

The therapeutic dilemma of immunosuppressive drugs for refractory cardiac sarcoidosis in COVID-19 infection

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Abstract

Patients with refractory cardiac sarcoidosis (CS) take a high dose of corticosteroid and immunosuppressive agents. During the pandemic outbreak of severe acute respiratory syndrome coronavirus 2, appropriate treatment of corticosteroids or immunosuppressive agents in CS patients with coronavirus disease 2019 (COVID-19) is unknown. Here, the woman with refractory CS receiving maintenance therapy with 15 mg of prednisolone daily and 10 mg of methotrexate weekly was emergently admitted to our hospital because of COVID-19. This case was successfully treated by the intravenous administration of dexamethasone 6 mg/day instead of prednisolone and interruption of methotrexate without resulting in recurrent life-threatening ventricular lethal arrhythmias or obvious sarcoidosis flare-ups. She started taking prednisolone and methotrexate at the maintenance dose immediately and at 2 weeks after discharge, respectively. Although the optimal regimen of immunosuppressive agents during COVID-19 is under intense debate, this report might provide an effective treatment strategy for CS patients with COVID-19.

Keywords Refractory cardiac sarcoidosis; Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Immunocompromised patient; Immunology

Received: 11 June 2021; Revised: 13 September 2021; Accepted: 5 October 2021

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Introduction

Coronavirus disease 2019 (COVID-19) has rapidly evolved into a worldwide pandemic. The characteristics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that differ from those of other common respiratory diseases include heterogeneity of clinical symptoms, ranging from asymptomatic presentations to acute respiratory distress syndrome and multi-organ involvement. A previous report revealed that infected patients with pre-existing cardiovascular disease ultimately suffer higher mortality rates than the general population.¹ However, reports of COVID-19 in patients with cardiac sarcoidosis (CS) have been limited.² Corticosteroid and immunosuppressive agents are often administered to CS patients to ameliorate myocardial inflammation. Continuation of these medications may exacerbate COVID-19, whereas its interruption may induce relapse of

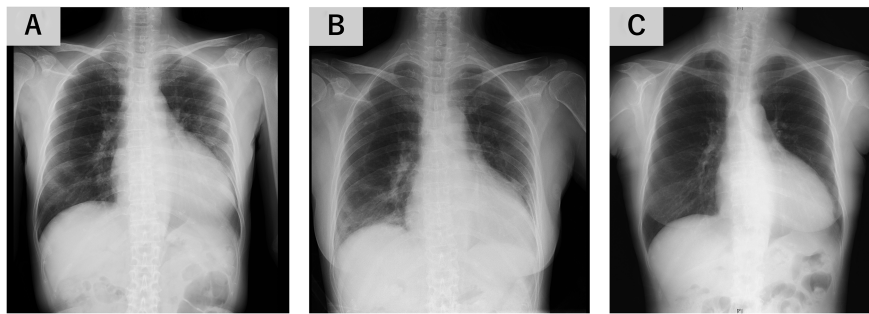
sarcoidosis. Thus, the use of corticosteroids or immunosuppressive agents in CS patients with COVID-19 is controversial.

Herein, we present the first case of refractory CS with COVID-19 pneumonia, successfully treated by increasing the dose of corticosteroid and discontinuing methotrexate without any severe complications and flare-ups of CS.

Case report

The patient was a 60-year-old woman who was diagnosed with sarcoid uveitis and CS presenting with heart failure and ventricular tachycardia. After the positive myocardial biopsy findings were acquired in 2015, she had been treated with prednisolone until March 2020; however, its tapering led to the relapse of CS, requiring the co-administration of methotrexate after increasing prednisolone dose. In

Figure 1 The chest X-ray findings. (A) Chest X-ray on admission revealed no congestion and pleural effusion. (B) Chest X-ray on the fourth hospital day revealed the congestion of bilateral lung fields. (C) After discharge, chest X-ray findings suggested compensated congestive heart failure.



December 2020, she suffered from cough a week before presentation, followed by headache, fatigue, and ageusia. Her polymerase chain reaction (PCR) test for SARS-CoV-2 performed in another hospital was positive. The patient was admitted to our hospital because she was considered at high risk for severe illness from COVID-19; her echocardiographic left ventricular internal dimension in diastole and ejection fraction were 80 mm and 23%, respectively, and she had taken 15 mg of prednisolone daily and 10 mg of methotrexate weekly, as well as cardioprotective drugs including β -blocker and angiotensin-converting enzyme inhibitor.

Her vital signs on admission were as follows: body temperature, 36.5°C; heart rate, 84 beats per min; blood pressure, 102/58 mmHg; respiratory rate, 16 breaths per min; and

oxygen saturation, 94% at room air. Her body mass index was 16.5 kg/m². Physical examination revealed no wheeze or crackle in the bilateral lung fields, but minimal respiratory distress with the use of accessory muscle was recognized. Cardiac auscultation revealed regular rhythm without murmur. No oedema or coldness was observed in the extremities. Chest X-ray (CXR) showed cardiac enlargement with cardiothoracic ratio of 59%; however, no congestion suggesting cardiac failure was observed [Figure 1(A)]. Computed tomography findings demonstrated peripheral and bilateral ground-glass opacification without consolidation, the typical appearance of COVID-19 pneumonia in the imaging classification (Figure 2).³ Laboratory data reflected acute inflammation due to COVID-19 pneumonia.

Figure 2 The computed tomography findings of the lung fields on admission. The peripheral and bilateral ground-glass opacification without consolidation was identified.

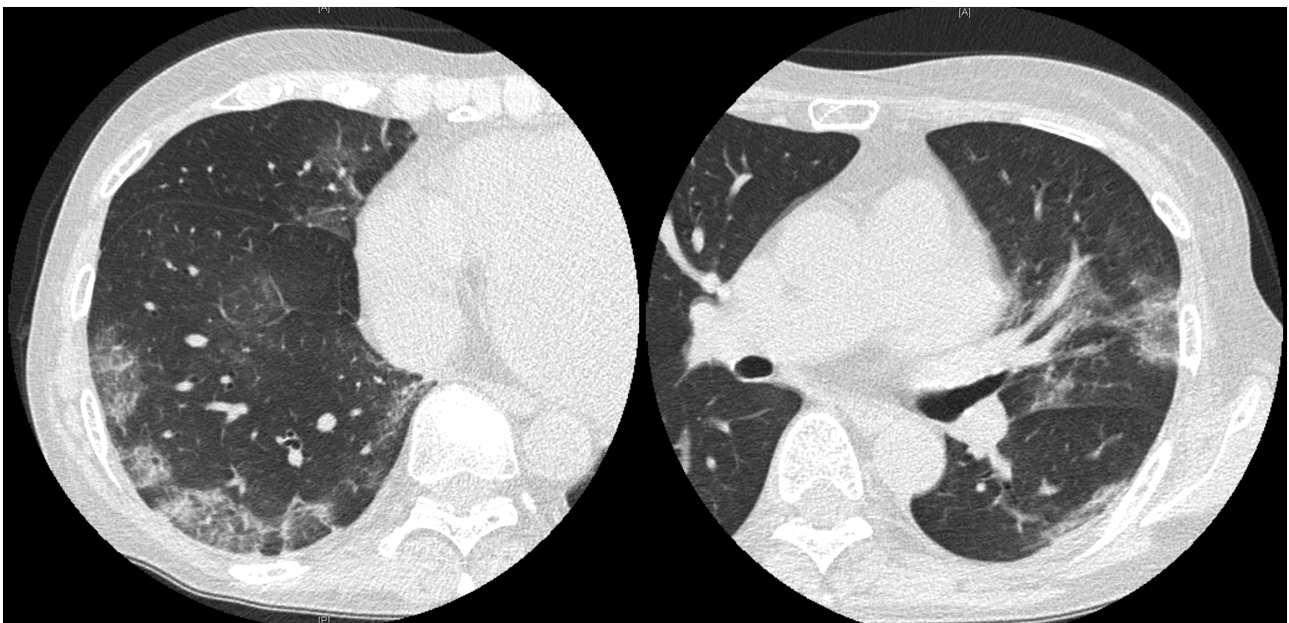
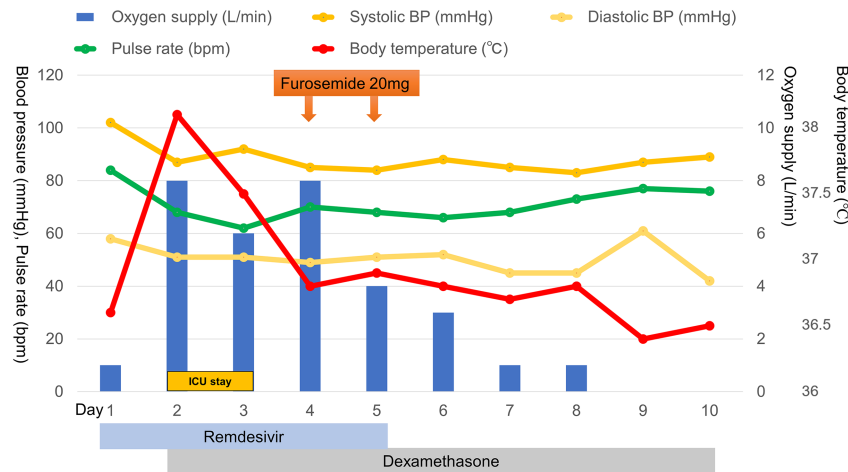


Figure 3 The clinical course during a hospital stay. On the following day of admission, the body temperature rose with increased oxygen demand. The use of dexamethasone with remdesivir alleviated fever; but COVID-19 resulted in heart failure exacerbation. The administration of furosemide was effective, and the patient finally maintained oxygenation without oxygen supply on ninth hospital day. The intense fluctuation in blood pressure (BP) and pulse rate was not observed through hospitalization. ICU, intensive care unit.



She was initially admitted to the general ward with 1 L/min of oxygen supply via nasal cannula. As the treatment for COVID-19, remdesivir (200 mg/day on the first day and 100 mg/day for 4 more days) was administered immediately after admission. Due to oxygen desaturation, the intravenous administration of dexamethasone 6 mg/day was also scheduled from the next day of admission, instead of 15 mg of prednisolone daily. With the positive PCR test result, we decided to discontinue the methotrexate. The patient’s condition dramatically changed in the early next morning. The body temperature exceeded 38°C, and the oxygen

requirement abruptly increased from 1 L/min via nasal cannula to 8 L/min via reservoir mask with exacerbation of pneumonia. She was transferred to the intensive care unit and monitored overnight. Fortunately, her oxygenation level did not deteriorate further, and oxygen saturation could be maintained with 6 L/min of oxygen supply via a mask afterwards. She was transferred to the general ward on the third hospital day. However, the amount of urine decreased, and CXR on the fourth hospital day revealed congestion of the bilateral lung fields [Figure 1(B)]. We decided to administer intravenous loop diuretics for acute exacerbation of heart

Figure 4 The transition of laboratory data, urine output, and body weight. After admission, the amount of urine was decreased, and body weight was increased by approximately 1 kg. The urine output was recovered without renal dysfunction after the administration of furosemide. The creatinine level did not increase during the hospitalization. C-reactive protein gradually decreased in response to the medication therapy. ICU, intensive care unit.

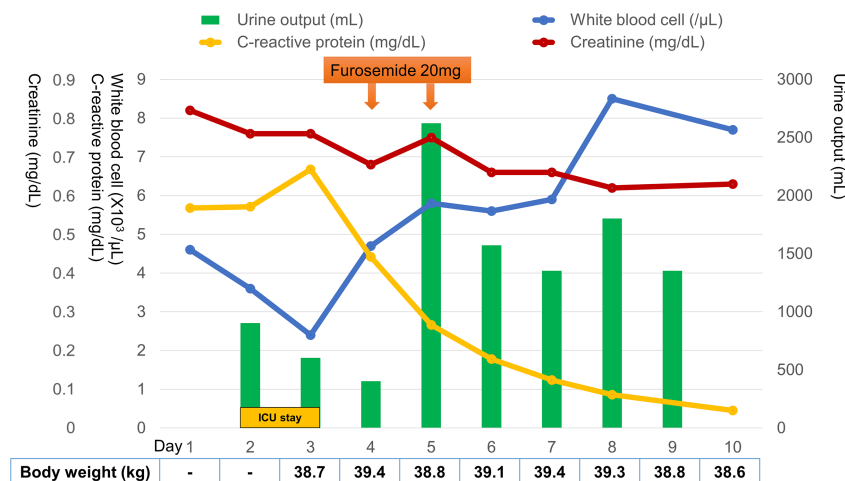
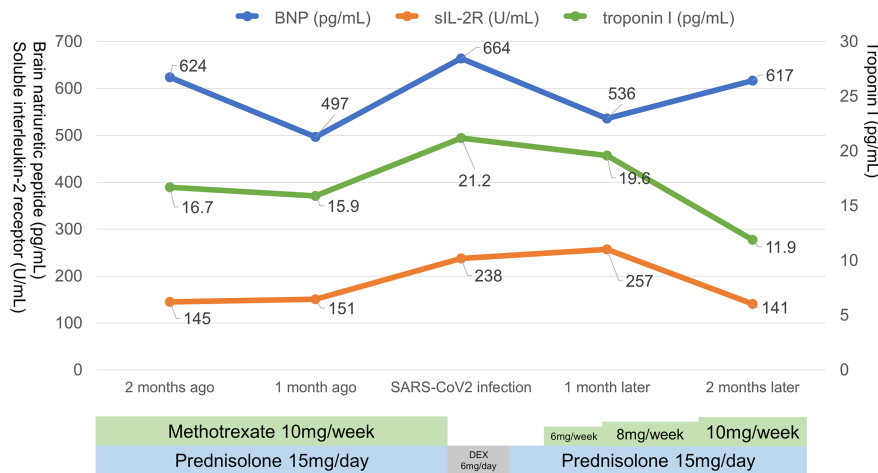


Figure 5 Temporal changes in the cardiac markers and soluble interleukin-2 receptor (sIL-2R) and the treatment of immunosuppressive drugs. During COVID-19 pneumonia, methotrexate was interrupted and dexamethasone 6 mg/day was administered instead of prednisolone. The maintenance dose of prednisolone was restarted from discharge, and subsequently methotrexate was also started again at the dose of 6 mg/week from 2 weeks after discharge. After the echocardiographic findings revealed no deterioration of cardiac function, methotrexate was increased to 8 mg/day. Two months later after discharge, the patient was treated by the original immunosuppressive dose. The acute exacerbation of these markers was not consistently observed. BNP, brain natriuretic peptide; DEX, dexamethasone.



failure. This administration of diuretics was effective, and CXR findings were improved within a few days. The sense of taste was recovered. The oxygen supply was terminated on the ninth hospital day. She was discharged on the 11th hospital day according to the domestic discharge criteria (Figures 3 and 4).

At post-discharge, corticosteroids were reversed to the maintenance dose of prednisolone (15 mg/day) from dexamethasone for the treatment of refractory CS. At the first outpatient visit 2 weeks after discharge [Figure 1(C)], there was no deterioration of her symptom (New York Heart Association II) and brain natriuretic peptide and troponin I levels compared with those before admission. We decided to restart methotrexate from 6 mg/week. Four weeks after discharge, the echocardiography also revealed no further deterioration of left ventricular ejection fraction and mitral valve insufficiency, and no decline in left ventricular outflow tract velocity time integral (Videos S1 and S2). Although heart failure was mildly exacerbated during hospitalization for COVID-19, her symptom was improved using a small amount of diuretics in combination with anti-COVID-19 therapy, without obvious sarcoidosis flare-ups including recurrent ventricular tachycardia and life-threatening lethal arrhythmia (Figure 5).

Discussion

We encountered a case of COVID-19 with refractory CS. During the pandemic outbreak of SARS-CoV-2, patients with co-

morbidities have been reported to be highly at risk for severe illness due to COVID-19. For example, the case fatality rate is 2.3% among the general population from a China report; however, the cardiovascular comorbidities increase the fatality rate to 10.5%.⁴ Especially, CS is thought to be associated with higher risk of poor outcome from COVID-19 for the following several reasons.⁵

First, sarcoidosis is characterized by the presence of granulomatous inflammation in various organs, particularly in the lung as the most frequently affected organ. Patients with lung and heart involvement may develop respiratory and heart failure during the viral infection. Second, CS patients receive corticosteroid therapies for a long duration. Hypertension and diabetes mellitus are the principal side effects of long-term steroid use, and these comorbidities may increase the mortality during the COVID-19.⁶ Finally, immunosuppressive medications such as methotrexate, azathioprine, and tumour necrosis factor alpha inhibitors are used to treat sarcoidosis. These medications may compromise immune system, increasing the severity of COVID-19, although there is no definite evidence on this possibility. Taken together, patients with sarcoidosis may have poorer prognosis from COVID-19 than those without.

The most important issue in the current case was whether immunosuppressive medications during the COVID-19 treatment should be continued or withheld. According to the existing evidence, the use of corticosteroids or immunosuppressive drugs during COVID-19 for the patients with CS is controversial. These drugs are generally considered to increase the risk for serious infection, whereas the abrupt interruption of these drugs could evoke sarcoidosis relapse.

The American College of Rheumatology guidance for the management of rheumatic disease during the COVID-19 pandemic indicated that methotrexate should be stopped or withheld regardless of COVID-19 severity because withholding methotrexate is unlikely to result in significant rheumatic disease flares, whereas corticosteroids should not be abruptly stopped regardless of infection status.⁷ However, a relapse of COVID-19 induced by corticosteroid in a patient with sarcoidosis was reported.⁸ Although whether the use of corticosteroids increases the relapse risk of COVID-19 remains unclear, these reports encourage the medication adjustment during COVID-19. On the other hand, there is a report that did not recommend the preventive interruption of disease-modifying antisarcoïd drugs (DMASDs) such as methotrexate and azathioprine, especially in patients with life-threatening manifestation including pulmonary sarcoidosis and CS.⁵ The authors emphasize that DMASDs may present lower risk of infections than corticosteroids and suggest continuing DMASDs during the COVID-19 treatment may prevent the risk of sarcoidosis relapse and unfavourable outcomes. Moreover, recent studies have revealed the resemblance of pathological findings of the lung lesion between COVID-19 and sarcoidosis and indicated that common mechanistic pathways might exist around the regulation of autophagy.^{9–12} This hypothesis may support the continuous administration of corticosteroids and immunosuppressive agents that could be effective for both sarcoidosis and COVID-19. Thus, the treatment strategy for CS during COVID-19 remains unsettled, and these conflicting discussions confuse clinicians in decision-making for the treatment.

In the current case, methotrexate was withheld immediately after admission, but corticosteroid was continued. Instead of continuing oral intake of prednisolone, 6 mg of

dexamethasone was administered, consistent with the regimen in the RECOVERY trial.¹³ Our case suggests that dexamethasone might be effective for COVID-19 pneumonia even in patients with corticosteroid users. We also showed that temporary withholding of immunosuppressive agents might not induce sarcoidosis flare-ups. Further studies are warranted to elucidate the appropriate treatment during the COVID-19 pandemic for infected patients with an autoinflammatory disease such as sarcoidosis.

Conflict of interest

Each author certifies that he or she has no actual or potential, commercial, financial, nor personal associations that might post a conflict of interest in connection with the submitted case report.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Parasternal long axis view (**Video S1**) and short axis view (**Video S2**) in transthoracic echocardiography after discharge. The left ventricular enlargement and severe systolic dysfunction were demonstrated, although there was no further deterioration of biventricular function compared with previous examinations.

Video S1. Supporting Information.

Video S2. Supporting Information.

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