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【 CASE REPORT 】

Multisystem Inflammatory Syndrome in Adults Accompanied with Kikuchi-Fujimoto Disease

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Abstract:

We herein report a case of multisystem inflammatory syndrome in adults (MIS-A) complicated with Kikuchi-Fujimoto disease (KFD). A previously healthy 41-year-old man presented with painful swelling of the cervical lymph nodes, fever, diarrhea, conjunctivitis, edema, and hypotension one month after the onset of asymptomatic coronavirus disease 2019. Laboratory investigations revealed an elevation of CRP, and echocardiography indicated diastolic dysfunction. We diagnosed the patient to have MIS-A. Histopathology of the lymph nodes showed necrotizing lymphadenitis. After the initiation of hydrocortisone and diuretics, his symptoms resolved immediately. This case suggested that post-viral immune dysregulation in MIS-A could play a role in the etiology of KFD.

Key words: COVID-19, SARS-CoV-2, multisystem inflammatory syndrome in adults, Kikuchi-Fujimoto disease

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Introduction

During severe coronavirus disease 2019 (COVID-19) pandemic, post-acute COVID-19 multisystem inflammatory syndrome (MIS) has been recognized as a rare, but severe, complication of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (1-3). After MIS in children (MIS-C) was first identified in April 2020, many physicians noted a similar syndrome occurring in adults (MIS-A) (4, 5). MIS presents approximately four weeks after acute COVID-19 hyperinflammation and extrapulmonary multiorgan involvement (6).

Kikuchi-Fujimoto disease (KFD) is a rare and self-limited condition, usually characterized by fever and cervical lymphadenopathy, and most reported cases are from Asia (7). Although the etiology and pathogenesis remain unclear, the clinical presentation, course, and laboratory and histologic findings suggest the contribution of immune responses by T cells and histiocytes and of cytokines, such as interferon-gamma and interleukin (IL)-6, to its pathogenesis (7-9). There have been several reports that these immune responses and cytokines in KFD are implicated in the induction of rare manifestations such as pulmonary infiltrates, hemophagocytosis, antiphospholipid syndrome, acute renal failure, bilateral papillary conjunctivitis, and autoimmune hepatitis (10-15). However, we found no case reports of patients with KFD who developed hypotension and multiple organ dysfunctions that suggested cytokine syndrome.

Numerous infectious agents are associated with the immune responses by T-cells and histiocytes in KFD (7). While there have been few reports of KFD presenting after COVID-19 infection, neither of them fulfil the criteria of MIS-A (16-18).

We herein report a case of MIS-A complicated by KFD one month after polymerase chain reaction (PCR)-confirmed mild COVID-19.

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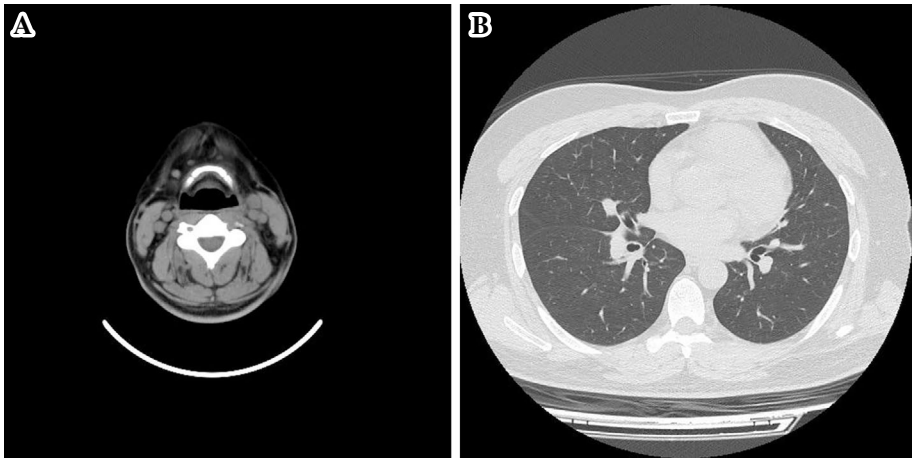

Figure 1. On the third day after admission, computed tomography (CT) revealed an enlargement of multiple cervical lymph nodes (A) but no abnormalities in the lungs (B).

Case Report

A previously healthy 41-year-old man was transferred to our intensive care unit (ICU) because of progressive respiratory failure, hypotension, liver dysfunction and thrombocytopenia.

Six weeks prior to this transfer, he noticed a loss of olfactory and gustatory sense, and on the next day a reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 was positive. He had no cough, fever, or dyspnea, and was isolated at home for ten days and thereafter returned to work. An annual medical checkup performed one week earlier revealed normal chest X-ray findings and a normal biochemical panel including liver and kidney functions. However, on the following day after the medical checkup, he presented with painful swelling of the left cervical lymph nodes and high fever (>38.5℃). His symptoms persisted for two days, and he was admitted to a local hospital. Computed tomography (CT) revealed an enlargement of the left cervical lymph nodes but no abnormalities in the lungs (Fig. 1). As a therapeutic trial, intravenous ceftriaxone and oral prednisolone 1 mg/kg (60 mg) were administered for two days. However, he continued to have fever and painful cervical lymphadenopathy, and he started to report fatigue, poor appetite and diarrhea.

Two days before being transferred to our hospital, he became dyspneic and drowsy, with arterial oxygen saturation (SpO2) of less than 90% on room air, and hypotension, for which oxygen supplementation and noradrenaline were initiated. Contrast-enhanced CT revealed airspace consolidation with air bronchograms in the middle lobe of the right lung and lower lobes of both lungs (Fig. 2A, B) and an enlargement of the right cervical and supraclavicular lymph nodes (Fig. 2C, D). We could not detect any splenomegaly on CT. An RT-PCR test for SARS-CoV-2 was negative. He was therefore transferred to our hospital for further investigation.

On physical examination, he had high fever (>39.4°C), hypotension (systolic blood pressure was 69 mmHg), enlarged right cervical lymph nodes, bilateral conjunctivitis and severe anasarca.

Initial laboratory investigations in our hospital revealed a white blood cell count of 13.6×10^3 /mm^3 (94.1% neutrophils, 2.9% lymphocytes, and 1.9% eosinophils), hemoglobin level of 11.9 g/dL, platelet count of 28×10^3/mm^3, C-reactive protein (CRP) level of 34.62 mg/dL, albumin level of 1.9 g/dL, total bilirubin level of 4.8 mg/dL, direct bilirubin level of 4.0 mg/dL, aspartate aminotransferase level of 29 U/L, alanine aminotransferase level of 66 U/L, fasting triglycerides level of 297 mg/dL, lactate dehydrogenase level of 161 U/L, N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP) level of 10,389 pg/mL, D-dimer level of 3.86 μg/mL, fibrinogen level of 703 mg/dL, and ferritin level of 2,350 ng/mL. He did not have any electrolyte abnormalities or diabetes mellitus, and his renal function was normal. A sputum culture was negative. Urinary legionella antigen was also negative.

On the next day, a biopsy of the cervical lymph node and bone marrow aspiration were performed. He was negative for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen and antibody, hepatis C virus (HCV) antibody, interferon-gamma release assay, rheumatoid factor, and antinuclear antibody. Tests for Epstein-Barr virus (EBV)-specific antibodies and Cytomegalo virus (CMV)-specific antibodies suggested that he had already been infected. According to the findings of echocardiography, the left ventricular ejection fraction (EF) was 62%, E/A ratio was 2.05, and deceleration time was 111 milliseconds, which indicated a diastolic dysfunction. We initiated levofloxacin and hydrocortisone 200 mg per day because of a presumptive diagnosis of severe community-acquired pneumonia with septic shock. As fluid retention was evident, we also initiated diuretics to consider the possibility of heart failure. Two days after the treatment, his symptoms remarkably improved and we stopped the norepinephrine treatment. All laboratory abnormalities had also improved. The results

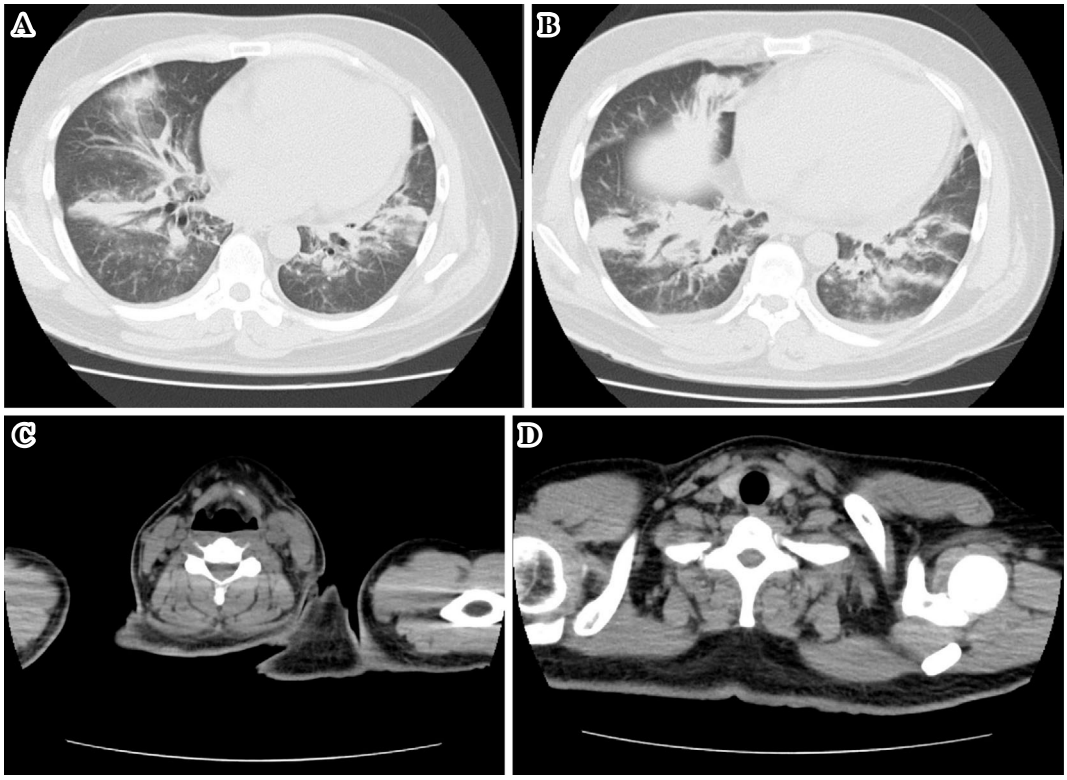

Figure 2. **On the sixth day, contrast-enhanced CT revealed airspace consolidation with air bronchograms in the middle lobe of the right lung and lower lobes of both lungs (A, B) and enlargement of the right cervical and supraclavicular lymph nodes (C, D).**

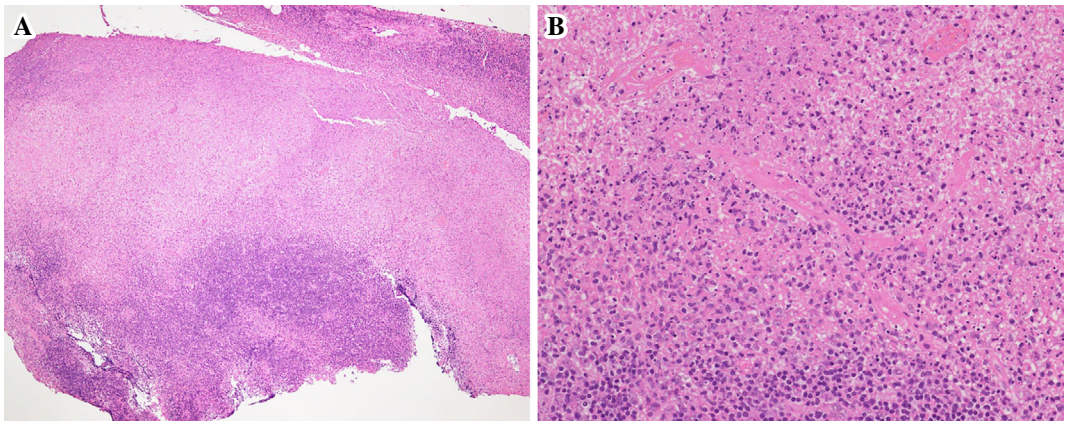

Figure 3. **A tissue sample obtained from a cervical lymph node showed extensive necrosis with surrounding histocytes and plasma cells (Hematoxylin and Eosin staining, A: ×10, B: ×100).**

of additional laboratory tests revealed an IL-6 level of 4.18 pg/mL (normal range <2.41 pg/mL) and soluble interleukin-2 receptor (sIL-2R) level of 7,040 U/m. Because he recovered quickly, no additional treatment was required after the use of hydrocortisone and levofloxacin for four days. Bone marrow aspiration revealed no specific findings; however, the histopathological findings of the biopsy specimen of the cervical lymph nodes showed extensive necrosis with surrounding histocytes and plasma cells with no atypia or malignancy (Fig. 3). Periodic acid-Schiff staining, Grocott and Ziehl-Neelsen staining showed no evidence of lymphoid malignancy, fungi, or acid-fact bacilli. He was discharged eleven days after admission. The clinical course is shown in Fig. 4.

As the clinical course suggested that the pulmonary infiltrate shadow was consistent with pulmonary edema due to heart failure, we diagnosed the patient to have MIS-A accompanied with KFD.

Discussion

We report a case of MIS-A complicated with KFD. Although several cases of co-occurrence of COVID-19 and KFD have been reported, cases of KFD in patients diag-

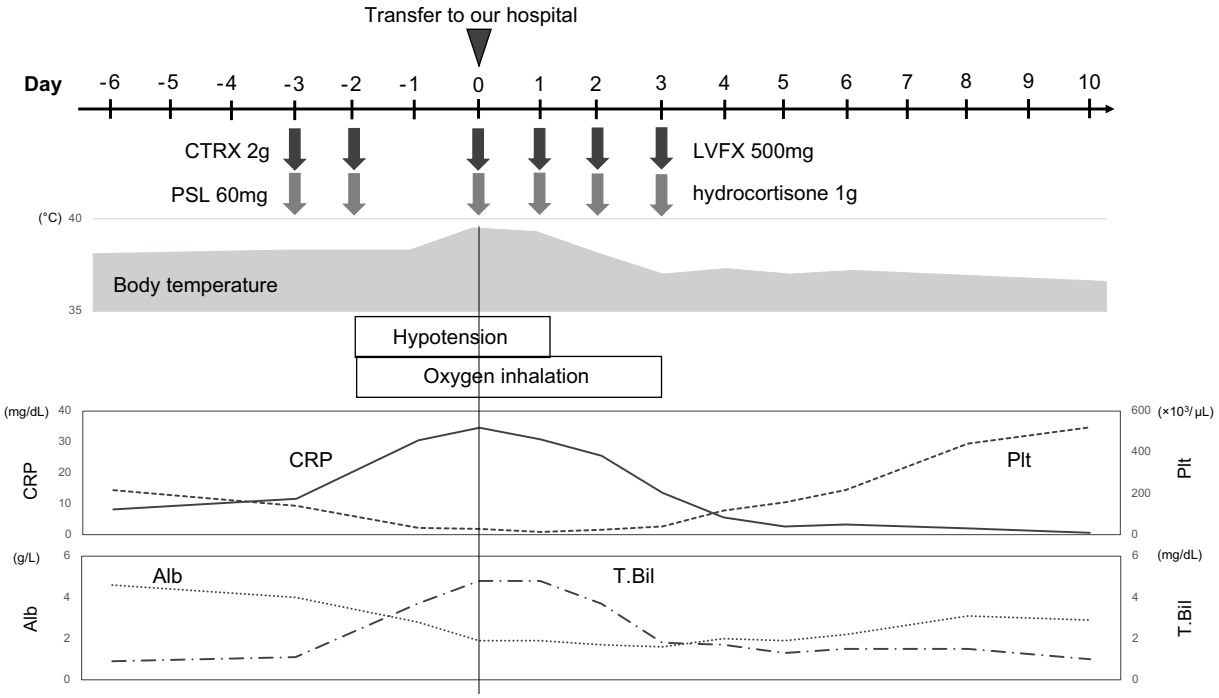

Figure 4. Clinical course of the patient. CTRX: ceftriaxion, LVFX: levofloxacin, PSL: prednisolone, mPSL: methylprednisolone, CRP: C-reactive protein, Plt: platelet, Alb: albumin, T.Bil: total bilirubin

nosed with MIS-A as well as with previous SARS-CoV-2 infections have so far only rarely been recognized.

Recently MIS-A has been recognized among the persons with hyperinflammatory illness and severe extrapulmonary multiorgan dysfunction, particularly cardiovascular, occurring within 2 to 5 weeks of antecedent COVID-19 or exposure to a person with diagnosed COVID-19 (6). In a recently published case series, case definition of MIS-A was described as fulfilling the following criteria: 1) severe illness requiring hospitalization in a person aged >21 years, 2) a positive test for recurrent or previous SARS-CoV-2 infection during admission or in the previous 12 weeks, 3) severe dysfunction of one or more extrapulmonary organ systems (e.g., hypotension or shock, cardiac dysfunction, arterial or venous thrombosis or acute liver injury), 4) laboratory evidence of severe inflammation (e.g., elevated CRP, ferritin, D-dimer, or interleukin-6) and 5) an absence of severe respiratory illness (to exclude patients in which inflammation and organ dysfunction might be attributable simply to tissue hypoxia) (5). According to a definition established by the Centers for Disease Control and Prevention (CDC), patients with MIS-A must meet at least one of the following primary clinical criteria: 1) severe cardiac illness, 2) rash and nonpurulent conjunctivitis (19). The patient in this case fulfilled the former criteria and met a part of the latter criteria. In this case, several echocardiographic parameters which show diastolic dysfunction while left ventricular EF was normal (20). Although a reduced EF was essential in the criteria which CDC proposed, Matsubara et al. reported echocardiographic findings of twenty-eight patients which showed a preserved left ventricle ejection fraction and diastolic dysfunction in a report of fifty-eight patients with the diagnosis of MIS-C (21). Therefore, we strongly suspected MIS-A in this case.

Our patient developed hypoxia and CT showed thoracic imaging abnormalities. While severe respiratory illnesses should be elucidated to diagnosed MIS, some thoracic imaging findings have been reported: including heart failure, acute respiratory distress syndrome pattern, and pulmonary embolism (22). We consider that results of laboratory investigations, echocardiography and clinical course after the initiation of diuretics were consistent with the diagnosis of heart failure.

In this case, the histopathological findings of the biopsy specimen of the cervical lymph nodes showed necrotizing lymphadenitis. Histiocytic necrotizing lymphadenitis, also known as KFD, was originally described in previously healthy young women, and most patients are younger than 40 years of age (7). It typically manifests as cervical lymphadenopathy with low-grade fever (7). While extranodal involvement of KFD other than cutaneous lesions is uncommon (6), some studies have shown that the immune responses by T-cells and histiocytes, and released cytokines such as interferon-gamma and IL-6 may contribute to the pathogenesis of KFD, these immune responses in KFD contribute to these rare manifestations (8, 9). Numerous infectious agents that trigger the immune response have been reported such as EBV, human herpes virus 6, human herpes 8, HIV, herpes simplex virus, hepatitis B, human T-lymphotrophic virus type 1, parvovirus B19, and parainfluenza virus (7). There has been three case reports of associations of KFD after COVID-19 (16-18). While Stimson et al.

and Racette et al. showed cases of mild KFD presenting cervical lymphadenopathy and fever two or three months after COVID-19 infections (16, 17), Masiak et al. reported a case of KFD with heart involvement five weeks after COVID-19 (18), which did not meet the criteria of MIS-A mentioned above. To the best of our knowledge, a case of the patient diagnosed with MIS-A and KFD has never been reported. The precise cause of MIS-C/A remains unclear, but it may be due to development of abnormal antibody responses that drive systematic hyperinflammation (23). While the precise etiology of KFD also remains unclear, post-viral immune dysregulation in MIS-A may play a role in the etiology of KFD.

The treatment of MIS-A included anticoagulants, corticosteroids, intravenous immunoglobulin, and immune modulators such as tocilizumab (6). In a systemic review, patients with MIS-A were often severely ill: almost half of the patients had hypotension requiring vasoactive medications, required respiratory support, and about seven percent of the patients died. On the other hand, KFD is a self-limited disease, and no effective treatment has yet been established (7). However, KFD associated with specific conditions, such as hemophagocytosis and aggressive or recurrent KFD, have been successfully treated with glucocorticoids (11, 24). In the present case, the severe symptoms resolved quickly after treatment with hydrocortisone was initiated, although a spontaneous resolution was a possibility. We initiated levofloxacin at the same time that we administered hydrocortisone, raising another possibility of atypical pneumonia which successfully responded to levofloxacin. However, we could find only one case report of community-acquired pneumonia associated with KFD-like mediastinal lymphadenopathy (25).

In conclusion, a previously healthy man developed MIS-A complicated with KFD one month after mild COVID-19. Physicians should therefore be aware that an immunological impairment due to COVID-19 may lead to both MIS-A and KFD.

We obtained the written informed consent to publish.

The authors state that they have no Conflict of Interest (COI).

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