ABSTRACT: On 27 April 2020, the National Health Service England issued an emergency alert for a new condition owing to the observation of an increasing number of cases of a COVID-19-related hyperinflammatory syndrome termed multisystem inflammatory syndrome in children (MIS-C). Some of the presenting symptoms appeared similar to the Kawasaki disease and toxic shock syndrome. We report the cases of six children fitting the criteria of MIS-C, admitted to Royal Hospital and Sohar Hospital, Oman, between the months of June and July in 2020. Four of these patients required admission at the paediatric intensive care unit for inotropic support while two were admitted to the paediatric ward on suspicion of appendicitis. MIS-C has been reported in a small number of individuals below the age of 21 years with a median age of 9–10 years. Five of the current patients were aged less than the median age reported in the existing literature. All of the patients showed complete recovery with supportive management, intravenous immunoglobulin and steroids, with one patient requiring interleukin-6 inhibitor (tocilizumab).

Keywords: COVID-19; SARS-CoV-2; Kawasaki Disease; Multisystem Inflammatory Syndrome in Children; Toxic Shock Syndrome; Case Report; Oman.

COVID-19 infections have been shown to occur less frequently in children and is usually associated with a milder clinical course among them. However, recent studies from Europe and the United States reported a surge of a COVID-19-related hyperinflammatory multisystem syndrome in individuals below the age of 21 years termed multisystem inflammatory syndrome (MIS-C). The National Health Service (NHS) England described this new severe inflammatory syndrome on 27 April 2020. MIS-C can be diagnosed at any time during the course of a COVID-19 infection. It mostly occurs 1–6 weeks following the infection. It may overlap with an acute COVID-19 presentation. The following are the current national guidelines for the diagnosis of MIS-C in Oman as per case definition by the WHO: patients must be <19 years of age with fever lasting longer than 3 days; any two of the following conditions must also be fulfilled: (1) any of the subconditions of (i) mucocutaneous manifestations, (ii) hypotension, (iii) myocardial dysfunction (echocardiography findings or elevated troponin), (iv) evidence of coagulopathy, (v) acute GI; (2) a high amount of inflammatory markers; (3) no other apparent microbes; (4) evidence of COVID-19 (reverse transcription polymerase chain reaction, serology) or contact. MIS-C appears to share many symptoms with Kawasaki disease (KD) such as mucocutaneous manifestations and high inflammatory markers. However, MIS-C is characterised by certain unique features including older age at onset with a median age of 10 years, abdominal symptoms and predominant cardiac manifestations. With only a few initial cases being reported from Europe and the United States, much remains to be understood about this syndrome. In this regard, there is a paucity of publications describing this syndrome in the Middle East with only one reported case of a female Saudi child with MIS-C who died following rapidly-developing multi-organ failure.

The total population of Oman has been estimated at 5,149,271. At the time of writing this case report, 68,400 cases of COVID-19 had been reported, out of which 4,379 were children accounting for approximately 6.6% of the total number of cases. To the best of the authors’ knowledge, this case series, describing the characteristics and outcomes of six children who were diagnosed with MIS-C in Oman, is the first of its kind in the Middle East with only one reported case of a female Saudi child with MIS-C who died following rapidly-developing multi-organ failure.

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Table 1: Clinical features of six children aged 1–11 years with multisystem inflammatory syndrome admitted to a tertiary care hospital in Oman

| Case | Age (in years) | Gender | PICU/HDU admission | Fever duration in days | Abdominal pain | Diarrhoea | Conjunctivitis/rash | Lymphadenopathy | Extremity oedema | Hepatosplenomegaly | Altered mental status | Shock | Respiratory symptoms |
|------|----------------|--------|-------------------|-----------------------|----------------|-----------|---------------------|----------------|----------------|-------------------|---------------------|-------|---------------------|
| Case 1 | 1              | M      | Yes               | 6                     | Yes/4 d        | Yes/4 d   | Yes/4 d            | No             | Yes            | Yes               | No                  | No    | No                  |
| Case 2 | 3              | M      | Yes               | 6                     | Yes            | Yes       | Yes               | Yes            | Yes            | Yes               | No                  | Yes   | Yes                 |
| Case 3 | 6              | M      | No                | 1                     | Yes            | No        | No                | No             | No             | No                | No                  | No    | No                  |
| Case 4 | 5              | M      | Yes               | 6                     | Yes            | No        | No                | No             | No             | No                | Yes                 | No    | Yes                 |
| Case 5 | 4              | F      | No                | 7                     | No             | No        | Yes               | Yes            | Yes            | No                | Yes                 | No    | Yes                 |
| Case 6 | 11             | F      | Yes               | 5                     | No             | No        | Yes               | Yes            | Yes            | No                | No                  | Yes   | No                  |

PICU = paediatric intensive care unit; HDU = high dependency unit.

Table 2: Laboratory test findings of six children aged 1–11 years with Multisystem Inflammatory Syndrome (MIS-C) admitted to a tertiary care hospital in Oman

| Case | NP SARS CoV-2 PCR | SARS-CoV-2 IgG assay-Abbot laboratories (<1.4) | CRP in mg/dL (<10 mg/dL) | Ferritin in ng/mL (13.7–78.8 ng/mL) | IL-6 in pg/mL (0–7 pg/mL) | Troponin in pc/mL (<4 pg/mL) | WBC (4.3–11.0 × 10⁹/µL) | ALC (1.9–9.8 × 10³/µL) | D-Dimer in mg/L (0.1–0.5 mg/L) | Sodium in mmol/L (136–145 mmol/L) | ALT in U/L (10–35 U/L) |
|------|------------------|-----------------------------------------------|--------------------------|------------------------------------|----------------------------|-----------------------------|--------------------------|------------------------|----------------------------|-----------------------------------|------------------------|
| Case 1 | Positive         | Positive                                      | 199                      | 277                                | 235                        | 8                           | 19.5                     | 1.5                    | Not Done                  | 133                               | 17                     |
| Case 2 | Positive         | Positive                                      | 240                      | 277                                | 85                         | 18                          | 8.5                      | 2.4                    | 3.6                       | 127                               | 100                    |
| Case 3 | Positive         | Positive                                      | 59                       | 336                                | 488                        | 29                          | 5.5                      | 12.4                   | 4                         | 137                               | 17                     |
| Case 4 | Positive         | Positive                                      | 158                      | 400                                | NA                         | 12                          | 3.8                      | 0.84                   | 4.64                      | 128                               | 97                     |
| Case 5 | Positive         | Positive                                      | 184                      | 538                                | NA                         | 15                          | 3.4                      | 1.4                    | 7.5                       | 136                               | 75                     |
| Case 6 | Negative         | Positive                                      | 219                      | 263                                | 300                        | 64                          | 3.2                      | 0.2                    | 4                         | 136                               | 30                     |

NP = nasopharyngeal; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; PCR = polymerase chain reaction; IgG = immunoglobulin G; CRP = C-reactive protein; IL-6 = interleukin-6; WBC = white blood cell count; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; NA = not available.
Case One

A 22-month-old male child from Barka was admitted to the paediatric intensive care unit (PICU) at Royal Hospital on 6 July 2020 with a fever and other KD-like symptoms followed by gastrointestinal (GI) symptoms. The father of the child had tested positive for COVID-19 five weeks earlier. On examination, the current patient was febrile and had mucocutaneous manifestations. Abdominal examination revealed ascites with the liver measuring 3 cm below the costal margin. Information on other specific symptoms and systemic laboratory findings are presented in Tables 1 and 2. Nasopharyngeal (NP) GeneXpert SARS-CoV-2 PCR (E gene: 0, N2 gene: 42; Cepheid, Sunnyvale, California, USA) and IgG (4.7 optical density [OD]) were positive on day eight of the illness. While the respiratory viral panel and other laboratory profiles were normal, an abdominal ultrasound (US) revealed ascites with the liver measuring 3 cm below the costal margin. Information on other specific symptoms and systemic laboratory findings are presented in Tables 1 and 2. Nasopharyngeal (NP) GeneXpert SARS-CoV-2 PCR (E gene: 0, N2 gene: 42; Cepheid, Sunnyvale, California, USA) and IgG (4.7 optical density [OD]) were positive on day eight of the illness. While the respiratory viral panel and other laboratory profiles were normal, an abdominal ultrasound (US) revealed hepatosplenomegaly with moderate ascites. The chest X-ray (CXR) and echocardiography were normal. The patient showed improvement within 24 hours of treatment [Table 3] and was discharged on day 12. The results obtained from repeated tests and echocardiography taken two weeks later were normal.

Case Two

A three-year-old male child from Sohar was admitted to the PICU of Sohar Hospital on 7 July 2020 for inotropic support on suspicion of MIS-C with toxic shock syndrome. The patient had a fever, acute gastroenteritis and mucocutaneous manifestations with a history of exposure to COVID-19 eight weeks prior to presentation. He was febrile, sleepy and in shock. The other systemic examinations were standard. Laboratory investigations were recorded as shown in Table 2 with positive NP GeneXpert SARS-CoV-2 PCR (E gene: 34.2, N2 gene: 38.8; Cepheid) and serology on day six of the illness. The patient was then started on treatment. The initial CXR was...
normal and echocardiography showed minimal pericardial effusion with an ejection fraction of 65%. On day two of admission, the patient started to have respiratory distress requiring ventilation. The liver was 3 cm below the costal margin. Repeated troponin was increased to 87 pg/mL. While repeated CXR demonstrated pulmonary oedema with infiltrates [Figure 1A], echocardiography demonstrated depressed left ventricular function at 46%. In view of his worsening condition, the patient was started on tocilizumab as anakinra was unavailable. A US of the abdomen revealed moderate ascites. The patient showed gradual improvement with ventilation and inotropic support. He was extubated on day five and transferred to the paediatric ward (PW) on day six. Repeated investigation demonstrated a decrease in inflammatory markers and improvement in the CXR [Figure 1B]. The patient was discharged on day 10 with follow-up appointments.

Case Three
A six-year-old male child from Al Seeb was admitted to the PW of Royal Hospital on 10 July 2020 on the suspicion of acute appendicitis. On examination, he was febrile with tenderness in the right iliac fossa. An appendectomy was performed and the histopathology showed no evidence of inflammation. The patient continued to have a persistent fever with abdominal pain and developed hypotension. A diagnosis of MIS-C was suspected based on the history of fever, abdominal pain, hypotension, evidence of coagulopathy and elevated inflammatory markers with evidence of positive NP GeneXpert SARS-CoV-2 PCR (E gene: negative), N2 gene: 43; Cepheid) and IgG (3.67 OD) on day six of the illness [Table 2]. The echocardiography was normal and the patient showed improvement within 24 hours of treatment [Table 3]. He was discharged on day five of admission and repeated echocardiography during follow-up was normal.

Case Four
A five-year-old male child from Wadi Bani Khalid was admitted to Royal Hospital on 21 July 2020 with the impression of acute appendicitis in combination with exposure to an individual with COVID-19 four weeks prior to presentation. On examination, he was febrile, hypotensive and required PICU care for inotropic support. An abdominal US revealed mesenteric lymphadenitis. MIS-C was suspected based on the patient’s history of hypotension, elevated inflammatory markers and coagulopathy with evidence of positive NP GeneXpert SARS-CoV-2 PCR (E gene: negative), N2 gene: 38.7; Cepheid) and IgG (3.65 OD) on day five of symptoms [Tables 1 and 2]. The echocardiography showed mild pericardial effusion. The patient showed improvement within 24 hours of treatment [Table 3], and he was discharged on day four of admission with follow-up appointments.

Case Five
A four-year-old female child from Al Seeb was admitted to Royal Hospital on 22 July 2020 with a fever associated with mucocutaneous manifestations and evidence of COVID-19 exposure one month prior to presentation. On examination, she was febrile with tachycardia and hepatosplenomegalgy. MIS-C was suspected based on the history, elevated inflammatory markers and coagulopathy with evidence of positive NP GeneXpert SARS-CoV-2 PCR (E gene: 0, N2 gene: 38.7; Cepheid) and IgG (3.65 OD) on day five of symptoms [Tables 1 and 2]. The echocardiography showed mild pericardial effusion. The patient showed improvement within 24 hours [Table 3]. She was discharged on day four of admission with follow-up appointments.

Case Six
An 11-year-old female patient from Al Amirat was admitted to Royal Hospital on 23 July 2020 with a fever and mucocutaneous manifestations. The patient was confirmed to have had COVID-19 exposure and subsequently tested positive, four weeks prior to presentation of the current symptoms. However, repeated testing for COVID-19 on the day of admission for the current symptoms showed a negative result. On examination, the patient was febrile, tachycardic, hypotensive and required inotropic support. The results of the laboratory investigations are presented in Table 2. The echocardiography was normal. The patient showed improvement within 72 hours of treatment [Table 3] and she was discharged with follow-up appointments.

The reporting of the current cases does not contravene with the regulations of the local institutional review board.

Discussion
To the best of the authors’ knowledge, the current case series is the first of its kind to be reported in the Middle East. The authors describe six children, five of
whom were Omani and one of whom was of Indian origin. All six of the patients were previously healthy with negative blood cultures. Testing for viral studies was limited during the reported period unless there were a strong need for further testing, which could have change the management plan. Five patients tested positive for COVID-19 via PCR testing. These patients also had a history of contact with indexed cases four to eight weeks before the onset of symptoms, in keeping with the trends in reported literature supporting the hypothesis that this syndrome is driven by a delayed immunological response following a COVID-19 infection.

Despite the similarities between the clinical features of both KD and MIS-C, there are observed differences in favour of a MIS-C diagnosis, including the prominent cardiac dysfunction and GI manifestations. While existing research has indicated that 10% of MIS-C cases had rare presentations mimicking acute appendicitis and peritonitis, the high incidence of GI involvement in MIS-C cases still remains unclear. It is noteworthy that two of the six currently reported patients presented with an acute surgical abdomen denoting the broad clinical manifestations of this condition. Studies have shown that MIS-C can lead to multi-organ failure requiring intensive care with 44–80% of patients needing admission to the PICU. Treatment procedures for these patients included inotropic support (47%) and invasive ventilation (20–43%).

Cardiac involvement in this condition typically included impairment in ventricular ejection, pericardial effusion and other coronary abnormalities. Five of the patients in the current case series required PICU admission with three of them requiring inotropic and respiratory support. Belhadjer et al. described 35 children with MIS-C, all of whom required intensive care including extracorporeal membrane oxygenation support which was needed in 28% of the patients. All 35 patients included in this study survived and were discharged.

Notwithstanding the critical nature of this syndrome, the reported survival rates remain high. Cardiac involvement in this syndrome is thought to be secondary to inflammatory cell infiltration of the myocardium leading to transient cardiac injury and dysfunction. This is in contrast to myocardial necrosis or fibrosis found in viral myocarditis.

The NHS England issued an emergency alert in April 2020 with regard to patients under 19 years of age who were admitted to hospitals with fever, shock, cardiac dysfunction and abdominal symptoms and tested positive for COVID-19 via PCR testing. Previous reports were found in non-Asian populations, with a median age range of 8–10 years. This is in contrast to KD, wherein the condition occurs predominately in children less than five years of age. Interestingly, five of the patients included in the current case series were aged below the reported median age for MIS-C [Table 1]. MIS-C often occurs 1–6 weeks following infection and may overlap with respiratory COVID-19 infection. The other difference between the two syndromes is the typical presentation of haemodynamic failure in MIS-C versus KD, a condition in which a minority of patients present with shock. Cardiac manifestations of KD typically include a dilated coronary artery and rare decrease in ventricular function. Due to the high risk of cardiac involvement in MIS-C, patients require frequent assessment during fluid resuscitation. As the features of MIS-C overlap with bacterial infections, antibiotics should be initiated. Ceftriaxone is often suggested for milder illness while metronidazole can also be included in case of GI manifestations. Vancomycin and clindamycin are also recommended in case of severe illness.

The hypothesis that MIS-C is not the result of acute viral infection but is rather a post-infectious immune response linked to IgG antibody-mediated intensification of disease remains to be understood. What is certainly known is that a multi-disciplinary team is required in the management of such patients when considering the various organs involved in this disease. This was the approach that was taken for all of the patients included in this case series.

Given the excessive C-reactive protein levels, interleukin-6 (IL-6) may be involved in the myocardial depression. The majority of patients in the current report received therapies that have been used for the treatment of KD including intravenous immunoglobulin and methylprednisolone with an excellent clinical and laboratory response. Biological drugs such as tocilizumab were used only in one patient to combat the indication of progressive respiratory failure and acute respiratory distress syndrome [Figure 1B]. Once the patient showed clinical improvement, he was extubated following 72 hours of invasive ventilation after receiving tocilizumab, an IL-6 inhibitor. All of the patients were discharged from the hospital in good condition with follow-up appointments [Table 3].

Conclusions

The clinical presentation of SARS-CoV-2-related MIS-C is broad with some patients presenting with features of acute abdomen. Leading to severe and life-threatening manifestations, this syndrome can steer patients into rapid clinical deterioration. Therefore, early diagnosis
and referral to centres equipped with the required subspecialties are recommended. It should be noted that the severity of this disease is transient, usually resulting in high survival rates with proper supportive treatment. A good evaluation of the possibility of acute abdomen related to MIS-C is essential to prevent unnecessary surgical intervention.

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