COVID-19-related ARDS [28]. Another study suggests that the cytokine storm in MIS-C patients is different from that in adult patients with severe acute COVID-19 and that autoantibodies, such as lupus anticoagulants, may play a role in COVID-19-linked coagulopathy and thrombosis [29].

Except for one, most patients in our case series initially required PICU care with inotropic support either to maintain blood pressure not responding to fluids or cardiac contractility being the primary cause of PICU admission, which was similar to prior MIS-C studies [7] [13] [14] [16] [19]. Previous studies reported a mortality rate of 1.7% - 1.8% [19] [30]. None of the cases in our case series resulted in death. All patients received aspirin for coronary thrombosis prevention, according to the American Heart Association (AHA) recommendations for treating patients with KD [25].

All eight patients were initially treated with antibiotics, similar to cases reported in other studies [10] [12] [13] [14] [15]. Although there is considerable

concern regarding antibiotic overuse in children with COVID-19 [27], the significant overlap between the clinical presentation of MIS-C and other life-threatening bacterial infections such as sepsis and TSS justifies the empirical use of broad-spectrum antibiotics in these patients until a diagnosis is established and negative culture results are available [31]. Most of our patients responded effectively to intravenous immunoglobulin (IVIG) plus IV corticosteroids in terms of fever reduction and fewer requirements for inotropic support. In contrast, a study in Qatar found that two individuals required an IL-1 inhibitor because they had ARDS and coronary artery disease aneurysm [14].

Because of the similarities between MIS-C and KD and their cardiac involvement, current cardiac treatment strategies are comparable [7] [19]. However, the long-term consequences of MIS-C, such as complications of coronary artery aneurysm development remain unclear. Long-term cardiac follow-up is needed to assess the impact on heart function and persistence or regression of coronary aneurysms.

5. Conclusions

Here, we report an eight-case series of COVID-19-associated MIS-C. Our patients frequently presented with fever and gastrointestinal problems that necessitated hospitalization. Leukocytosis and thrombocytosis were the most prevalent laboratory results, with increased CRP, ferritin, fibrinogen, D-dimer, PT, pro-BNP, and troponin. Despite high cardiac enzymes in most of the cases, cardiovascular involvement was observed in two patients, one with mitral valve regurgitation and a dilated left ventricle, and the other with a depressed left ventricle. Most patients were administered IVIG, antibiotics, aspirin, and steroids. All the patients recovered completely.

Children infected with SARS-CoV-2 are at risk of encountering MIS-C. Even though the clinical characteristics and outcomes are not significantly different from those previously reported, practitioners must have a high index of suspicion for this diagnosis and begin therapy as soon as possible to avoid unfavorable outcomes. Further research is needed to provide a comprehensive picture of this illness to develop evidence-based clinical guidelines. Long-term follow-up studies are necessary to investigate the potential consequences of MIS-C.

Declaration

- **Ethics approval and consent to participate:** Case series was approved by Security Forces Hospital IRB no 2155770. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.
- **Consent for publication:** Not applicable.
- **Availability of data and materials (ADM):** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- **Competing interests:** The authors declare that they have no competing interests
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- **Authors' contributions:** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yara AlGoraini, Mona Jawish, Shadia Ahmed, and Elsharif Bazie. The first draft of the manuscript was written by Yara AlGoraini, Alaa Şeyhibrahim, Azzam Alabdulqader, and Mohammed Al Awad. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

Coronavirus Disease 2019	(COVID-19)
Multisystem Inflammatory Syndrome In Children	(MIS-C)
World Health Organization	(WHO)
Severe Acute Respiratory Syndrome Coronavirus 2	(SARS-Cov-2)
United Kingdom	(UK)
Kawasaki Disease	(KD)
Center For Disease Control	(CDC)
Polymerase Chain Reaction	(PCR)
United States	(US)
United Arab Emirates	(UAE)
Pediatric Intensive Care Unit	(PICU)
Upper Respiratory Infection	(URI)
White Blood Cell	(WBC)
C-Reactive Protein	(CRP)
Erythrocyte Sedimentation Rate	(ESR)
Computed Tomography	(CT)
Ejection Fractions	(EF)
ProBNP	(ProB-Type Natriuretic Peptide)
Acute Respiratory Distress Syndrome	(ARDS)
Intravenous	(IV)
Toxic Shock Syndrome	(TSS)
Interleukin	(IL)
American Heart Association	(AHA)
Intravenous Immunoglobulin	(IVIG)