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An 11-Year-Old Saudi Arabian Girl Who Presented with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 Infection with Coronary Artery Aneurysm and Cardiac Involvement: A Case Report

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CDE **Mohammed Al Qahtani**
ACDEF **Mohammed Shahab Uddin**
B **Saleh Al fulayyih**
G **Sarah Al Baridi**
F **Zuhair Hamid**

Department of Pediatrics, Ministry of National Guard Health Affairs, Dammam, Saudi Arabia

Corresponding Author: Mohammed Shahab Uddin, e-mail: uddinmo@nga.med.sa
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Patient: Female, 11-year-old
Final Diagnosis: Pediatrics multisystem inflammatory syndrome
Symptoms: Cough • fever • shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual clinical course
Background: Early in the COVID-19 pandemic, children who were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with vascular inflammation were described as having a vasculitis similar to Kawasaki's disease. There are now consensus clinical guidelines that have described the presentation and diagnosis of multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection. This report aims to describe a case of MIS-C in an 11-year-old Saudi Arabian girl who presented with coronary artery aneurysm and cardiac involvement.

Case Report: We describe an 11-year-old Saudi girl who was asymptomatic for 3 weeks after contracting SARS-CoV-2. Three weeks after suffering a mild flulike illness, she developed a high fever, cough, and severe clinical deterioration within 12 h of admission, including shock, rash, pleural effusion, high inflammatory markers, and a coronary aneurysm. As per current practice, the diagnosis was confirmed as multisystem inflammatory syndrome based on a SARS-CoV-2 test with reverse transcription polymerase chain reaction (RT-PCR) from 2 nasopharyngeal aspirates. Her condition was successfully treated with antibiotics, inotropes, IVIG, aspirin, and Tocilizumab, in addition to high-flow oxygen therapy. Eventually, she was able to return home after fully recovering.

Conclusions: The findings in this report suggest that children with MIS-C due to SARS-CoV-2 infection can have a good prognosis, even when they suffer from coronary artery and cardiac involvement. The increasing number of emerging SARS-CoV-2 variants that affect children supports the importance of RT-PCR for the COVID-19 diagnostic test for children with multisystem or cardiovascular inflammation, which may guide the most appropriate clinical management of the variants of MIS-C.


Keywords: COVID-19 • Severe Acute Respiratory Syndrome Coronavirus 2 • Pediatric Multisystem Inflammatory Disease, COVID-19 Related • Coronary Aneurysm • Case Reports • COVID-19 Diagnostic Testing

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/933053>

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Background

Since the middle of spring 2020, a new cluster of cases of multisystem inflammatory syndrome (MIS-C) in children has been identified. The MIS-C variant of SARS-CoV-2 infection is characterized by acute febrile illness, stomach pain, gastrointestinal symptoms, shock, and cardiac involvement. There were many similar cases reported initially in Europe, and later in the USA, indicating the possibility of SARS-CoV2 infection, especially in northern Italy and France. However, diagnosis requires either RT-PCR, serological testing, or contact with a COVID-19 patient [1-3]. The incidence of the multisystem inflammatory syndrome in the USA person was 316 (95% CI, 278-357) persons per 1 million SARS-CoV-2 infections [4]. Although the prevalence of MIS-C is unknown, more than 4018 cases have been reported so far in the USA by the Centers for Disease Control and Prevention (CDC) [3]. A case definition of MIS-C has been published by the World Health Organization (WHO) and the Disease Control and Prevention Centers (CDC) [5,6].

In the study of 95 confirmed MIS-C patients in New York, the pro-B-type natriuretic peptide (proBNP) level was elevated in 74 out of 82 (90%). Sixty-three out of 89 patients (71%) showed increased troponins with echocardiographic features indicative of perimyocarditis, heart function defects, and shock, but with normal coronaries. Around 62% of the cases required vasopressors, with predominant clinical features of gastrointestinal and mucocutaneous involvement [7]. The prospective Brazilian multicenter study by Fernanda Lima-Setta et al documented 56 cases of MIS-C, and more than half of the affected patients had gastrointestinal symptoms, nearly 60% had rash, and more than 60% were in shock. Furthermore, approximately two-thirds of MIS-C case studies show echocardiographic features such as pericardial effusion, depressed left ventricular function, and coronary artery ectasia of about 27% [8]. A case series experiment was conducted at the Tertiary Care Hospital in southern Turkey with 52 children diagnosed with MIS-C. The median age of the patients was 9 (5-13) years. There was significant left ventricular dysfunction of 17.3%, along with fever (92.3%), nausea (76.9%), rash (48.1%), and vomiting (48.1%). Neither coronary artery disease nor myocarditis has been diagnosed [9].

There have been other studies showing a median age of 7 years, with a significant number of patients having comorbidities and elevated D-dimers, as in previous cohort studies, as well as fever, abdominal pain, vomiting, mucocutaneous involvement, and elevated inflammation markers. Lymphopenia and thrombocytopenia were both found in 24 (53%) and 17 (38%) patients, respectively. Among 25 patients (56%) who were diagnosed with cardiac involvement, 31% had coronary artery involvement and 18% had myocarditis [10]. The SARS-CoV-2 infection associated with this novel syndrome, MIS-C, has been associated

with a number of cardiovascular complications, including heart failure, pericardial effusions, myocarditis, and rhythm irregularities. A severe case may present with cardiogenic shock or distribute shock, requiring fluid resuscitation and inotropic support [11-14]. Among 10 patients in Saudi Arabia, 30% experienced cardiovascular involvement, shock, left ventricular dysfunction, and pericardial effusion, but coronary artery ectasia and aneurysms were not observed [15]. A similar echocardiographic finding was noted in more than half of MIS-C cases with coronary artery ectasia rather than aneurysm [16]. Further, a few published case reports indicated no coronary lesion [17-19]. We believe this to be the first reported case of coronary artery aneurysm associated with MIS-C in Saudi Arabia. The purpose of this report is therefore to describe a case of MIS-C in an 11-year-old Saudi Arabian girl who presented with a coronary artery aneurysm and cardiac involvement.

Case Report

An 11-year girl with a high-grade fever and a productive cough was admitted to the pediatric ward on 25 October 2020. Three weeks prior to her presentation, she had become infected with SARS-CoV-2. Initially, the symptoms of her illness appeared similar to that of mild flu. At home, she was able to cope with her illness. In terms of systemic review, the symptoms were unremarkable aside from mild abdominal pain, throat pain, and a lack of appetite without taste distortion. She had no unusual history of drugs, allergies, medical history, or surgical procedures. Her family lives in the eastern region of Saudi Arabia. She is a first-degree relative of her parents. Although her mother and 3 siblings are healthy, the family was in crisis after her father died from complications caused by SARS-CoV-2.

She had a fever of 39.5°C, was looking unwell, with congested tonsils, but no conjunctivitis or lymphadenopathy and no skin rash. The patient was fully oriented, did not experience respiratory symptoms, and her hemodynamic state was stable. An examination of the abdomen revealed no anomalies. In the initial laboratory tests, 2 nasal aspirates were positive for SARS-CoV-2 via reverse transcription polymerase chain reaction (RT-PCR). Tests of the blood found elevated levels of inflammatory markers, notably C-reactive protein (CRP) 127 and ferritin 1313.9. However, white blood cell totals were normal at 5.29. A differential count revealed that the neutrophil count was normal, lymphocytopenia was present, and the D-dimer was 4.02, with normal prothrombin time (PT), partial thromboplastin time (aPTT), and international normalized ratio (INR). An X-ray of the chest (**Figure 1**) and a renal and liver profile (**Table 1**) revealed no abnormalities.

Initially, she was admitted to the general pediatric ward for observation, but her condition deteriorated 12 h after admission.



Figure 1. Chest X-ray on admission. Both lung fields are over-aerated. No parenchymal consolidation or ground-glass opacities in either lung field. Normal chest X-ray finding.

A progressive cough was accompanied by a spiked temperature of 39.8°C, hypotension, tachycardia, and an erythematous maculopapular rash with no itching, mostly on the face, trunk, and neck. She did not have lymphadenopathy or non-purulent conjunctivitis. After receiving fluid boluses, she was transferred to the pediatric intensive care unit. Due to persistent high-grade fever, the patient underwent additional testing, including blood culture, urine culture, and chest X-ray. At 12 h after admission, a chest X-ray demonstrated bilateral basal pneumonic patches (**Figure 2**).

Azithromycin and Ceftriaxone were started after consultation with the infectious disease team at the time of admission to the PICU. Additionally, norepinephrine 0.3 microg/kg/min was administered to help maintain blood pressure during this time. At 48 h after admission, the inflammatory markers D-dimer 5.21, ferritin 4538.6, procalcitonin 12.7, and CRP 139.1 had increased along with higher oxygen consumption via the non-rebreathing face mask. Dexamethasone, A low molecular weight heparin, and tocilizumab were further recommended as per institutional guidelines for SARS-CoV-2 infections, along with a cardiology referral for a high suspicion of Kawasaki-like vasculitis.

In spite of 2 doses of tocilizumab, her condition remained critical at 96 h after admission, with a persistent fever of 39.8°C, respiratory distress, and bilateral pleural effusions, as well as need for a high-flow nasal cannula oxygen (25 L/min). Moreover, the levels of inflammatory markers (**Table 1**) remained high,

with CRP 186.7, ferritin 4543, and D-dimer 4.59. In the meantime, echocardiographic findings revealed mildly diminished left ventricular function, dilated main left coronary artery 4.3 mm (Z score=3.9), and left descending coronary artery 3.4 mm (Z score=3.1). Due to the sustained high-grade fever, high inflammatory markers, rash, shock, and positive SARS-CoV-2 RT-PCR tests, the diagnosis of MIS-C was established. The possibility of other differential diagnoses was ruled out since all cultures were negative.

The antibiotics were switched to Piperacillin+Tazobactam 100 mg/kg/dose every 8 h after 96 h of illness. In addition to aspirin, intravenous immunoglobulin was introduced. The patient was treated with intravenous immunoglobulin (IVIG) infusions of 2 g/kg, given slowly over 12 h, and given a high dose of aspirin (80-100 mg/kg/day). After a single dose of IVIG and a few doses of aspirin, her condition dramatically improved with no spike of fever within the next 48 h of illness. Subsequently, inflammatory markers decreased. The daily aspirin dose was reduced. She developed bilateral pleural effusion (**Figure 3**) during her stay in the Pediatric ICU, which was completely resolved on the follow-up chest X-ray taken on the 14th day of illness. Within 10 days of starting dexamethasone, the dose is gradually tapered off. There was no additional intervention needed in the PICU. Following a restful week at the Pediatric High-Dependent Unit, she was eventually discharged home from the general pediatric unit on her 17th day of illness after full recovery and normal electrocardiogram results. She was advised to follow up with her pediatric cardiologists after 2 weeks. Cardiologists conducted a follow-up exam on December 3, 2020, and determined that the patient's cardiac function and coronary arteries were normal, so she was advised not to use aspirin anymore.

Discussion

Researchers have found that MIS-C is a serious variant of SARS-CoV-2, which is different from both KD and severe COVID-19 [20]. Classically, manifestation of MIS-C typically occurs 3-4 weeks after SARS-CoV-2 infection. Positive antibodies to SARS-CoV-2 were prevalent in many cases, but the RT-PCR test was negative at the time of the diagnosis of MIS-C. It consists of 6 main components: persisting fever, pediatric age group, high laboratory marker of inflammation, signs or symptoms of organ damage, lack of other diagnoses, and clinically confirmed COVID-19 infection or exposure [21]. According to the published literature, our patient fulfilled the MIS-C case definition [5-6,22], manifesting unremitting fever >38°C with rash, shock, and cardiac involvement in the form of myocardial dysfunction, or coronary ectasia, as well as abdominal pain [7,23-25]. In addition, there is laboratory evidence of elevated inflammatory markers, CRP, and procalcitonin [20,26,27] and negative blood culture.

Table 1. The results of laboratory testing for the first 172 h of hospitalization. Neutrophil counts were normal, lymphocytopenia and thrombocytopenia were present, and inflammatory markers, such as CRP, Procalcitonin, Ferritin, and high D-dimer, peaked at 96 h after the illness began. Normal prothrombin time (PT), partial thromboplastin time (aPTT), and international normalized ratio (INR).

Lab test	Admission	48 hrs	96 hrs	120 hrs.	148 hrs	172 hrs	Reference
WBC	5.29	10.60	15.30	13.00	7.12	6.13	4-12×10 ⁹ /L
Neutrophil	4.08	8.78	8.87	4.80	3.01	0.92	1.10-7.2×10 ⁹ /L
Lymphocyte	0.55	0.40	0.64	1.14	1.28	3.17	1.30-7.20×10 ⁹ /L
Hb	10.2	9.2	8.7	6.6	8.5	8.3	113-150 gm/L
Platelet	199	108	114	99	129	143	150-400×10 ⁹ /L
CRP	127.5	139.1	186.7	225.4	46.1	23.1	(≤1.20 mg/L)
Procalcitonin	2.13	12.7	24.8	36.1	21.9	11.6	≤0.05 ug/L (ng/mL)
ESR	25	45	49	64	42	31	0-20
Ferritin	1313.9	4538.62	4543.0	1120.0	437.4	125.4	4.6-204 ug/L
LDH	276	231	218	X	244	X	125-220 u/L
D-dimer	4.02	3.21	4.59	3.1	2.4	1.7	0.00-0.50 mg/L
aPTT	34.9	31.3	31.2	29.4	24.9	22.1	26.2-37.0 sec
PT	11.6	9.5	10.9	14.4	9.8	9.9	7.6-10.4 sec
INR	1.1	1.1	1.6	1.1	X	1.1	0.8-1.2
Fibrinogen	3.3	X	0.5	1.5	X	1.5	1.50-4.10 gm/L
Troponin	X	48.3	X	29.3	23.4	17.9	≤15.6 pg/mL
Sodium	130	130	132	134	133	135	138-145 mmol/L
Potassium	3.4	3.6	3	3.8	3.5	4.1	3.4-4.7 mmol/L
Urea	2.3	2	3	4.2	3.5	2.5	2.5-6.0 mmol/L
Creatinine	52	39	40	46	40	45	27-62 umol/L
AST	47	30	21	22	X	13	5-34 U/L
ALT	33	41	32	24	27	25	5-55 U/L
Calcium	2.05	1.84	1.74	1.89	2.03	2.14	2.20-2.70 mmol/L
Magnesium	0.82	0.73	0.78	0.86	0.83	0.87	0.70-0.86 mmol/L

WBC – white blood cell; CRP – C-reactive protein; LDH – lactate dehydrogenase; AST – aspartate transaminase; ALT – alanine aminotransferase.

The further point of relevance is an epidemiological link with a SARS-CoV-2-positive case because she had contact with a family member who acquired the virus, as confirmed by a reverse transcription polymerase chain reaction (RT-PCR) manufacturer, Cepheid, kit type Xpert Xpress SARS-CoV2 test, approved by the Saudi Food and Drug Authority in October 2020.

This is the first case report of multisystem inflammatory syndrome in children (MIS-C) in Saudi Arabia involving coronary

artery aneurysm, left ventricular dysfunction, hyperinflammation, and multiorgan damage associated with SARS-CoV-2 infection. Rapid clinical deterioration has been shown in most studies as a cardinal feature, associated with shock, poor capillary refilling times, and skin rashes, and necessitating fluid bolus administration followed by inotrope support, as in our case [15-17,24] In fact, shock is either cardiogenic or distributive in nature [28,29]. de Lama Caro-Paton published a case series in a pediatric intensive care unit in Madrid, Spain, with

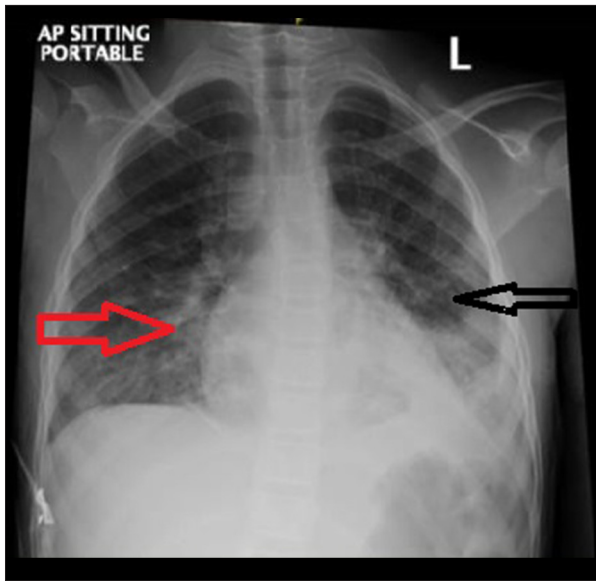


Figure 2. Chest X-ray 12 h after admission, showing moderate-size patchy area of consolidation in the left lower lobe. Also, there is an area of glass-ground opacity and consolidation noted in the right lower zone medially, suggestive of bronchopneumonia.

12 patients with MIS-C ages 5-14 years old. All patients presented with shock and received volume resuscitation, 75% required vasoactive/inotropic support, 67% had a high hs-cTnI, and 33% demonstrated left ventricular dysfunction [29].

Kawasaki disease (KD), Behcet's syndrome, Takayasu disease, connective tissue disorders, HIV, and fungal and syphilitic infections are among the prominent causes of coronary artery ectasia or aneurysm in adults [30]. However, KD, polyarteritis nodosa, and other vasculitis are more commonly responsible for coronary artery ectasia and aneurysms in children [13], but MIS-C in association with SARS-CoV-2 has only recently been observed as a common cause of coronary artery involvement. This has not been documented in Saudi Arabia in published case reports.

In a systematic review published by Rodriguez-Gonzalez et al, 688 MIS-C cases were identified as having cardiovascular events. Cardiogenic shock was present in 53.20% (48.70-57.80%), pro-BNP increased was present in 86.80% (83.60-89.40%), and ECG abnormalities were present in 27.6% (23.9-31.6%). The incidence of myocardial dysfunction was 52.20% (48.40-56.00%), coronary artery ectasia/aneurysm was 15.40% (12.40-17.80%), and 53.4% of patients required PICU (Pediatric Intensive Care Unit) care [31]. There have been a number of cohort studies and meta-analyses that reached similar conclusions [12,32,33,35]. Although coronary artery aneurysm rates in MIS-C are unknown, patients with MIS-C but without KD features have been reported to have coronary

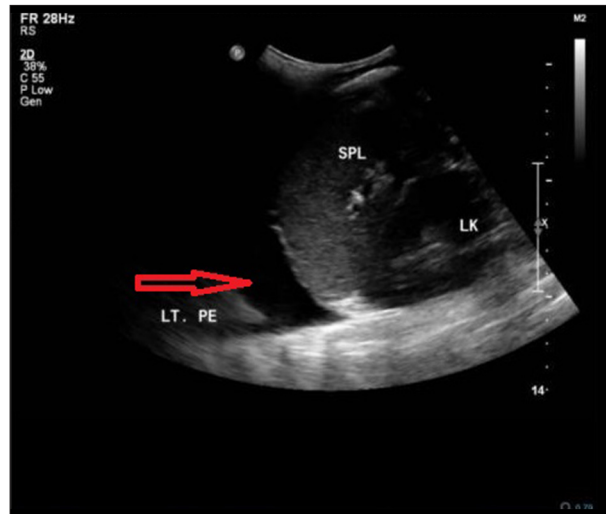


Figure 3. Left subdiaphragmatic longitudinal view ultrasonography, showing a moderate left pleural effusion with collapsed left lung.

artery aneurysms [34,36]. The American College of Cardiology called attention to the risks of cardiac involvement in patients infected with Covid-19 in Feb 2020 [37]. According to existing evidence, worldwide published articles reported major cardiac manifestations, including ventricular dysfunction, coronary artery ectasia, arrhythmia, conduction abnormalities, and vasodilatory shock requiring fluid resuscitation, along with inotropic support [38].

Nonetheless, the pathophysiology of cardiac lesions caused by MIS-C in children has not been fully described. Various theories suggest that SARS-CoV-2 spike proteins, infecting cardiomyocytes through the angiotensin converting enzyme 2 (ACE2) receptor, caused myocardial damage and deregulated immune function, and the subsequent cytokine storm leads to multiorgan failure and severe cardiotoxicity [31]. Further, due to prolonged hypoxia and ischemia, microvascular thrombosis, coronary artery disease, right heart strain, and stress cardiomyopathy, a consequence of oxygen demand and supply imbalance, all contribute to cardiac muscle damage [29]. Medications like lopinavir/ritonavir, hydroxychloroquine, and tocilizumab, whose safety margins are less clear, could worsen cardiac dysfunction in pediatric patients with COVID-19 infection [31]. As reported by biopsy, a COVID-19 viral particle localized in the myocardium [39] leads to severe necrotizing myocarditis [40]. High levels of troponin I (Trop I), myoglobin (myo), and n-terminal brain natriuretic peptide (NTBNP) generally indicate severe, fulminant myocarditis [39]. In terms of intensive care unit admission, ventilation, and death, abnormally elevated cardiac markers provide valuable prognostic information [13]. There is a significant role for genetic susceptibilities in the pathogenesis of MIS-C in both immunological and non-immune ways [41]. Cardiovascular magnetic

resonance imaging (MRI) on T2-STIR sequences and native-T1 mapping without late gadolinium enhancement clarified post-infectious myocarditis in children [42].

At 12 h after admission, her condition was rapidly deteriorating, with severe lung consolidation, which required administration of a high-flow nasal cannula. This led to the physician misdiagnosing her illness as severe COVID-19, rather than MIS-C. As a consequence, despite adequate antibiotic coverage and steroid treatment, as well as 2 doses of tocilizumab, she remained ill and febrile. Moreover, her overall health rapidly deteriorated, as she developed persistent fever, worsening respiratory distress, and progressive elevation of inflammatory markers. As a rule, respiratory manifestations such as breathlessness, coughing, increased oxygen demand, and progressive lung consolidation do not occur in MIS-C [43]. As other papers have documented, the clinical presentation of MIS-C has sometimes resembled that of severe COVID-19 disease [44-47].

At 96 h after hospital admission, her CRP was 186.7, ferritin was 4543, and D-dimer was 4.59. Meanwhile, echocardiography reported mildly depressed left ventricular function, dilated main left coronary artery 4.3 mm (Z score=3.9), and left descending coronary artery 3.4 mm (Z score= 3.1). Our patient's ECHO finding was consistent with a minor coronary aneurysm. A normal coronary artery Z score is less than 2, ectasia is Z score 2-2.5, and a minor aneurysm is Z score greater than 2.5 to less than 5 [48]. In fact, coronary artery involvement was described in the majority of studies [47,49-54]. Skin rash, which appeared in the early course of illness of our patient, is another cardinal sign of MIS-C. Our findings agree with previous findings that 36-81% of MIS-C patients had rash [45,47,55-61]. Laboratory findings of our case are in keeping with similar publications on leukopenia and thrombocytopenia [20,62,63] high ferritin, abnormal D-dimer, and elevated troponin [20,46,64,65]. In contrast to other findings, acute kidney injury (AKI) [64,66-69], prolonged coagulation profile, abnormal fibrinogen, and abnormal liver function[70-73] were not observed in our case.

According to a recent literature review, the vast majority of multisystem inflammatory syndrome patients recovered from treatment with intensive care, which typically included respiratory support, inotropes, intravenous immunoglobulin (IVIG), and steroids [74-76], as well as Anakinra or tocilizumab for immunomodulation [24,77]. A second dose of immunoglobulin and pulse methylprednisolone may be considered prior to immunomodulatory adjuvants [74]. Our case provides a noteworthy example of the failure of both tocilizumab and steroids to control the symptoms rather than IVIG, since most references suggest IVIG combined with steroids and Anakinra as the second-line treatment option, and then tocilizumab as the third. In Saudi Arabia there were no guidelines on MIS-C management, so most patients were treated according to COVID-19

procedures, which included antiviral drugs, interleukin-6 (IL-6) inhibitors, and low molecular weight heparin [70]. Anakinra was unavailable to all the patients in the Saudi Arabian case series, which had a fatality rate of 20% [16]. It is currently included in hospital guidelines, to the best of our knowledge.

The fever gradually subsided and inflammatory markers began to fall after adding IVIG in addition to steroids after 96 h of hospitalization. The treatment was augmented with high-dose aspirin and standard-dose IVIG 2.4 gm/kg/dose. We observed coronary artery dilation in 17% of cases of MIS-C, either observed shortly after hospitalization or at follow-up, which is mainly short-term cases either observed during hospital recovery or at follow-up [13]. Additionally, a giant coronary aneurysm with a Z score >10 was reported, which required prolonged anticoagulant treatment and cardiac monitoring [76]. No appropriate treatment scheme for pediatric multisystem inflammatory syndrome has yet been identified, but some guidelines have been established [27,77]. Antiplatelet-dose aspirin may be prescribed for patients who have coronary artery aneurysms, and anticoagulants may be prescribed for coagulopathic patients (high D-dimer level) or patients with large or giant aneurysms [16]. The conclusion on the optimal treatment of MIS-C will be determined by improved understanding of the disease and randomized multicenter double-blind controlled studies.

Conclusions

The MIS-C illness is a completely distinct condition following SARS-CoV-2 infection. There is very little risk of mortality, even if there are some long-term effects. Most patients get better quickly. The most effective clinical management requires a multidisciplinary approach that includes critical care, infectious disease, immunology, cardiology, and rheumatology. Various therapies have been proven to be successful, including intravenous immunoglobulins, steroids, and other immunomodulatory drugs. Long-term follow up is recommended for those with significant cardiac damage.

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Department and Institution Where Work Was Done

Department of Pediatrics, Imam Abdulrahman Bin Faisal Hospital, Ministry of National Guard, Dammam, Saudi Arabia

Conflict of Interest

None declared.

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Declaration of Figures Authenticity

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