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CASE BASED REVIEW

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

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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

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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/per 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,

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
References			Morris et al. [4]	Morris et al. [4]	Morris et al. [4]	Morris et al. [4]	Morris et al. [4]	Morris et al. [4]	Morris et al. [4]	Morris et al. [4]	Morris et al. [4]	Sokolovsky et al. [6]
Age (years)/ gender	40 years, male	18 years, female	27 years, female	50 years, male	46 years, male	21 years, male	33 years, male	22 years, female	21 years, female	47 years, female	42 years, male	36 years, female
Clinical presentation	Fever, diarrhea, abdominal pain, rash × 4 days	Fever, chills, epigastric pain, dyspnea × 4 days	Diarrhea, rash × 5 days, hypovolemic shock	Sweating × 3 days, hemodynamic instability	Fatigue, vomiting × 4 days, chest pain	Fever, nausea, vomiting lymphadenopathy cough × 6 days	Fever, gastrointestinal symptoms respiratory symptoms	Fever, chills, throat pain, odynophagia × 2 days	Fever, fatigue, throat, nausea, vomiting × 1 day	Sore throat, fatigue, respiratory symptoms	Fever, gastrointestinal and respiratory symptoms	Fever abdominal pain, vomiting, and diarrhea × 7 days diffuse rash and arthralgias × 2 days
Comorbidities	None	None	None	None	Obesity	Obesity	Obesity, hypertension	None	Obesity	None	Obesity	None
Race/ethnicity/ location	Caucasian Ankara	Caucasian Ankara	African American Maine	African American Florida	African American Florida	African American Louisiana	African American Georgia	African American New York	African American New York	African American New York	Asian New York	Hispanic New York
BP/ HR/ RR	Hypotension	Hypotension	ND	ND	Hypotension	ND	ND	ND	ND	ND	ND	Hypotension, tachycardia
COVID-19 PCR /Ab	(−)/(+)	(−)/(+)	(−)/(+)	(+)/(+)	(−)/(+)	(−)/(+)	(+)/(+)	(+)/(+)	(+)/(+)	(+)/ND	(−)/ND	(+)/(+)
Previous COVID-19 history	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes	No
Time from COVID-19 to symptom onset (days)	23	60	ND	ND	ND	ND	41	ND	25	ND	37	ND

Table 1 (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
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	None	ND	None	ND
Length of hospital stay (days)/ outcome	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, gastrointestinal symptoms, dyspnea, 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	Black
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, IVIG	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	9/alive	8/alive	No data/ex	5/alive	7/alive	13/alive	18/alive	7/alive	8/alive	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]	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, headache, diarrhea, dyspnea, 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	ND	ND	ND	ND	ND	ND	Caucasian
BP/HR/RR	Hypotension, tachycardia	Tachycardia	Hypotension, tachycardia	Hypotension, tachycardia	Tachycardia	Hypotension, tachycardia	Tachycardia	Hypotension	Hypotension, tachycardia	Hypotension, tachypnea, tachycardia
COVID-19 PCR /Ab	(+)/(+)	(+)/(+)	(+)/(−)	(−)/(+)	(+)/(−)	(−)/(+)	(−)/(+)	(−)/(+)	(−)/(+)	(−)/(+)

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	Patient 31	Patient 32	Patient 33	Patient 34	Patient 35	Patient 36	Patient 37	Patient 38
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, cough, myalgia, diarrhea, vomiting, and abdominal pain	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	ND	Caucasian	ND	Hispanic	ND	ND	African–American
BP/HR/RR	Hypotension	Hypotension	Tachycardia	Tachycardia	Tachycardia	Tachycardia	Hypotension	Hypotension, tachycardia, tachypnea
COVID-19 PCR/Ab	(+)/(+)	(−)/(+)	(−)/(+)	(−)/(+)	(−)/(+)	(−)/(+)	(−)/(ND)	(−)/(+)
Previous COVID-19 history	ND	ND	ND	Yes	Yes	Yes	ND	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	Steroid, IVIG, vasopressor, tocilizumab	Steroid	ND	Steroid, heparin, IVIG, vasopressor	Steroid, aspirin, IVIG, vasopressor	Steroid, heparin, aspirin, IVIG
Organ support	ND	ND	MV	ND	None	MV	MV	ND
Length of hospital stay (days)/outcome	ND	10/alive	22/alive	ND	12/alive	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	ND	ND	Fever, myalgia, dyspnea, dry cough, hypogeusia, vomiting, diarrhea, and pruritic rash, conjunctivitis, edema of hands and feet	Fevers, myalgias, and dyspnea	Fever, epigastric and right upper quadrant abdominal pain, vomiting, diarrhea, headache, and myalgia, rash, conjunctivitis
Comorbidities	No	Asthma	No	ND	ND	ND	ND	ND	ND	None	Obesity
Race/Ethnicity	Hispanic	Hispanic	Non-hispanic, white	East African	African	African	New York city, hispanic	New York city, black	African	ND	ND
BP/HR/RR	81/52; 133; 27	ND	83/45; 137; 18	ND	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

Table 1 (continued)

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
Previous COVID-19 history	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Yes
Time from COVID-19 to symptom onset (days)	ND	ND	ND	21	ND	ND	ND	ND	ND	ND	30
Treatment	Steroid, vasopressor, tocilizumab	IVIG, heparin, tocilizumab	Vasopressor	IVIG, tocilizumab	Steroid, IVIG	Steroid, IVIG	Steroid, Convalescent plasma	Steroid	Hydroxychloroquine	Colchicine, aspirin, and montelukast	Vasopressor, steroid, IVIG
Organ support	MV	NIMV	ND	ECMO, MV	ND	ND	IABP	ND	ND	ND	MV
Length of hospital stay (days)/outcome	13/alive	4/alive	9/alive	45/alive	ND	ND	ND	ND	ND	ND	18/alive

Ab Antibody, *ASA* Acetyl salicylic acid, *BP* blood pressure, *CRP* C-reactive protein, *ECMO* extracorporeal membrane oxygenation, *HR* heart rate, *IABP* Intra Aortic balloon pump, *IVIG* Intravenous immunoglobulin, *MV* Mechanical ventilation, *ND* No data, *NIMV* non-invasive mechanical ventilation, *PCR* Polymerase chain reaction, *RR* respiratory rate

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 hypokinesis 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, he 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

Table 2 Imaging and laboratory results 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
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 minimal pericardial effusion, LVEF 45%	Mild global hypokinesis, LVEF 45%	Mild global hypokinesis, LVEF 45%, pericardial effusion	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	LVEF %60	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	ND	Bilateral lower lobe opacities/ airspace disease	Revealed normal lung parenchyma and a trace right pleural effusion

Characteristics of the patients	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20
CRP (mg/L)	547	338	580	90	217	402	125	326	317	45
Procalcitonin (µg/L)	79	ND	ND	ND	ND	ND	ND	ND	ND	ND
Ferritin (ng/mL)	21,196	1249	793	798	196	13,252	3595	983	11,483	2660
D-Dimer (ng/mL)	2.97	4.2	0.45	1.9	1.2	3.39	6.4	1.4	14.23	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	139	3530
Elevated liver enzyme	Yes	Yes	Yes	No	Yes	ND	ND	ND	ND	ND
WBC/lymphocyte count (cells/µL)	700	390	2120	1150	120	ND	ND	ND	ND	ND
ECG	ND	ND	Sinus tachycardia	Right axis deviation	ND	Sinus tachycardia, diffuse ST elevation	Sinus tachycardia	Sinus tachycardia, inferolateral ST elevation	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 Inferolateral hypokinesis mild RV dysfunction mild MVR	LVEF: 35%. LVEDD 5.5 cm moderate RV dysfunction mild MVR and TVR	LVEF: 35%, LVEDD 5 cm mild RV dysfunction
Control echo	Normal echocardiogram	ND	ND	ND	ND	LVEF 50%, normal RV, No valve disease	LVEF 50%, normal RV, No valve disease	LVEF 50%, mild RV dysfunction mild MR	LVEF 50%, normal RV, mild MVR	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
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	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: 25–30%. LVEDD 5.5 cm Normal RV	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	LVEF 60%, normal RV	LVEF: 60%	LVEF: 40%	LVEF: 60%	LVEF: 60%	LVEF: 50%	LVEF: 60%	LVEF: 60%	ND
CT/CXR	Normal	Mild bilateral opacities	Severe COVİD-19 infiltrate	Mild COVİD-19 infiltrate	Severe COVİD-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

Table 2 (continued)

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	4260	1507
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	ND	ND	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	Atrial fibrillation with rapid ventricular response	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
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	ND	ND	ND	ND	ND	5384	92	4688
D-Dimer (ng/mL)	1.91	0.45	14.23	3.32	ND	ND	ND	ND	ND	0.35	2.23
Troponin (ng/L)	2.73	0.01	0.33	2.71	ND	ND	ND	ND	ND	ND	0.79
BNP (pg/mL)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Elevated liver enzyme	ND	ND	ND	ND	ND	ND	ND	ND	Yes	ND	Yes
WBC/Lymphocyte count (cells/μL)	ND	ND	ND	ND	ND	ND	ND	ND	ND	1000	918
ECG	ND	ND	ND	ND	ND	ND	ND	ND	Sinus tachycardia	ND	ND

Table 2 (continued)

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
Echo	ND	ND	Decreased left ventricular systolic function, LVEF: 40%	ND	Myocardial dysfunction	Myocardial dysfunction	LVEF: 29%	LVEF: 44%	Normal	ND	LVEF: 35–40%
Control echo	ND	ND	ND	ND	ND	ND	LVEF: 50%	LVEF: 56%	ND	ND	LVEF: 60–65%
CT/CXR	Lung opacities, pleural effusion	Right middle lobe opacities	Atelectasis	ND	ND	ND	ND	ND	Peripheral interstitial infiltrates	ND	Normal

BNP Brain natriuretic peptide, *CRP* C-reactive protein, *CTA* computed Tomography, *CXR* chest X-ray, *Echo* echocardiography, *EF* ejection fraction, *LV* left ventricle, *LVEDD* left ventricle end diastolic diameter, *MVR* mitral valve regurgitation, *ND* no data, *RV* right ventricle, *TVR* tricuspid valve regurgitation

*Normal ranges for laboratory parameters: BNP = CRP 0–10 mg/L; D-dimer < 0.1 ng/mL. Ferritin = 22–322 µg/L, lymphocyte counts = 1000–4000 cells/µL; procalcitonin < 0.03 µg/L, troponin < 45 ng/L

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 ± mucocutaneus 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,

- The new onset gastrointestinal symptoms such as abdominal pain, vomiting, diarrhea.

The present cases had a history of positive test results 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-corporeal 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 was1265 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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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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