Multiple system inflammatory syndrome associated with SARS-CoV-2 infection in an adult and an adolescent

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CASE BASED REVIEW

Abstract
Multisystem inflammatory syndrome in adults (MIS-A) is a new syndrome related with COVID-19. A case-based review was performed to present real-life experiences in terms of main findings and treatment options. We described two cases with the diagnosis of MIS and searched the literature to review all reported ≥ 18-year-old cases. The PubMed, Scopus, and Web of Science databases were searched. All relevant articles from January 2020 to February 2021 were reviewed. An adolescent and an adult patient (18 and 40 years-old, respectively) with the diagnosis of MIS were presented. Both had the consistent clinical findings with the case definition criteria. Although steroid, intravenous immunoglobulin (IVIG) and supportive care treatments have been suggested in the literature, there exists no treatment guideline for MIS-A. The clinical and laboratory findings of the patients progressively improved with the implementation of the IVIG and the pulse steroid treatments. A total of 51 cases (≥ 18 years-old) with MIS were analyzed. Mean age was 29.4 ± 10 years. Fever (80.4%), gastrointestinal (72.5%), and respiratory symptoms (54.9%) were the predominant symptoms. Cardiovascular abnormalities were the most frequent reported findings (82.4%, 42/51). The dermatological and conjunctival findings were reported in 39.2% and 35.3% of the patients, respectively. The increased level of inflammatory biomarkers was remarkable. Most of the patients were treated successfully with steroid and IVIG. Clinicians managing adult patients should keep in mind the development risk of MIS related with SARS-CoV-2 infection to perform necessary interventions properly without delay. IVIG and pulse steroid treatments are the effective options on clinical improvement.

Keywords Multisystem inflammatory syndrome · MIS-A · Pulse steroid · IVIG · COVID-19

Introduction
COVID-19-related multisystem inflammatory syndrome (MIS) has been reported in children (MIS-C) and rarely in adults (MIS-A) since April and June 2020, respectively.

Since the clinical characteristics of MIS-C are similar to Kawasaki disease, it was defined initially as a Kawasaki-like illness. Thereafter, a prominent increase was observed in the number of MIS-C reports worldwide. After the reports of cases similar with MIS-C in adults, which was named...
as MIS-A, the accumulation of data has been increasing. Although the underlying immunopathology is not well defined, adaptive immunity is thought to be responsible [1]. The fever is the main finding of the syndrome and gastrointestinal, cardiovascular, hematological, and dermatological findings are the predominant ones. MIS should be kept in mind in a patient with recent COVID-19 infection and presenting findings and laboratory abnormalities indicating hyper inflammation (such as elevated ferritin, C-reactive protein (CRP), d-dimer and lymphocytopenia). The treatment options recommended for MIS-C include high-dose steroid and intravenous immunoglobulin (IVIG) [2]. There are case definitions and center-specific treatment protocols, but there exists no widely accepted guideline especially for MIS-A [3, 4]. However, the same treatment modalities have been reported to be used successfully for MIS-A in previous reports. As the SARS-CoV-2 pandemic is currently quite effective and involves increasing number of people around the world, it is important to introduce clinical findings based on real-life experiences regarding the ways to manage these cases.

In this case-based review, we present the two cases of COVID-19-associated MIS in an adult and an adolescent. In addition, literature search was performed to analyze the main findings of MIS reported in ≥ 18-year-old adolescents and adults. It was aimed to increase the awareness of the clinicians providing care to adults and to propose treatment modalities to be used in this new emergent syndrome.

**Case 1**

A 40-year-old male patient presented to the Emergency Department (ED) with the complaint of high fever in November 2020. He had a fever, diarrhea, and abdominal pain for the previous 4 days. He had COVID-19 23 days ago. He was admitted to the Infectious Disease Clinical ward for further investigation and treatment. On physical examination, he had a 39 °C fever, tachypnea, tachycardia, skin rash, and abdominal tenderness. Nasopharyngeal swab samples were tested for SARS-CoV-2 PCR yielded negative results, and blood samples tested for SARS-CoV2- IgM + IgG antibody yielded positive results (Table 1). Laboratory analysis revealed the followings: leukocytosis, neutrophilia, lymphopenia, elevation in liver function tests, d-dimer, troponin, N-terminal pro-B-type natriuretic peptide (pro-BNP), ferritin, fibrinogen, C-reactive protein (CRP), procalcitonin, and IL-6 (Table 2). Chest computed tomography (CT) was normal. Abdominal CT revealed a small amount of effusion, mesenteric adenopathy, and inflammation in the intestine and mesentery. Abdominal CT findings were interpreted as terminal ileitis. Echocardiography was performed since he had persistent fever, tachypnea, and tachycardia. Increased cardiac wall thickness, mild global hypokinesis, and minimal pericardial effusion were the pathologic findings of echocardiography. Ejection fraction (EF) was 45% (Table 2). The diagnosis of MIS-A was considered primarily, but blood, urine, throat, and stool samples were obtained to exclude other possible causative infectious agents. Since he had a high level of procalcitonin with the other indicators of inflammation, the possible causative bacterial agents could not be excluded until the culture results were obtained. Hence, ceftriaxone and vancomycin therapy was started to cover potential causative agents. On the physical and radiological examination and with the results of basic laboratory tests, we could not find any focus for infection. When evaluated with the history of COVID-19 in the previous 3 weeks, MIS-A was strongly considered as the possible diagnosis. Therefore, pulse methylprednisolone 1 gr/day for 3 days, intravenous immunoglobulin (IVIG) 20 gr/per day for 5 days, and anticoagulant therapy with low molecular weight heparin were given without waiting for the results of other laboratory tests. On the second day of treatment, the fever of the patient regressed, and laboratory abnormalities started to improve. After the implementation of 1 g methylprednisolone therapy for 3 days, its dose was reduced and completed to 10 days (80 mg/day for 3 days, then 40 mg/day for 4 days). The antibiotics were discontinued on the fifth day as there was no growth in the cultures. Echocardiography was performed again at the end of the treatment. It was observed that the pericardial effusion regressed and the EF increased to 60%. The clinical and laboratory findings of the patient improved and he was discharged fully recovered. On the post-discharge follow-up (on day 15 after discharge), the patient did not have any symptoms and findings.

**Case 2**

An 18-year-old female patient was admitted to the ED with fever, chills, abdominal pain, and dyspnea, which had been ongoing for four days. She had COVID-19 about 2 months ago. She was admitted to the Infectious Diseases Clinic for advanced diagnosis and treatment. On physical examination, she had 38 °C fever, pulse rate 110/min, blood pressure 70/40 mmHg, and abdominal tenderness. Laboratory analysis revealed leukocytosis, neutrophilia, lymphopenia, and high levels of d-dimer (1.9 mg/L), CRP (245 g/L) and procalcitonin (1.53 µg/L). Nasopharyngeal swab samples were tested for SARS-CoV-2 PCR yielded negative results, and the blood sample tested for SARS-CoV-2 IgM + IgG antibody yielded positive results. There was no pathological sign on chest CT. A little amount of free liquid was detected in the pelvic region and among some parts of small intestine on abdomen CT. After obtaining blood, urine, and stool samples for cultures,
| Characteristics of the patients | Case 1 | Case 2 | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 |
|---------------------------------|-------|-------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Age (years) | 40 | 18 | 27 | 40 | 47 | 21 | 22 | 21 | 47 | 42 | 22 | 36 |
| Gender | male | female | male | male | male | male | female | male | male | male | male | female |
| Clinical presentation | Fever, diarrhea, rash, abdominal pain, rash × 4 days | Fever, chills, abdominal pain, rash × 4 days | Diarrhea, rash × 5 days, hypovolemic shock | Sweating, fatigue × 4 days, chest pain, hypotension | Fatigue, vomiting, pharyngitis, dyspnea, rash × 6 days | Fever, chest pain, hypotension, diarrhea, hypotension, rash × 3 days | Fever, nausea, vomiting, chest pain, dyspnea | Fatigue, vomiting, chest pain, hypotension, rash × 2 days | Fever, chills, cough, dyspnea, rash × 1 day | Fever, chills, cough, dyspnea, rash × 1 day | Fatigue, vomiting, chest pain, hypotension, rash × 2 days |
| Comorbidities | Obesity | Obesity | Obesity | Obesity | Obesity | Obesity | Obesity | Obesity | Obesity | Obesity | Obesity | Obesity |
| Race/ethnicity/location | Caucasian Ankara, ND | Caucasian Ankara, ND | African American Maine, Florida | Hypertension, New York, ND | Hypertension, New York, ND | Hypertension, New York, ND | Hypertension, New York, ND | Hypertension, New York, ND | Hypertension, New York, ND | Hypertension, New York, ND | Hypertension, New York, ND |
| BP/HR/RR | Hypotension | Hypotension | Hypertension | Hypertension | Hypertension | Hypertension | Hypertension | Hypertension | Hypertension | Hypertension | Hypertension | Hypertension |
| COVID-19 PCR/Ab | (+)/(+) | (+)/(+) | (+)/(+) | (+)/(+) | (+)/(+) | (+)/(+) | (+)/(+) | (+)/(+) | (+)/(+) | (+)/(+) | (+)/(+) | (+)/(+) |
| Previous COVID-19 history | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Time from COVID-19 to symptom onset (days) | 23 | 60 | ND | ND | ND | ND | 41 | ND | ND | ND | 41 | 37 |

**Table 1** Demographic and clinical characteristics of the patients
| Characteristics of the patients | Case 1 | Case 2 | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 |
|--------------------------------|-------|-------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Treatment                      | Steroid | Steroid, IVIG | Steroid, heparin, vasopressor | Steroid | Heparin, vasopressor, tocilizumab | Steroid, ASA, IVIG | Steroid, heparin | Steroid, heparin | Steroid, heparin, vasopressor | Heparin | Steroid, heparin, vasopressor | Steroid, ASA, IVIG |
| Organ Support                  | None | None | None | ND | None | ND | ND | ND | ND | ND | ND | ND |
| Length of hospital stay (days) | 10/alive | 10/alive | 13/alive | 17/alive | No data/ex | 6/alive | 5/alive | 19/alive | 12/alive | 8/alive | 9/alive | 7/alive |
| Characteristics of the patients | Patient 11 | Patient 12 | Patient 13 | Patient 14 | Patient 15 | Patient 16 | Patient 17 | Patient 18 | Patient 19 | Patient 20 |
| References                     | Shaigany et al. [7] | Jones et al. [8] | Fox et al. [9] | Kofman et al. [10] | Ventura et al. [28] | Chau et al. [11] | Chau et al. [11] | Chau et al. [11] | Chau et al. [11] | Chau et al. [11] |
| Age (years)/Gender             | 45 years, male | 21 years, male | 31 years, female | 25 years, female | 38 years, female | 34 years, male | 33 years, male | 42 years, male | 20 years, male | 24 years, male |
| Clinical presentation          | Fever, sore throat, diarrhoea, bilateral lower extremity pain, conjunctivitis, and diffuse exanthem | Fever and abdominal pain × 6 days, maculopapular palmar rash × 4 days, non-exudative conjunctivitis, cervical lymphadenopathy | Fever, throbbing, left sided neck pain, nausea and vomiting | Weakness, dyspnea, and fever, mild cough, sore throat, vomiting, diarrhea, and lymph node swelling, conjunctivitis | Fever, myalgia, maculopapular rash on chest and arms, conjunctivitis | Fever, chest pain, dyspnea, gastrointestinal symptoms, neck pain, rash | Fever, chest pain, cough, rash | Fever, headache, gastrointestinal symptoms, neck pain | Fever, dyspnea |
| Comorbidities                  | None | ND | Hypertension, diabetes | None | None | None | Alcohol abuse | None | None | None |
| Race/ethnicity/location        | Hispanic, New York | African | African, American, New Orleans | Atlanta, Georgia | Hispanic, Houston | Middle Eastern | Black | White | Middle Eastern |
| BP/HR/RR                       | Hypotension, tachycardia | ND | Tachycardia | Hypotension | Tachycardia | Tachycardia | Tachycardia | Tachycardia | Hypotension, tachycardia | Hypotension, tachycardia |
| COVID-19 PCR/Ab                 | (+)/ND | (-)/(+) | (-)/ND | (+)/(+ | (+)/(+ | (+)/(+ | (+)/(+ | (+)/(+ | (+)/(+ | (-)/(+ |
Table 1 (continued)

| Characteristics of the patients | Patient 11 | Patient 12 | Patient 13 | Patient 14 | Patient 15 | Patient 16 | Patient 17 | Patient 18 | Patient 19 | Patient 20 |
|--------------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Previous COVID-19 history     | No         | No         | Yes        | No         | Yes        | ND         | ND         | ND         | ND         | ND         |
| Time from COVID-19 to symptom onset (days) | ND | ND | 14 | ND | 28 | ND | ND | ND | ND | ND |
| Treatment                      | Steroid, heparin, IVIG, Tocilizumab | Steroid, ASA, IVIG | ND | ASA, IVIG, vasopressor | Steroid, ASA, vasopressor | Steroid, ASA, heparin, vasopressor | Steroid, ASA, heparin, vasopressor | Steroid, ASA, heparin, vasopressor | Steroid, ASA, heparin, vasopressor | Steroid, ASA, heparin, vasopressor |
| Organ support                  | ND         | ND         | ND         | None       | None       | None       | IABP       | None       | None       | None       |
| Length of hospital stay (days)/outcome | ND 9/alive | ND 8/alive | ND No data/ex | None 5/alive | None 7/alive | None 13/alive | IABP 18/alive | None 7/alive | None 8/alive | None 10/alive |
| Characteristics of the patients | Patient 21 | Patient 22 | Patient 23 | Patient 24 | Patient 25 | Patient 26 | Patient 27 | Patient 28 | Patient 29 | Patient 30 |
| References                      | Chau et al. [11] | Chau et al. [11] | Hékimian et al. [12] | Hékimian et al. [12] | Hékimian et al. [12] | Hékimian et al. [12] | Hékimian et al. [12] | Hékimian et al. [12] | Moghadam et al. [13] |
| Age (years)/gender              | 20 years, male | 24 years, male | 40 years, male | 19 years, female | 22 years, male | 19 years, male | 25 years, female | 37 years, male | 29 years, female | 21 years, male |
| Clinical presentation           | Fever, dyspnea, myalgia, gastrointestinal symptoms, neck pain | Fever, myalgia, gastrointestinal symptoms, respiratory symptoms | Dyspnea, severe asthenia | Fever, dyspnea, cough | Fever, dyspnea, cough, severe asthenia | Fever, dyspnea, cough, severe asthenia | Fever, headache, abdominal pain, diarrhea, chest pain, dyspnea, severe asthenia, myalgia, arthralgia, adenopathy | Fever, headache, diarrhea, severe asthenia | Fever, fatigue, gastrointestinal symptoms, dermatological findings, conjunctivitis | Fever, chest tightness, non-bloody watery diarrhea, chest tightness erythematous round-shaped macules, conjunctivitis |
| Comorbidities                   | None       | Alcohol abuse | Diabetes mellitus | None       | Diabetes mellitus, asthma | None       | None       | Hypertension | None       | None       |
| Race/ethnicity                  | Hispanic   | Hispanic     | ND           | Hypotension, tachycardia | ND         | Hypotension, tachycardia | ND         | ND         | Hypotension, tachycardia | ND |
| BP/HR/RR                        | Hypotension, tachycardia | Hypotension, tachycardia | ND | Hypotension, tachycardia | ND | Hypotension, tachycardia | ND | Hypotension, tachycardia | ND | Hypotension, tachycardia |
| COVID-19 PCR/Ab                  | (+)/(+ | (+)/(+) | (+)/(−) | (−)/(+) | (−)/(+) | (−)/(+) | (−)/(+) | (−)/(+) | (−)/(+) | (−)/(+) |

References:
- Chau et al. [11]
- Hékimian et al. [12]
- Moghadam et al. [13]
### Table 1 (continued)

| Characteristics of the patients | Patient 21 | Patient 22 | Patient 23 | Patient 24 | Patient 25 | Patient 26 | Patient 27 | Patient 28 | Patient 29 | Patient 30 |
|---------------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Previous COVID-19 history       | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | Yes        | ND         |
| Time from COVID-19 to symptom onset (days) | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | 30         | ND         |
| Treatment                       | Steroid, aspirin, heparin, vasopressor | Steroid, aspirin, heparin, vasopressor | Vasopressor | Vasopressor | ND         | Vasopressor | None       | Steroid, IVIG | IVIG       | Vasopressor |
| Organ support                   | MV, IABP   | IABP       | MV         | MV, ECMO   | MV, ECMO   | None       | None       | None       | None       | Highflow   |
| Length of hospital stay (days)/outcome | 12/alive  | 10/alive   | 50/alive   | 40/alive   | 41/alive   | 7/alive    | 7/alive    | 19/alive   | 3/alive    | 8/alive    |

### Characteristics of the patients

| References          | Lidder et al. [14] | Chowdhary et al. [15] | Cogan et al. [16] | Ahsan et al. [17] | Malangu et al. [18] | Gulersen et al. [19] | Vieira et al. [5] | Razavi et al. [20] |
|---------------------|--------------------|-----------------------|-------------------|-------------------|---------------------|---------------------|-------------------|-------------------|
| Age (years)/gender  | 45 years, male     | 26 years, male        | 19 years, male    | 28 years, male    | 46 years, male      | 31 years, female   | 18 years, male    | 23 years, male    |
| Clinical presentation | Fever, sore throat, diarrhoea, dermatological findings, conjunctivitis | Fever, cervical adenopathy, erythematous rash and bilateral conjunctivitis | Fever, fatigue, myalgia, nausea, vomiting, generalized morbilliform rash and conjunctivitis | Fever, sore throat, fatigue, myalgia, cough, general malaise, pleuritic chest pain, and conjunctivitis | Fever, respiratory symptoms | Fever, abdominal pain, vomiting and diarrhea, dermatological findings, and conjunctivitis | Fever, fatigue, myalgia, orthopnea paroxysmal nocturnal dyspnea, diarrhea, temporal headache and conjunctivitis |
| Comorbidities       | None               | None                  | None              | Thalassemia minor | None                | Obesity            | None              | Obesity          |
| Race/ethnicity      | ND                 | Caucasian             | ND                | Hispanic          | ND                  | ND                 | African–American  | Hypotension      |
| BP/HR/RR            | Hypotension        | Tachycardia           | Tachycardia       | Tachycardia       | Hypotension         | Tachycardia        | Hypotension       | Tachycardia      |
| COVID-19 PCR/Ab     | (+)/(+))           | (-)/(+))              | (-)/(+))          | (-)/(+))          | (-)/(+))            | (-)/(+))           | (-)/ND)          | (-)/(+))         |
| Previous COVID-19 history | ND               | ND                    | Yes               | Yes               | Yes                | ND                 | Yes               | Yes               |
Table 1 (continued)

| Characteristics of the patients | Patient 31 | Patient 32 | Patient 33 | Patient 34 | Patient 35 | Patient 36 | Patient 37 | Patient 38 |
|---------------------------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Time from COVID-19 to symptom onset (days) | ND | ND | ND | 14 | 45 | 28 | ND | 30 |
| Treatment | IVIG, tocilizumab | Aspirin, vasopressor, IVIG, tocilizumab | Steroid, IVIG, vasopressor, tocilizumab | Steroid | ND | Steroid, heparin, IVIG, vasopressor | Steroid, aspirin, IVIG, vasopressor | Steroid, heparin, aspirin, IVIG |
| Organ support | ND | ND | ND | ND | ND | ND | ND | ND |
| Length of hospital stay (days)/outcome | ND | 10/alive | 22/alive | ND | ND | ND | ND | 6/alive |

| Characteristics of the patients | Patient 39 | Patient 40 | Patient 41 | Patient 42 | Patient 43 | Patient 44 | Patient 45 | Patient 46 | Patient 47 | Patient 48 | Patient 49 |
|---------------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| References | Riollano-Cruz et al. [21] | Riollano-Cruz et al. [21] | Riollano-Cruz et al. [21] | Othenin-Girard [22] | Parker [23] | Parker [23] | Kaushik et al. [24] | Kaushik et al. [24] | Chérif et al. [25] | Downing et al. [26] | Shan et al. [27] |
| Age (years)/gender | 20 years, male | 20 years, male | 20 years, male | 22 years, ND | 27 years, ND | 22 years, male | 20 years, male | 20 years, male | 35 years, female | 51 years, male | 34 years, male |
| Clinical presentation | Fever, diarrhea, abdominal pain x 3 days | Fever, dyspnea, cough x5days | Fever, headache, vomiting, diarrhea x3days | Myalgia, abdominal pain, diarrhea, cough and rash x5days | Conjunctivitis, abdominal pain, mucocutaneous rash | Conjunctivitis, abdominal pain, mucocutaneous rash | Con | Con | Con | Con | Con |
| Comorbidities | No | No | No | ND | ND | ND | ND | ND | ND | ND | ND |
| Race/Ethnicity | Hispanic | Hispanic | Non-hispanic, white | East African | African | African | New York city, Hispanic | New York city, Black | African | ND | None |
| BP/HR/RR | 81/52; 133; 27 | ND | 83/45; 137; 18 | ND | ND | ND | ND | Tachycardia | ND | ND |
| COVID-19 PCR/Ab | ND/(+) | ND/(+) | ND/(+) | ND/ND | ND/ND | ND/ND | ND/ND | ND/(+) | ND/(+) | ND/(−) | ND/(−) |
empirical ceftriaxone 2 gr/day was started. On the follow-up, hypotension, tachycardia, and hypoxia developed on the first day of treatment, and procalcitonin, troponin, and pro-BNP levels were found increased. A hydration therapy with crystalloids was given and the ceftriaxone therapy was escalated to broader spectrum antibiotics. The electrocardiography (ECG) showed sinus tachycardia. The examination of transthoracic echocardiography (TTE) revealed no pathologic findings on the cardiac valve. Global hypokinesia was detected and ejection fraction was 45%. The diagnosis of MIS-A was considered according to these clinical and laboratory findings. Methyl prednisolone 250 mg/day intravenously for 3 days and IVIG 20 gr/day for 5 days, and low molecular weight heparin as an anticoagulant prophylaxis, beta blocker and angiotensin converting enzyme (ACE) inhibitor were given to the patient. Antibiotic treatment was discontinued on the 4th day of treatment when the culture tests resulted in negative. The blood oxygen saturation was detected as 86% and the need of oxygen support increased (4 L with nasal cannula) on the second day of admission. Intravenous furosemide treatment was given since the control chest radiography revealed pulmonary edema. The fever decreased after the first day of methylprednisolone and IVIG treatment, but the need of slightly supplemental oxygen therapy was continued for 3 days. Thereafter, the patient had a significant improvement in respiratory effort capacity on the 3rd day of pulse steroid and IVIG treatment, and abdominal pain began to regress. The dose of the methylprednisolone was reduced and completed to 10 days (250 mg pulse steroid for 3 days, 80 mg/day for 3 days, and 40 mg/day for 4 days). The control TTE, on the follow up, revealed no deterioration in the previous findings. The furosemide and supplemental oxygen therapy were stopped on the fifth day. After the sixth day of the therapy, she was able to move without help. After 10 days of follow-up, she was discharged from hospital fully recovered. On the follow-up visit on day 15 after discharge, she was completely healthy.

**Search strategy**

The PubMed, Scopus, and Web of Science Core Collection databases were searched for published case reports of MIS in adults and adolescents aged ≥ 18 years-old from January 2020 to February 2021. The following keywords were used for literature search: ‘multisystem inflammatory syndrome in adults and COVID-19’, ‘multisystem inflammatory syndrome in adolescents and COVID-19’ and ‘Kawasaki-like syndrome in adults and COVID-19’. After exclusion of irrelevant articles, a total of 11 adolescent cases of MIS-C aged 18–20 years and 38 cases of MIS-A were reviewed [4–28]. The reports regarding ≥ 18-year-old adolescents and adult patients diagnosed with multisystem inflammatory disease...
| Characteristics of the patients | Case 1 | Case 2 | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 |
|---------------------------------|--------|--------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| CRP (mg/L)                      | 397    | 245    | 344       | 84        | 217       | 318       | 182       | 355       | 319       | 485       | 387       | 300       |
| Procalcitonin (μg/L)            | 2.16   | 9.57   | ND        | ND        | ND        | ND        | ND        | ND        | ND        | ND        | ND        | ND        |
| Ferritin (ng/mL)                | 2319   | 363    | 1082      | 1919      | 100.000   | 4400      | 375       | 378       | 351       | 948       | 7529      | 684       |
| D-Dimer (ng/mL)                 | 3.8    | 2.1    | 2.8       | 2.3       | 3.7       | 1.76      | 0.37      | 1.88      | 0.71      | 1.36      | 3.5       | 0.65      |
| Troponin (ng/L)                 | 5.8    | 3.6    | 0.43      | 0.48      | 2.5       | 0.65      | 1.8       | 0.06      | 0.04      | 0.24      | 0.65      | 0.07      |
| BNP (pg/mL)                     | 18,627 | 2431   | ND        | ND        | ND        | ND        | ND        | ND        | ND        | ND        | ND        | ND        |
| Elevated liver enzyme           | No     | Yes    | No        | Yes       | Yes       | Yes       | No        | Yes       | Yes       | Yes       | Yes       | Yes       |
| Lymphocyte count (cells/µL)     | 430    | 530    | 420       | 2500      | 400       | 700       | 2070      | 360       | 260       | 1980      | 1780      | 900       |
| ECG                             | Sinus tachycardia | Sinus tachycardia | ND | Atrial fibrillation | ST-T changes | ND | ND | Intermittent complete heart block with narrow junctional escape without hemodynamic compromise | ND | First degree AV block and non-specific T-wave abnormalities | ND | ND |
| Echo                            | Increased cardiac wall thickness, mild global hypokinesis LVEF 45% | Mild global hypokinesis LVEF 45% | Minimal pericardial effusion, LVEF 45% | Global hypokinesis LVEF 25–30% | ND | LVEF severely decreased | Mitral and tricuspid valve regurgitation | LVEF: 50% | Mild to moderate left ventricular hypokinesis LVEF: 40%, minimal pericardial effusion, Mild TVR and MVR | LVEF: 55% | Mildly dilated left ventricle, moderately dilated right ventricle, moderate ventricular hypokinesis LVEF: 35% | LVEF: 65%, moderate TVR |
### Table 2 (continued)

| Characteristics of the patients | Case 1 | Case 2 | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 |
|---------------------------------|--------|--------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| **Control echo**                |        |        |           |           |           |           |           |           |           |           |           |           |
| **LVEF %60**                    | ND     | ND     | ND        | ND        | ND        | ND        | ND        | ND        | ND        | ND        | ND        | ND        |
| **CT/CXR**                      | No pathological finding | No pathological finding | Bilateral ground-glass opacities, pleural effusion | Minimal pleural effusion | Ground glass opacities | Atelectasis and ground glass opacities | Atelectasis | Bilateral lower lobe air-space disease | Bilateral patchy ground-glass opacities, pleural effusion |
| **Patient 11**                  |        |        |           |           |           |           |           |           |           |           |           |           |
| **CRP (mg/L)**                  | 547    | 338    | 580       | 90        | 217       | 402       | 125       | 326       | 317       | 45        |           |           |
| **Procalcitonin (μg/L)**        | 79     | 42     | 4.2       | 1.9       | 1.2       | 3.39      | 6.4       | 1.4       | 1.4       | 20        |           |           |
| **Ferritin (ng/mL)**            | 21,196 | 1249   | 793       | 798       | 196       | 13,252    | 3595      | 983       | 11,483    | 14.23     | 2660      |           |
| **D-Dimer (ng/mL)**             | 2.97   | 4.2    | 0.45      | 1.9       | 1.2       | 3.39      | 6.4       | 1.4       | 1.4       | 20        |           |           |
| **Troponin (ng/L)**             | 8.1    | 3.3    | ND        | 0.06      | 0.03      | 2.23      | 6.7       | 3.12      | 1.95      | 7.8       |           |           |
| **BNP (pg/mL)**                 | 170    | ND     | 46,000    | 378       | 404       | 1525      | 10,921    | 819       | 819       | 3530      |           |           |
| **Elevated liver enzyme**       | Yes    | Yes    | Yes       | No        | Yes       | ND        | ND        | ND        | ND        | ND        | ND        |           |
| **WBC/Lymphocyte count (cells/µL)** | 700   | 390    | 2120      | 1150      | 120       | ND        | ND        | ND        | ND        | ND        | ND        |           |
| **ECG**                         | ND     | ND     | Sinus tachycardia | Right axis deviation | ND        | Sinus tachycardia, diffuse ST elevation | Sinus tachycardia, infrolateral ST elevation | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | Atrial fibrillation |
| **Echo**                        |        |        |           |           |           |           |           |           |           |           |           |           |
| **Global hypokinesis of the left ventricular wall, LVEF: 40%** | ND     | ND     | Dilated inferior vena cava, right-sided ventricular dysfunction LVEF: 60% | Pericardial effusion, and normal LVEF | LVEF 23%, LVEDD 5 cm severe RV dysfunction moderate TVR mild MVR | LVEF: 35%, LVEDD 5.7 cm severe MVR, and TVR | LVEF: 35%, LVEDD 6.4 cm Infravalvular hypokinesis mild RV dysfunction mild MVR | LVEF: 35%, LVEDD 5.5 cm Infrolateral hypokinesis mild RV dysfunction mild MVR | LVEF: 35%, LVEDD 5 cm mild RV dysfunction |
| **Control echo**                |        |        |           |           |           |           |           |           |           |           |           |           |
| **Normal echocardiogram**       | ND     | ND     | ND        | ND        | ND        | ND        | ND        | LVEF 50%, normal RV, No valve disease | LVEF 50%, normal RV, No valve disease | LVEF 50%, normal RV, No valve disease | LVEF 55%, normal RV, No valve disease |           |
Table 2 (continued)

| Characteristics of the patients | Patient 11 | Patient 12 | Patient 13 | Patient 14 | Patient 15 | Patient 16 | Patient 17 | Patient 18 | Patient 19 | Patient 20 |
|---------------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| CT/CXR                          | ND         | ND         | Bibasilar ground glass opacities, LAP | Peripheral ground-glass opacities | Ground glass opacities, pleural effusions | Bilateral multifocal opacities cervical lymphadenopathy | Mild bilateral opacities | Mild atelectasis | Normal | Bilateral diffuse opacities |
| CRP (mg/L)                      |            |            |            |            |            |            |            |            |            |            |
| Ferritin (ng/mL)                |            |            |            |            |            |            |            |            |            |            |
| D-Dimer (ng/mL)                 |            |            |            |            |            |            |            |            |            |            |
| Troponin (ng/L)                 |            |            |            |            |            |            |            |            |            |            |
| BNP (pg/mL)                     |            |            |            |            |            |            |            |            |            |            |
| Elevated liver enzyme           |            |            |            |            |            |            |            |            |            |            |
| WBC/lymphocyte count (cells/µL)|            |            |            |            |            |            |            |            |            |            |
| ECG                             |            |            |            |            |            |            |            |            |            |            |
| Echo                            |            |            |            |            |            |            |            |            |            |            |
| Control echo                    |            |            |            |            |            |            |            |            |            |            |
| CT/CXR                          |            |            |            |            |            |            |            |            |            |            |
| Characteristics of the patients | Patient 21 | Patient 22 | Patient 23 | Patient 24 | Patient 25 | Patient 26 | Patient 27 | Patient 28 | Patient 29 | Patient 30 |
| CRP (mg/L)                      | 339        | 309        | 321        | 438        | 202        | 280        | 389        | ND         | 206        | 365        |
| Procalcitonin (µg/L)            | ND         | ND         | 170        | 68         | 3.5        | 15         | 12         | 8.7        | 0.5        | 3.4        |
| Ferritin (ng/mL)                | 3265       | 76.19      | 3280       | 645        | 16,576     | 2124       | 712        | 4485       | 456        | 1282       |
| d-Dimer (ng/mL)                 | 3.8        | 20         | 7.53       | 4.2        | 3.93       | ND         | 3.1        | 4.3        | 1.2        | ND         |
| Troponin (ng/L)                 | 3.67       | 0.07       | 0.43       | 10.6       | 0.16       | 0.8        | 2.5        | 1.1        | 0.2        | 5.5        |
| BNP (pg/mL)                     | 432        | 2830       | 6025       | 2585       | ND         | 26,956     | 24,540     | 35,000     | 21,298     | ND         |
| Elevated liver enzyme           | ND         | ND         | Yes        | Yes        | Yes        | Yes        | Yes        | Yes        | No         | No         |
| WBC/lymphocyte count (cells/µL)| ND         | ND         | 480        | 310        | 1860       | 2300       | 870        | 1500       | 1400       | 900        |
| ECG                             | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | New first-degree atrioventricular block with left bundle branch block | Sinus tachycardia | Diffuse negative T waves |            |
| Echo                            | LVEF: 20%, LVEDD 4.3 cm severe RV dysfunction | LVEF: 45% | LVEF: 30% | LVEF: 30% | LVEF: 15% | LVEF: 20%, 8 cm | LVEF: 45% | LVEF: 50% | Hyperkinetic left ventricle with normal LVEF |            |
| Control echo                    | LVEF: 50%, normal RV | LVEF60%, normal RV | LVEF: 60% | LVEF: 40% | LVEF: 60% | LVEF: 60% | LVEF: 50% | LVEF: 60% | LVEF: 60% | ND         |
| CT/CXR                          | Normal     | Mild bilateral opacities | Severe COVID-19 infiltrate | Mild COVID-19 infiltrate | Severe COVID-19 infiltrate | None | None | None | None | None |
| Characteristics of the patients | Patient 31 | Patient 32 | Patient 33 | Patient 34 | Patient 35 | Patient 36 | Patient 37 | Patient 38 |            |            |
| CRP (mg/L)                      | ND         | 419        | 217        | 131        | 74         | 314        | 310        | 281        |            |            |
| Characteristics of the patients | Patient 31 | Patient 32 | Patient 33 | Patient 34 | Patient 35 | Patient 36 | Patient 37 | Patient 38 |
|---------------------------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Procalcitonin (μg/L)            | ND         | 164        | ND         | ND         | ND         | ND         | ND         | ND         |
| Ferritin (ng/mL)                | ND         | 3275       | 285        | 613        | 827        | ND         | ND         | 4260       |
| d-Dimer (ng/mL)                 | ND         | 2.7        | ND         | ND         | 4.4        | 1.2        | 9.2        | 0.58       |
| Troponin (ng/L)                 | ND         | 2          | ND         | ND         | ND         | 0.14       | 0.96       | 0.53       |
| BNP (pg/mL)                     | ND         | ND         | ND         | Yes        | No         | ND         | ND         | 262        |
| Elevated liver enzyme           | ND         | ND         | Yes        | No         | Yes        | ND         | ND         | Yes        |
| Lymphocyte count (cells/µL)     | ND         | 640        | 490        | ND         | ND         | ND         | ND         | 500        |
| ECG                             | ND         | ND         | ND         | Normal     | ND         | Sinus tachycardia | ND         | ND         |
| Echo                            | Global hypokinesis and LVEF: 40% | LV systolic dysfunction with pericardial effusion | LVEF: 40%, minimal pericardial effusion | ND | Left ventricular eccentric hypertrophy with LVEF: 31% | Hyperdynamic left ventricle LVEF: 65–70% and pericardial effusion | MVR, LVEF: 35% | LVEF: 40–45% and global hypokinesis | ND |
| Control echo                    | ND         | Improving LV function | ND         | ND         | ND         | ND         | LVEF: 63%, absence of MVR and coronary aneurysms | ND |
| CT/CXR                          | Unilateral cervical lymphadenopathy | Bilateral pulmonary basal round-glass opacities | ARDS | Normal | Middle lobe opacity and basilar linear opacities | Normal | Abdominal CT scan only revealed minor gall bladder distension | ND |
| Characteristics of the patients | Patient 39 | Patient 40 | Patient 41 | Patient 42 | Patient 43 | Patient 44 | Patient 45 | Patient 46 | Patient 47 | Patient 48 | Patient 49 |
| CRP (mg/L)                      | 284        | 181        | 304        | 275        | ND         | ND         | ND         | ND         | 367        | 2.18       | > 30 |
| Procalcitonin (μg/L)            | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         |
| Ferritin (ng/mL)                | 519        | 1597       | 10,170     | 3.32       | ND         | ND         | ND         | ND         | ND         | 5384       | 92         | 4688 |
| d-Dimer (ng/mL)                 | 1.91       | 0.45       | 14.23      | 2.71       | ND         | ND         | ND         | ND         | ND         | ND         | 0.35       | 2.23 |
| Troponin (ng/L)                 | 2.73       | 0.01       | 0.33       | 0.79       | ND         | ND         | ND         | ND         | ND         | ND         | ND         |
| BNP (pg/mL)                     | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         |
| Elevated liver enzyme           | ND         | ND         | ND         | ND         | ND         | ND         | ND         | Yes        | ND         | Yes        | ND         |
| WBC/Lymphocyte count (cells/µL) | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | ND         | 1000       | 918        |
| ECG                             | ND         | ND         | ND         | ND         | ND         | ND         | Sinus tachycardia | ND         | ND         | ND         | ND         |
were selected and included into this review to increase the awareness of the clinicians providing care in these age groups.

**Discussion**

There have been 49 case reports of a MIS in adults and adolescents aged ≥18 years-old since June 2020. The Centers for Disease Control and Prevention (CDC) published a report in October 2020 to define the clinical and laboratory characteristics and the treatment modalities used in reported and published case series of MIS-A [4]. There is a lack of clear evidence on immune-pathophysiology of the syndrome, but an antibody-related immune response may be responsible. It is thought as a post-infectious syndrome rather than an infection in acute stage of development [4, 5]. Although there is a heterogeneity of symptoms and findings, gastrointestinal symptoms such as abdominal pain, diarrhea, vomiting, and myocarditis, fever, hypotension via capillary leak syndrome, and shock are the predominant ones. The World Health Organization (WHO) and CDC categorized the multisystem inflammatory syndrome according to the age of the patients. WHO accepted patients aged 0–19 years with the defined characteristic features as MIS-C, whilst CDC accepted those <21 years-old in this group. The main determinative characteristics of the syndrome used in case definitions are the followings [4, 5]:

1. Increase in inflammatory biomarkers (CRP, ferritin, d-dimer etc.) accompanying fever;
2. Laboratory confirmation of recent COVID-19 infection (with positive test results of RT-PCR and/or SARS-CoV-2 antibody), within previous 12 weeks before the symptom onset;
3. The exclusion of other specific causative microbial agents;
4. The lack of the severe respiratory illness (to exclude the effect of tissue hypoxia as the cause of the organ dysfunction);
5. In addition to the above criterions, the two of the following features are necessary:
   - Rash ± non-purulent conjunctivitis ± mucocutaneous inflammation findings,
   - Low blood pressure ± shock,
   - Findings of cardiac involvement such as myocarditis, valvulitis or pericarditis, abnormalities on echocardiography or laboratory tests (increased proBNP, troponin),
   - Clinical or laboratory findings of coagulation abnormalities (elevated d-dimer, prothrombin time, active partial thromboplastin time) and/or liver injury,
IgM + IgG resulted positive. Of the previously reported 49 and resulted negative, whilst the tests of SARS-CoV-2 for SARS-CoV-2 PCR, 23 days and 2 months ago, respectively. The RT-PCR tests for SARS-CoV-2 were repeated and resulted negative, whilst the tests of SARS-CoV-2 IgM + IgG resulted positive. Of the previously reported 49 cases, 35 had positive SARS-CoV-2 antibody results, 18 had only positive antibody test results, and 18 had both positive SARS-CoV-2 PCR and antibody results. The five of the remained 10 cases were PCR positive, and three cases were PCR negative and antibody test were not performed. The results of antibody and PCR tests were not given for previously reported four patients (Table 1) [4–28]. The interval between COVID-19 and the development of MIS-A symptoms reported previously as about 2–5 weeks [4]. When the time interval from positive PCR results to symptoms of MIS was evaluated, it was determined mean 31.25 ± 13.03 days. Hékimian et al. reported 11 adolescent and adult patients with MIS, who were presented with fever, abdominal pain, nausea, vomiting, various mucocutaneous findings, and symptoms indicating myocardial dysfunction accompanied by severe inflammation. They reported normalization of EF in 54.5% of the patients and improvement in about 1 week in 36.4% of the patients whilst one of the patients died despite the implementation of extra-corpeoreal membrane oxygenation (ECMO) [13]. Both of the present cases had fever, abdominal pain, hypotension, and myocarditis in addition to elevated inflammation biomarkers. Additionally, the patient with the diagnosis of MIS-A had terminal ileitis and rash. The EF was normalized in both patients on the control echocardiography performed at the end of the therapy on the 10th day of admission. A total of 51 patients with MIS-A were analyzed and the mean age was determined as 29.4 ± 10 years. Cardiovascular abnormalities such as global hypokinesis and decreased left ventricular ejection fraction (LVEF) were the most frequently reported findings (82.4%, 42/51). The other prominent symptoms were as follows: 80.4% fever, 72.5% gastrointestinal symptoms (abdominal pain, nausea, vomiting and, diarrhea), 54.9% respiratory symptoms (cough and, dyspnea), and 36% myalgia. When the relevant findings of the cases were evaluated, requirement of vasopressor therapy for hypotension was detected in 44% of the patients. The dermatological findings (erythematous rash, periorbital rash, annular targeted lesions etc.) were defined in 39.2% of the patients. Conjunctival findings, such as non-exudative conjunctivitis, were determined in 35.3% of the patients. Lymphadenopathy was detected in 17.6% of the patients. Most of the patients with MIS-A had higher levels of inflammatory biomarkers such as CRP, d-dimer, and ferritin. The mean level for CRP was 293.7 ± 119.3 mg/L and the mean level for lymphocyte was 999 cell/µL (± 119.3), the median level for ferritin was 1265 µg/L (21–100.000) and the median level for d-dimer was 2.8 µg/L (0.35–20) (Table 2) [4–28]. Since MIS-A is an emergent condition and may have a risk of rapidly worsening clinical progression, patients with clinical suspicion should be treated promptly. The American College of Rheumatology published a diagnosis and treatment guideline for pediatric patients diagnosed with MIS-C associated with SARS-CoV-2 [29]. The pulse steroid treatment with methylprednisolone 20–30 mg/kg per day, for 1–3 days up to 1 gr/day, then tapering doses (2 mg/kg per day, maximum 60 mg/day) were recommended previously in moderate and severe cases [30]. Additionally, it was reported that a combination of IVIG and steroid therapy may be more effective for symptom relief than IVIG monotherapy in Kawasaki Disease (KD), which has pathophysiologic characteristics similar to MIS-C [30]. For MIS-C patients, supportive care in addition to therapy against underlying inflammatory process with IVIG, steroid, aspirin, anticoagulant treatment are recommended [31]. However, there exist no widely accepted guidelines yet for the diagnosis and treatment for MIS-A. Treatment modalities have been extrapolated from suggested therapies for MIS-C since the syndrome is similar. Each center implements its own treatment protocol on the basis of reported cases. The present case-based review revealed that 60.8% (31/51) of the patients were treated with steroid, and 37.3% (19/51) with IVIG. The tocilizumab treatment was given to only 13.7% (7/51) of the patients. When the disease severity was evaluated, it was observed that 19.6% (10/51) of the patients required respiratory support with mechanical ventilation, 7.8% (4/51) required intra-aortic balloon pump (IABP), and 5.9% (3/51) required ECMO [4, 6–28]. Two of the reported patients died during the follow-up period [4, 10]. In the present cases, a combination of IVIG and pulse methylprednisolone treatment was proposed fast clinical resolution. For quick intervention, we started antibiotic treatment along with steroid, anticoagulant, and IVIG treatments without waiting the exclusion of other infectious agents. As a consequence, it is important to start the treatment immediately by rapid diagnosis and careful monitoring. MIS-A may be a quite serious clinical condition that needs urgent and effective treatment and may result in worse outcomes without appropriate management. IVIG and pulse steroid treatments are the effective options on clinical improvement.

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intellectual content: all authors. Final approval of the version to be published: all authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors. We acknowledge Osman Topac for performing language editing.

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Data availability Possible.

Declarations

Conflict of interest The authors declare that they have no known competing interests.

Informed consent It was obtained from the patients for publication of the present case report.

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