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Case Report

Multisystem inflammatory syndrome in adults after acute coronavirus disease 2019 in a Japanese woman: A case report

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ABSTRACT

Multisystem inflammatory syndrome in adults (MIS-A) is a rare and emerging syndrome after coronavirus disease 2019 (COVID-19). To the best of our knowledge, Japanese cases of MIS-A are rarely reported. Here, we describe a case of MIS-A in a 44-year-old Japanese woman presenting with multiorgan dysfunction (i.e., cardiovascular and mucocutaneous involvement) and markedly elevated inflammatory markers 2 weeks after recovery from COVID-19. Treatment with intravenous immunoglobulins and corticosteroids resolved her symptoms. On the 13th day, she was discharged from the hospital with no recurrences on follow-up. This study highlights the importance of recognizing this emerging syndrome when treating patients with multiorgan dysfunction after COVID-19.

1. Introduction

Multisystem inflammatory syndrome (MIS) after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection mainly affects children. However, a case series from the United States Centers for Disease Control and Prevention in October 2020 reported the first case of MIS in adults (MIS-A) [1,2]. MIS-A is characterized by extrapulmonary multiorgan dysfunction with marked elevation of levels of inflammatory markers occurring several weeks after acute SARS-CoV-2 infection [1,3].

The incidence of MIS-A is variable among ethnic groups and may be disproportionately high in Asian populations [1,3]. Because clinical manifestations may also be different between ethnicities, elucidating these ethnicity-based symptoms may further guide the diagnosis of MIS-A. However, to the best of our knowledge, studies regarding MIS-A in Japanese patients are greatly limited [4]. Here, we report a case of MIS-A related to coronavirus disease 2019 (COVID-19) in a Japanese

patient.

2. Case report

A previously healthy 44-year-old Japanese woman presented to our hospital for fever, skin rash, diarrhea, and hypotension with a history of COVID-19 pneumonia 33 days ago. On the previous admission, reverse transcription-polymerase chain reaction (RT-PCR) confirmed infection with the SARS-CoV-2 B.1.1.7 variant. Treatment with dexamethasone, remdesivir, and unfractionated heparin improved her condition; supplemental oxygen was not required. Nineteen days before the second admission to our hospital, she was discharged without complications. A week later, she was able to return to work without any symptoms. However, another week later, she developed fever (>38 °C) with watery diarrhea and generalized skin rash. The presence of hypotension prompted referral to the emergency department of our tertiary care hospital.

Abbreviations: Multisystem inflammatory syndrome in adult, MIS-A; Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2; Multisystem inflammatory syndrome in adults, MIS-A; Coronavirus disease 2019, COVID-19; Reverse transcription-polymerase chain reaction, RT-PCR; Hemophagocytic lymphohistiocytosis, HLH; Severe fever with thrombocytopenia syndrome, SFTS.

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On admission, her blood pressure was 83/45 mmHg, heart rate was 130 bpm, body temperature was 39.4 °C, respiratory rate was 34 bpm, oxygen saturation was 95% on room air, and Glasgow Coma Scale score was E4V5M6. Physical examination revealed conjunctival congestion and generalized erythematous skin rash on the trunk and extremities (Fig. 1). There was no swelling of lymph nodes, reticulated rash, or arthralgia. Contrast-enhanced chest and abdominal computed tomography did not show any pathologic findings, including pneumonia. The RT-PCR test for SARS-CoV-2 yielded negative results. Laboratory tests revealed lymphocytopenia, elevated levels of cardiac markers, and markedly elevated levels of inflammatory markers, such as C-reactive protein (25.17 mg/dL) and interleukin-6 (1970 pg/mL) (Table 1). Her electrocardiogram showed no abnormal findings such as ST/T wave change or arrhythmia other than sinus tachycardia. Her transthoracic echocardiogram showed slightly decreased left ventricular ejection fraction (53%), which improved on the fourth hospital day (ejection fraction of 67%). We found no pericardial effusion. The patient was admitted to the intensive care unit where she was treated with noradrenaline for hypotension and piperacillin/tazobactam for suspected bacterial infection.

These findings were highly suggestive of MIS-A after acute COVID-19. However, a comprehensive workup was performed to exclude the differential diagnoses of MIS-A. Bone marrow aspiration showed no evidence of malignant lymphoma or hemophagocytic lymphohistiocytosis (HLH). Her skin biopsy revealed no abnormal findings suggestive of vasculitis. Her blood and urine cultures were negative. There was no evidence of skin-and-soft-tissue infection or menstruation-related toxic-shock syndrome. Serologic tests for Epstein-Barr virus, measles virus, and rubella virus indicated prior infections. The result of antinuclear antibody test was negative, indicating a minimal likelihood of collagen diseases (e.g., systemic lupus erythematosus). Despite the absence of tick bites or any history of travel to forests or mountains, her blood specimens were sent to an external reference laboratory to check for infection with the severe fever with thrombocytopenia syndrome (SFTS) virus and rickettsia (i.e., Tsutsugamushi disease and Japanese spotted fever) because the hospital was located in an area endemic for these tick-borne diseases. Since there were no abnormal findings on her electrocardiogram or symptoms suggesting heart failure, endomyocardial biopsy for diagnosis of myocarditis was not considered necessary.

Due to our initial working diagnosis of MIS-A, we initiated immunomodulatory therapy with a 2-day course of intravenous immunoglobulin (25 g per day) and methylprednisolone (1 g) (Fig. 2). On the third hospital day, her skin erythema and conjunctival congestion showed improvements. The RT-PCR for the SFTS virus turned out to be positive, which prompted discontinuation of methylprednisolone. Noradrenaline was also discontinued because of the resolution of hypotension. Because of the suspicion of co-existent rickettsia infections, minocycline was administered. On the eighth hospital day, she became



Fig. 1. Dermatologic examination revealed erythematous skin rash in the patient's back.

Table 1
Laboratory results on admission.

Variable	Value
White cell count (cells/mm ³)	10200
Lymphocyte count (cells/mm ³)	204
Hemoglobin (g/dL)	10.5
Hematocrit (%)	30.8
Platelet count (cells/mm ³)	90000
Sodium (mmol/L)	135
Potassium (mmol/L)	3.2
Chloride (mmol/L)	102
Blood urea nitrogen (mg/dL)	10.9
Creatinine (mg/dL)	0.53
Aspartate aminotransferase (IU/L)	18
Alanine aminotransferase (IU/L)	13
Lactate dehydrogenase (IU/L)	217
Creatine kinase (IU/L)	72
Total bilirubin (mg/dL)	1.2
International normalized ratio	1.32
Fibrinogen (mg/dL)	561
D-dimer (µg/mL)	17.0
Erythrocyte sedimentation rate (mm/h)	52
C-reactive protein (mg/dL)	25.17
Procalcitonin (ng/mL)	1.87
Interleukin-6 (pg/mL)	1970
Ferritin (ng/mL)	464
Brain natriuretic peptide (pg/mL)	611.4
Troponin I (pg/mL)	1119.5
Lactate (mmol/L)*	3.9

* Lactate level was measured from the arterial blood gas analysis.

afebrile. On the 13th hospital day, she was discharged from the hospital.

At the 1-month follow-up exam, she was found to be generally healthy, and her coronary computed tomography angiography revealed no aneurysm or stenosis of the coronary artery. All serologic tests using specimens from one acute phase (8 days after symptom onset) and two convalescent phases (18 and 26 days after symptom onset) showed negative IgG and IgM titers (<40) for the SFTS virus. We also found no elevation of IgG and IgM titers for *Orientia tsutsugamushi*, *Rickettsia japonica*, and *Rickettsia typhi*. These findings imply that the RT-PCR result for the SFTS virus was a false positive. Finally, our patient was diagnosed with MIS-A associated with COVID-19.

3. Discussion

We present the case of a 44-year-old Japanese woman with MIS-A, who presented with multiple extrapulmonary organ dysfunction (i.e., cardiovascular, hematologic, gastrointestinal, and mucocutaneous involvement) that rapidly improved with immunomodulatory therapy. Due to its rare incidence and broad differential diagnosis, comprehensive testing was performed to establish the diagnosis of MIS-A. While the RT-PCR test results for the SFTS virus was positive initially, further tests revealed that it was a false-positive result.

The most widely used working definition of MIS-A includes the following: (1) a severe illness requiring hospitalization of a person aged ≥21 years, (2) a positive test result for current or previous SARS-CoV-2 infection during admission or in the past 12 weeks, (3) severe dysfunction of one or more extrapulmonary organ systems, (4) laboratory evidence of severe inflammation, and (5) absence of severe respiratory illness [1]. In our patient's case, all of these were present. The time between previous acute SARS-CoV-2 infection and onset of MIS-A was 25 days. Moreover, the SARS-CoV-2 RT-PCR was negative during admission. Our findings were concordant with those in previous studies, suggesting the importance of careful history taking for previous acute SARS-CoV-2 infection for the diagnosis of MIS-A [1,3,4]. Although immunomodulatory therapy is an effective treatment for MIS in children, its efficacy is not yet established in adults [5]. Fortunately, the hemodynamic instability of our patient rapidly improved after treatment with intravenous immunoglobulins and corticosteroids.

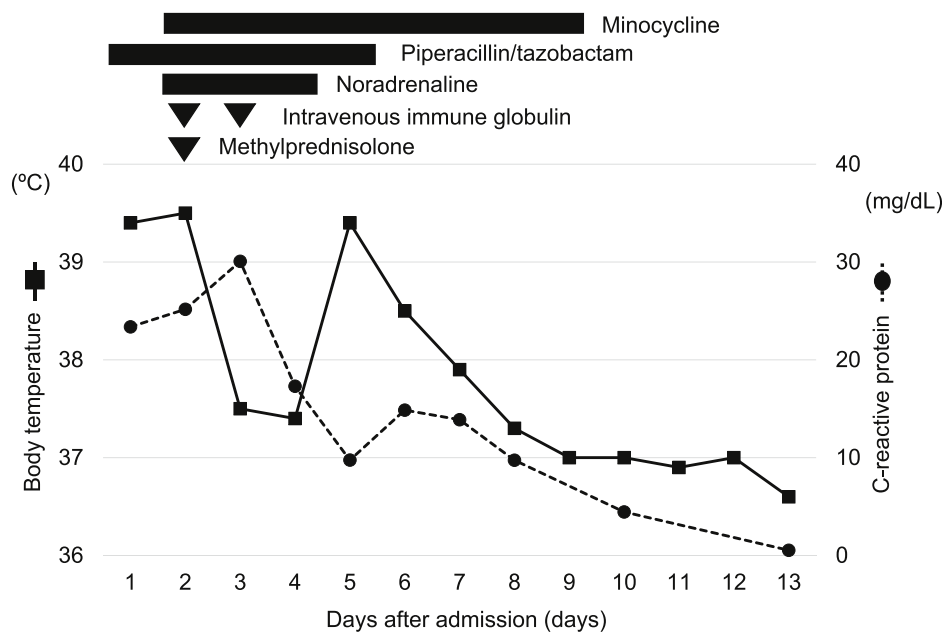


Fig. 2. Body temperature (left, in °C) and serum C-reactive protein levels (right, in mg/dL) of the patient during hospitalization. We administered methylprednisolone (1 g) on the second hospital day and intravenous immunoglobulin (25 g/day) on the second and third hospital days. Body temperature and serum C-reactive protein levels improved with time. She was discharged from the hospital on the 13th hospital day.

Nevertheless, the efficacy of these therapies for MIS-A should be further elucidated.

In this case, the positive SFTS virus RT-PCR result delayed the diagnosis of MIS-A. Although RT-PCR is the gold standard for pathogen detection owing to its high sensitivity and specificity, false-negative and false-positive results have been reported. A previous study examining the diagnostic value of RT-PCR for SFTS reported one false-positive result among 21 patients with no SFTS [6].

We could distinguish MIS-A from SFTS by some aspects. First, the incubation period of SFTS is reported to be 7–14 days, with an average of 9 days [7]. It is not impossible to be infected by SFTS virus immediately after discharge from acute SARS-CoV-2 infection. However, we prioritized Occam's razor over Hickam's dictum in this middle-aged previously healthy woman. Furthermore, there was no history of travel to forests or mountains. Second, a case series of SFTS in Japan reported that most patients with SFTS were elderly and the incidence of SFTS in patients aged less than 50 years old was only 4% [8]. In our case, the patient was under 50 years old, making the likelihood of SFTS very low. Third, although both MIS-A and SFTS involve multiorgan dysfunction and marked inflammatory response, several clinical manifestations in our patient were more indicative of MIS-A than of SFTS. Erythematous skin rash is a relatively rare manifestation of SFTS [9]. Moreover, conjunctival congestion or Kawasaki disease-like syndrome has been reported in some MIS-A patients [10]. A previous case series showed that up to 80% of patients with SFTS had HLH [8]. We also previously described that mild SFTS cases could manifest HLH [11]. However, in our patient, bone marrow aspiration yielded negative results for HLH. Lastly, the results of serologic testing of paired samples, including convalescent sera taken nearly 1 month after symptom onset, showed low IgG and IgM titers for SFTS virus. In SFTS patients diagnosed by RT-PCR including immunocompromised patients, the seropositive rates for IgG or IgM reached 100% two or three weeks after symptom onset [12].

In general, the RT-PCR test has high specificity, and serology test using paired specimens shows high sensitivity in diagnosing acute infection. In the present case, the positive result of PCR test conflicted with the negative result of the serology test.

The false-positive result of the RT-PCR test could be attributed to the

contamination of specimens from collection to laboratory and cross reaction to other pathogens. During this season, several patients with SFTS were admitted to our ICU (not concurrently with the present case), which could not exclude the possibility of contamination of the specimen. However, we could not find literature about the cross reaction between SFTS virus and SARS-CoV-2.

In contrast, the false-negative result of the serology test could be attributed to impaired immune function (e.g., B cell dysfunction) or immunomodulatory drugs. While our patient had no comorbidities of immunocompromise, she received immunoglobulin and corticosteroid for treatment of MIS-A, which might have delayed her humoral immune response.

Hence, we could not conclude which result was false merely on the basis of the results of the PCR test and serology test. Considering the patient's history and clinical manifestations as discussed above, we carefully judged the result of PCR as false-positive and confirmed the diagnosis of MIS-A.

Other than SFTS, we excluded a broad range of differential diagnosis to diagnose this case as MIS-A. In recent case reports of MIS-A, clinicians also excluded other causes, mainly infectious causes or autoimmune causes [13–15]. For the diagnosis of MIS in children, some experts recommends excluding other causes of inflammation, including bacterial sepsis, staphylococcal or streptococcal toxic shock syndrome, and myocarditis [16]. When MIS-A is suspected, the range of differential diagnosis should be decided on a case-by-case basis until a sophisticated definition is achieved.

In conclusion, we presented the case of our patient with MIS-A who presented with multiorgan failure and marked inflammation. The clinical course was concordant with that reported in previous studies involving patients of other ethnicities. Because MIS-A is a rare, novel, and emerging condition with diverse differential diagnoses, a comprehensive diagnostic workup was necessary, resulting in an increased possibility for false-positive results. This study highlights the importance of a targeted diagnostic work-up for excluding the differential diagnoses of MIS-A.

Informed consent

Written informed consent was obtained from the patient for the publication of this paper.

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Author contributions

KM wrote the original manuscript. YK, ST, TN, KK, RT, MS, NS, SN, NF, and SK helped during the drafting and revising of the article. All authors read and approved the final manuscript.

Declaration of competing interest

None.

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