Case Report

Two cases of multisystem inflammatory syndrome in adults after improvement in severe acute respiratory distress syndrome due to coronavirus disease 2019

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Background: Multisystem inflammatory syndrome in adults (MIS-A) is a postacute coronavirus disease 2019 (COVID-19) syndrome occurring weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Although this hyperinflammatory syndrome causes significant morbidity, mortality is low. Reports of MIS-A following acute respiratory distress syndrome (ARDS) due to SARS-CoV-2 infection have rarely been reported. We describe two cases of MIS-A that developed after recovery from critical acute COVID-19.

Case Presentation: We present two cases of MIS-A. In both cases, approximately 4 weeks after the onset of COVID-19, the patients developed gastrointestinal disorders, complicated by other organ damage, and died.

Conclusion: ARDS and MIS-A can occur in a patient with COVID-19 at different times of onset. Clinicians should consider MIS-A when unexplained multisystemic abnormalities are noted after the treatment of ARDS due to COVID-19.

Key words: Acute respiratory distress syndrome, coronavirus disease 2019, extracorporeal membrane oxygenation, gastrointestinal disturbance, multisystem inflammatory syndrome in adults

INTRODUCTION

MULTISYSTEM ORGAN DAMAGE due to abnormal immune response has been shown to develop in adults and children a few weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] In adults, this phenomenon is called multisystem inflammatory syndrome in adults (MIS-A).[2,3]

Various case definitions have been used in the literature. Patel *et al*. and Davogustto *et al*.[3,4] used the definition that includes the following clinical criteria: (i) an individual >21 years presenting with fever; (ii) laboratory evidence of inflammation; (iii) evidence of clinically severe illness requiring hospitalization with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); (iv) no plausible alternate diagnoses; and (v) positive results for current or recent SARS-CoV-2 infection by real-time polymerase chain reaction (PCR), serologic analysis, or antigen test; or (vi) have exposure to a suspected or confirmed coronavirus disease 2019 (COVID-19) case within the 4 weeks prior to the onset of symptoms. We use this widely accepted definition. However, because it is a new disease concept, the case definition is nonspecific and there have been no confirmatory laboratory test results.[5]

The proportion of patients with MIS-A who had COVID-19-like symptoms 28 days before the onset of the disease is reported to be 68%.[4] However, it is difficult to distinguish between MIS-A and critical acute COVID-19, leading to the likely underdiagnosis of this important clinical syndrome.[4] The respiratory symptoms of MIS-A have been reported to be asymptomatic or mild. In addition, most of the cases reported so far have recovered. In this case series, pulmonary damage caused by severe acute respiratory distress syndrome (ARDS) with COVID-19 tended to improve, but the patients died of multiple organ failure due to MIS-A. Patients with any severe illness can develop MIS-A after SARS-CoV-2 infection.

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CASE PRESENTATION

CASE 1 THE first case was a 68-year-old man with a medical history of hypertension and type 2 diabetes mellitus (Table 1). His first symptom was fever (38.5°C). Five days later, the patient tested positive for SARS-CoV-2 by PCR. Seven days after onset, he was placed on a mechanical ventilator due to respiratory failure, while there was no other organ damage. Favipiravir, ciclesonide, nafamostat, heparin, and methylprednisolone were administered.

His respiratory failure worsened, and veno-venous extracorporeal membrane oxygenation (VV-ECMO) was introduced 12 days after onset. The fever of >37°C persisted until this day. His pulmonary injury improved slowly, and VV-ECMO was discontinued on day 42 after the initiation (Fig. 1A).

He had copious watery diarrhea, and inflammatory response by day 29 after onset (Table 1). Body temperature was maintained in the 36–37°C range by ECMO. At this time, the oxygen supply was well maintained by ECMO, and organ reflux pressure (mean blood pressure >65 mm Hg) was maintained with vasopressor. Antigen testing result for *Clostridioides difficile* (CD) was negative, and stool culture testing was negative. Cytomegalovirus (CMV) was in a pre-existing infection pattern. Diagnostic treatment included metronidazole, ganciclovir, and plasma exchange, but there was no improvement. Extensive erosions were observed in the intestine, from the duodenum to the ileum (Fig. 2A1, A2). Gastrointestinal bleeding gradually appeared with diarrhea. We tried endoscopic hemostasis many times, but this could not stop the bleeding. The patient had a small intestinal hemorrhage and underwent arterial embolization as well as small intestine resection on day 57. Ischemia was suspected but intraoperative examinations did not reveal any obvious ischemic findings. The biopsies showed extensive inflammatory granulation tissue, inflammatory exudates containing neutrophils, erosions, and bleeding in the resected small intestine. The patient developed prolonged shock requiring fluids replacement and vasopressors to maintain organ perfusion. In addition to gastrointestinal disorders, other organ disorders, including sick sinus syndrome, liver failure, and coagulopathy, were observed. The patient died on day 87.

Case 2: The second case was a 63-year-old man with a medical history of hypertension, type 2 diabetes, and asthma (Table 1). The PCR test for SARS-CoV-2 was positive, but the patient was asymptomatic. Seven days later, he needed oxygen due to hypoxia. Respiratory failure worsened. The patient was placed on a mechanical ventilator on day 11 after onset, and VV-ECMO was introduced on the same day. Favipiravir, remdesivir, ciclesonide, nafamostat, and heparin were administered. Subsequently, pulmonary damage was improved, and ECMO was discontinued on day 17(Fig. 1B). However, watery diarrhea appeared on day 28 after onset. He also had an elevated inflammatory response, but his oxygen levels were normal (Table 1). Body temperature was maintained at a normal level by ECMO. The maximum stool volume was 9,000 mL/day. Vasopressors were administered due to prolonged hypotension. Antibiotic therapy and vasopressor were used, but these interventions did not improve the gastrointestinal disorders or shock. CD antigen test and stool culture were both negative. Ganciclovir and foscarnet were administered for positive CMV antigenemia, but there were no improvement. Immunostaining of tissue from the ulcer base by endoscopy showed no CMV-positive cells. Extensive erosion of the intestinal tract was observed (Fig. 2B1, B2). The biopsies showed inflammatory granulation tissue, inflammatory exudates containing neutrophils, and erosions in the colon. To be cautious and considering the possibility of immunological abnormality, high-dose methylprednisolone (1,000 mg/day) was administered from days 91 to 93 after onset. The stool volume decreased markedly to approximately one-third, but increased again after the administration of high-dose methylprednisolone. High-dose methylprednisolone was tapered again, but the stool volume could not be controlled. Subsequently, we then administered infliximab, but there was no response. Acute myocardial infarction, liver dysfunction, and coagulation dysfunction could not be controlled, and the patient died on day 142.

DISCUSSION

WE DESCRIBED TWO cases of MIS-A after recovery from COVID-19–associated ARDS. In both cases, the onset time of MIS-A was 4–5 weeks after the initial symptoms of COVID-19. The patients developed multiple organ damage, such as gastrointestinal damage, liver damage, cardiac damage, and shock, at approximately 4 weeks after disease onset, which resulted in fatal outcomes.

In patients with minor pulmonary lesions a few weeks after SARS-CoV-2 infection, the typical symptoms of MIS-A were fever, cutaneous symptoms, gastrointestinal disturbances, and cardiac dysfunction. The US Centers for Disease Control and Prevention (CDC) defines of MIS-A as the presence of fever, multiorgan involvement (with major criteria including severe cardiac event or mucocutaneous findings), laboratory findings of inflammation, and virologic testing showing previous infection.[6] In some case reports,[7,8] there have been deaths due to myocarditis caused by MIS-A. In a recent systematic review,[4] gastrointestinal symptoms occurred in 83% of patients, and there were patients with no

Table 1. Clinical features and laboratory results of the patients with MIS-A

	Case 1	Case 2
Age (year)	68	62
Sex	Male	Male
BMI (kg/m^2)	33	25.95
Comorbidities	Hypertension, diabetes mellitus (type2)	Hypertension, diabetes mellitus (type2), asthma
Body temperature at the time of MIS-A (°C)	38.2	38.4
Delay between symptoms at time (days)	29	28
SBP (mm Hg)/DBP (mm Hg)/heart rate (bpm) at the time of hospital admission	100/68/105, norepinephrine 0.09 μg/kg/min	120/62/120
SBP (mm Hg)/DBP (mm Hg)/heart rate (bpm) at the time of MIS-A	110/72/100, norepinephrine 0.18 μg/kg/min	99/59/119, norepinephrine 0.2 γ/kg/min and vasopressin 2 U/h
pH/PaO_2(mm Hg)/$PaCO_2$ (mm Hg)/lactate(mmol/L) at the time of hospital admission	7.398/63/39.5/20	7.352/62.8/41.3/20
pH/PaO_2(mm Hg)/$PaCO_2$ (mm Hg)/lactate(mmol/L) at the time of MIS-A	7.298/88.5/56/1.4	7.388/112/56.5/1.3
Laboratory studies at hospital admission	CRP, 37.92 mg/dL; ferritin, nil; PCT, 3.08 ng/dL; D-dimer, 16.6 ng/mL; troponin T, nil; NT-proBNP, 253 pg/mL; AST, 46 U/L; ALT, 22 U/L; total bilirubin, 1.6 mg/dL	CRP, 0.59 mg/dL; ferritin, nil; PCT, 0.96 ng/dL; D-dimer, 2.2 ng/mL; troponin T, 0.044 ng/mL; NT-proBNP, 35 pg/mL; AST, 75 U/L; ALT, 54 U/L; total bilirubin, 1.0 mg/dL
Laboratory studies during MIS-A	CRP, 20.82 mg/dL; ferritin, 3776 ng/mL; PCT, 6.66 ng/dL; D-dimer, 62.7 ng/mL; troponin T, nil; NT-proBNP, 3,980 pg/mL; AST, 139 U/L; ALT, 92 U/L; total bilirubin, 23.2 mg/dL	CRP, 26.97 mg/dL,; ferritin, 9,630 ng/mL; PCT, 19.6 ng/dL; D-dimer, 54.4 ng/mL; troponin T, 0.163 ng/mL; NT-proBNP, 1,326 pg/mL; AST, 175 U/L; ALT, 202 U/L; total bilirubin, 16.7 mg/dL
Severe cardiac illness	Sick sinus syndrome, LVEF30%	Acute myocardial infarction, ventricular tachycardia, LVEF40%
Rash and nonpurulent conjunctivitis	No	No
Shock or hypotension	Yes	Yes
Gastrointestinal symptoms	Diarrhea	Diarrhea
SARS-CoV-2 testing	RT-PCR(+), nasopharyngeal	RT-PCR(+), nasopharyngeal
Clostridioides difficile toxin/GDH	Negative/negative	Negative/negative
CMV antigenemia/IgG/IgM/PCR/immunohistochemistry	Negative/positive/negative/negative/negative	Positive/positive/negative/negative/negative
Stool culture	Normal flora	*Candida glabrata*
Outcome	Died	Died

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CMV, cytomegalovirus; CRP, C-reactive protein; DBP, diastolic blood pressure; GDH, glutamate dehydrogenase; Ig, immunoglobulin; LVEF, left ventricular ejection fraction; MIS-A, multisystem inflammatory syndrome in adults; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen in the arterial blood; PCT, procalcitonin; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBP, systolic blood pressure.

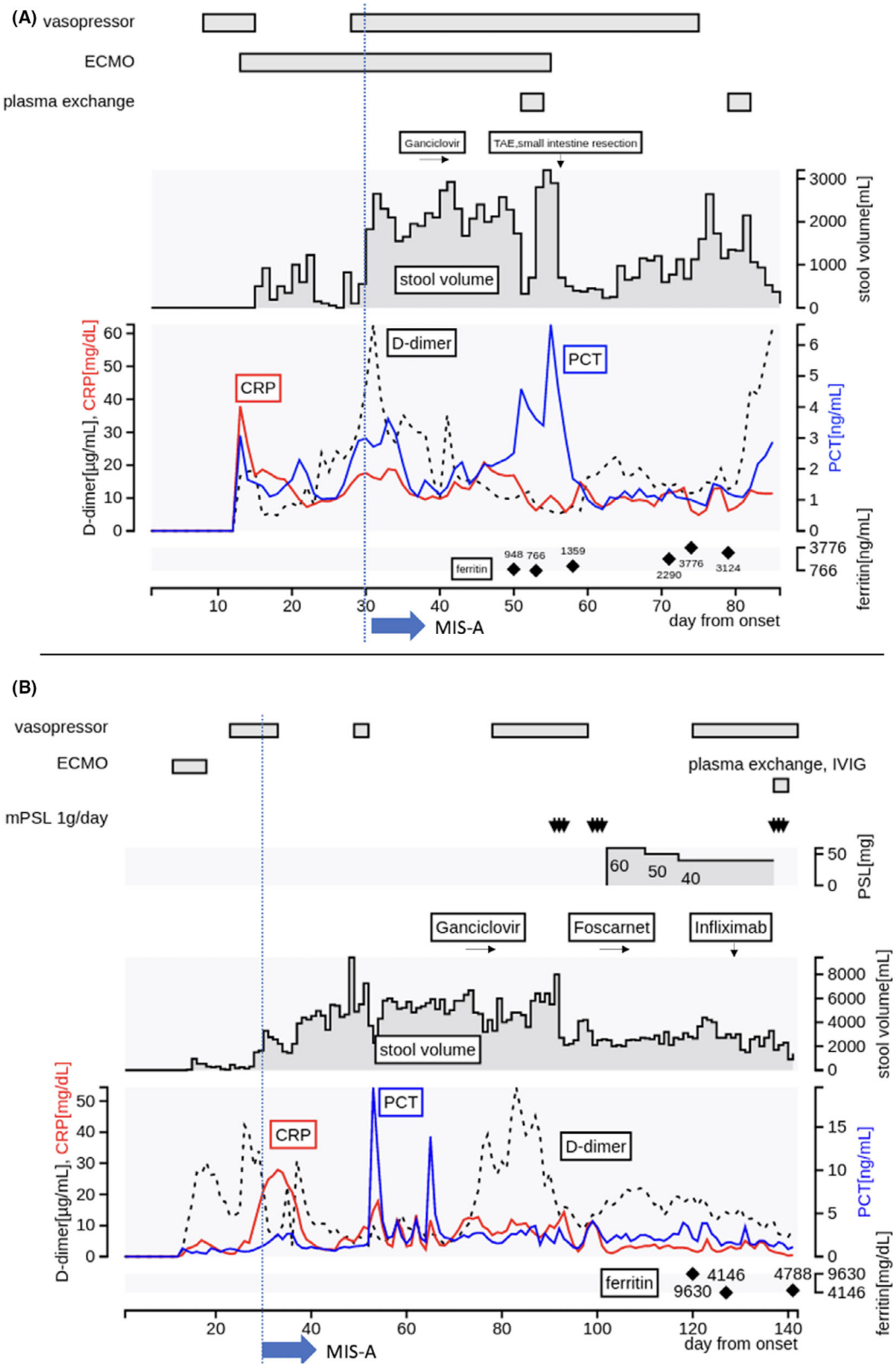

Fig. 1. (A) Case 1: Copious watery diarrhea appeared on day 29 after onset. At that same time, blood tests showed an elevated inflammatory response. Plasma exchange did not improve the patient's condition, and gastrointestinal bleeding became difficult to control. Therefore, the patient underwent transcatheter arterial embolization and small bowel resection. (B) Case 2: Watery diarrhea appeared on day 28 after onset. In that period, an elevated inflammatory response was noted. The highest volume of diarrhea was 9,000 mL/day. High-dose methylprednisolone transiently reduced the volume of diarrhea, but it later increased again. Cytokine storm was recalled, and the patient was treated with IVIG and PE; however, his condition did not improve. CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; IVIG, intravenous immunoglobulin; MIS-A, multisystem inflammatory syndrome in adults; mPSL, methylprednisolone; PCT, procalcitonin; PE, plasma exchange; TAE, transcatheter arterial embolization.

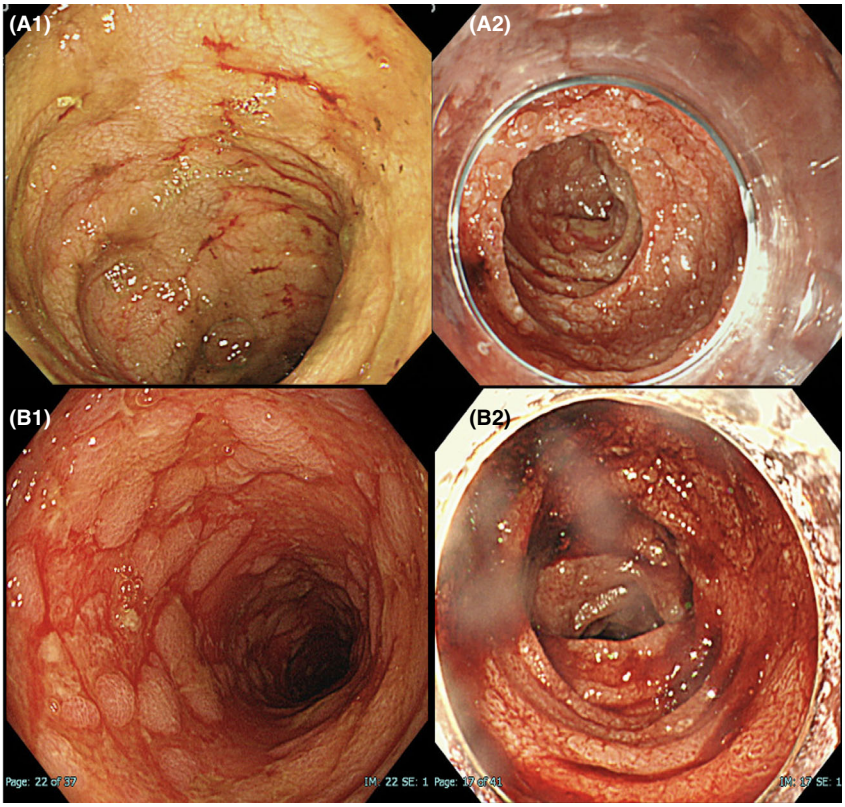

Fig. 2. (A1) Case 1: Endoscopic findings on day 45 after onset showing ulceration with erosions in the sigmoid colon. The ulcer extended to the entire colon. (A2) Case 1: Endoscopic findings on day 58 after onset showing ulceration of the duodenum. (B1) Case 2: Endoscopic findings on day 30 after onset. There was pseudopolyposis-like mucosa in the colon. (B2) Case 2: Endoscopic findings on day 90 after onset. Extensive bleeding ulcers in the entire colon and ileum were seen.

heart defects.[3] The high incidence of gastrointestinal symptoms suggests that MIS-A should not be ruled out despite the absence of severe heart disease or rash. In children, mucocutaneous manifestations are more common in younger age groups, suggesting that myocarditis and gastrointestinal disorders may be more common in older age groups.[9] Thus, gastrointestinal disorders should be given more attention in adults with COVID-19.

It is difficult to distinguish between SARS-CoV-2 infection with prolonged multiorgan damage and MIS-A. MIS-A can also occur in the elderly, but the symptoms are more complex and difficult to diagnose.[4] In these cases, respiratory status and computed tomography findings tended to show improvement upon lung-protective ventilation, including VV-ECMO. The pulmonary damage was improved compared with that on the day of

hospitalization. Therefore, multiple organ damage was not caused by hypoxia. If subsequent re-elevation of the inflammatory response and multiple organ failure cannot be explained, MIS-A should be considered as a clinical etiology. ARDS due to COVID-19 requires long-term respiratory management and prolonged hospitalization. If the patient is hospitalized for a long period, there is a possibility that MIS-A may develop during the same hospitalization period, as observed in our cases.

CONCLUSION

SEVERE ARDS AND MIS-A can occur in the same patient with COVID-19 with different times of onset. Clinicians should consider MIS-A when they are encountering unexplained multisystemic abnormalities during the treatment of severe ARDS due to COVID-19. Early recognition of this syndrome will emerge to be important in the establishment of a cure in future studies.

DISCLOSURE

Approval of the Research Protocol with Approval No. and Committee Name: N/A.
Informed Consent: Informed consent was obtained from the patient.
Registry and the Registration No. of the Study/Trial: N/A.
Animal Studies: N/A.
Data Sharing and Accessibility: N/A.
Conflict of Interest: None declared.

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