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Severe acute respiratory failure due to Sai-rei-to-induced lung injury successfully treated by multi-modal therapy including immunosuppressive therapy, plasma exchange, and intravenous immunoglobulin: A case report

Midori Yamada [a,b,c,*], Kei Nakashima [b], Hiroyuki Ito [b], Masahiro Aoshima [b]

[a] Department of General Medicine, Awa Regional Medical Center, 1155, Yamamoto, Tateyama-shi, Chiba, 294-0014, Japan
[b] Department of Pulmonology, Kameda Medical Center, 929 Higashi-cho, Kamogawa-shi, Chiba, 296-8602, Japan
[c] Department of Family Medicine, Kyoto Min-iren Asukai Hospital, 89 Tanaka Asukai-cho, Sakyo-ku, Kyoto-shi, Kyoto, 606-8226, Japan

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ABSTRACT

Corticosteroid therapy may not be enough to control pneumonitis in some cases of severe drug-induced lung injury (DLI); however, an advanced treatment strategy for such cases is lacking. Here, we report the case of an 88-year-old man who presented with severe DLI, caused by Sai-rei-to. The patient visited our hospital complaining of progressive dyspnea. High-resolution computed tomography of the chest demonstrated bilateral patchy ground-glass opacities and infiltrative shadows. Nasal high-flow oxygen therapy was initiated because of severe hypoxemia. Bronchoalveolar lavage on admission revealed diffuse alveolar hemorrhage. Further, as the patient had started taking Sai-rei-to a month earlier, DLI caused by Sai-rei-to was the most likely diagnosis. Therefore, Sai-rei-to was stopped and steroid pulse therapy was initiated. However, he still required high-flow oxygen therapy. We considered an alternative diagnosis of Goodpasture syndrome or anti-neutrophil cytoplasmic antibody (ANCA) related vasculitis. We initiated the administration of cyclosporin A and therapeutic plasma exchange (TPE), but his respiratory condition did not improve satisfactorily. Therefore, we also initiated intravenous immunoglobulin (IVIG) therapy for the treatment of potential vasculitis. Subsequently, his respiratory status began to improve. Further, tests for anti-glomerular basement membrane antibody, myeloperoxidase-ANCA, and proteinase 3-ANCA revealed negative results. Drug-induced lymphocyte stimulation test performed six months after withdrawing methylprednisolone was positive for Sai-rei-to. Thus, the final diagnosis was DLI due to Sai-rei-to. Our findings demonstrate that in cases of severe acute respiratory failure due to DLI, the multi-modal therapy with plasma exchange and IVIG in addition to conventional treatment with prednisolone and immunosuppressant may be beneficial.

1. Introduction

Drug-induced lung injury (DLI) is defined as a lung injury caused by drugs, including prescription drugs, over-the-counter drugs, herbal medicines, supplements, and illegal narcotics [1]. Sai-rei-to is a herbal medicine that has previously been implicated in DLI [2]. Discontinuation of the causal drug is the first step in the management of DLIs. However, in many cases, DLI progresses despite this action, and immunosuppressive therapy with glucocorticoids is required [1]. In fact, some case reports and one review article show that stopping Sai-rei-to and performing corticosteroid therapy were often effective in Sai-rei-to-induced lung injury cases [3–5]. Nevertheless, no advanced treatment strategy has been established for severe DLI in cases where corticosteroid therapy is not enough to control pneumonitis [1]. Unresponsive cases have a poor prognosis, and even if the condition resolves, fibrosis remains as a sequela [1].

For idiopathic interstitial pneumonia, immunosuppressive therapies, such as cyclophosphamide (CPA) and cyclosporin (CyA), can be administered as additional treatment options for patients receiving glucocorticoid therapy [3]. Although the use of immunosuppressive agents for the treatment of DLI has not been reported to date [6], the effectiveness of polymyxin-B direct hemoperfusion treatment in DLI patients with severe acute respiratory failure has been reported [6]. In addition, therapeutic plasma exchange (TPE) has been reported to be

* Corresponding author. Department of General Medicine, Awa Regional Medical Center, 1155, Yamamoto, Tateyama-shi, Chiba, 294-0014, Japan.
E-mail addresses: greeeeen.1014@gmail.com (M. Yamada), kei.7.nakashima@gmail.com (K. Nakashima), ito.hiroyuki.5@kameda.jp (H. Ito), aoshima.masahiro@kameda.jp (M. Aoshima).

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effective for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis or Goodpasture syndrome, because removal of certain pathologic autoantibodies from the plasma will reduce further damage and may permit reversal of the pathological process [7,8]. Intravenous immunoglobulin (IVIG) containing various immunoregulatory substances has also been administered for polymyositis (PM)/dermatomyositis (DM) [9] and ANCA-associated vasculitis with persistent disease activity after standard therapy [10,11]. There have been no reports of the effect of TPE or IVIG in patients with DLI.

Herein, we present the case of a patient with DLI caused by Sai-rei-to, with severe acute respiratory failure, which was successfully treated by a multi-modal therapy with plasma exchange and IVIG in addition to conventional treatment with prednisolone and immunosuppressant.

2. Case report

An 88-year-old man with a history of hypertension and chronic kidney disease visited our hospital complaining of progressive dry cough, dyspnea, fever, and chills. He had been prescribed Sai-rei-to 25 days before admission, and these symptoms developed two weeks after initiating Sai-rei-to therapy. He was an ex-smoker (Brinkman index: 800), had taken no medication except for Sai-rei-to, and had no history of any pulmonary disease and allergy.

The body temperature was 38.0 °C, and percutaneous oxygen saturation was 99% on 12 L/minute reservoir mask oxygen. The respiratory rate was 20 breaths/minute, blood pressure was 189/91 mmHg, and heart rate was 72 bpm. On chest auscultation, bilateral late inspiratory crackles were detected. He also had bilateral pretibial edema. Laboratory test results showed that the white blood cell count was 8000/mm^3, with 78.8% neutrophils and 7.8% eosinophils, and platelet count was 155,000/mm^3. The brain natriuretic peptide level was elevated to 406 pg/mL, and serum C-reactive protein level was 10.51 mg/dL.

Sialylated carbohydrate antigen Krebs von den Lungen-6 level was 374 U/mL, and surfactant protein-D level was 339 ng/mL. Blood coagulation test findings were within the normal range. Bacteriological tests did not detect any bacterial or viral pathogens. Serum complement fixation test value for *Mycoplasma pneumoniae* was elevated fourfold. The indices of serum IgM, IgA, and IgG for *Chlamydia pneumoniae* were 0.565, 1.706, and 1.590, respectively. These single sample serum data did not reach the reference value required for a positive result. Arterial blood gas analysis revealed severe hypoxemia. Echocardiographic examination showed that the ejection fraction was 60% and wall motion was almost normal.

Chest radiography showed ground-glass opacities in both lung fields (Fig. 1). High-resolution computed tomography (HRCT) demonstrated bilateral patchy ground-glass opacities, infiltrative shadows, and pleural fluid (Fig. 1). Nasal high-flow (NHF) oxygen therapy was initiated because of severe hypoxemia. Bronchofiberscopy and bronchoalveolar lavage (BAL) revealed diffuse alveolar hemorrhage, with an elevated neutrophil proportion (total cell count 325,000/mL, with 26% lymphocytes, 62% neutrophils, and 12% macrophages; the CD4/CD8 ratio was 0.49).

The patient's clinical course is shown in Fig. 2. Drug-induced interstitial lung disease (ILD) caused by Sai-rei-to was the most likely diagnosis, because he had no history of interstitial pneumonia or collagen disease, and he had started taking Sai-rei-to a month earlier. However, we could not exclude heart failure and community-acquired pneumonia. Therefore, all his ongoing oral therapies, including Sai-rei-to, were stopped and steroid pulse therapy (1000 mg/day of methylprednisolone [mPSL] for three days), furosemide, and combination antibiotic therapy, with ceftriaxone and azithromycin, were initiated from the day of admission.

On the 4th hospital day, he required oxygen therapy (FiO2 0.65 on NHF) despite the administration of steroid pulse, diuretic, and antibiotic therapies. As his BAL findings suggested alveolar hemorrhage, we considered an alternative diagnosis of Goodpasture syndrome or ANCA related vasculitis. Therefore, we initiated TPE treatment (fresh frozen plasma; 3000 mL/day) and CyA (CyA; 180 mg/day) on that day. TPE was performed thrice in 5 days, and FiO_2 decreased from 0.65 to 0.30 during this period.

However, on the 10th hospital day, his respiratory condition had worsened; FiO_2 had again increased from 0.30 to 0.35, and the bilateral patchy ground-glass opacities and infiltrative shadows on HRCT had worsened (Fig. 3). On the same day, we again conducted BAL. The diffuse alveolar hemorrhage persisted, and the differential white blood cell count was still neutrophil-predominant (total cell count 50,000/mL, with 29% lymphocytes, 42% neutrophils, and 25% macrophages).

IVIG therapy (25 g/day) was introduced from the 11th hospital day for five days because we could not exclude that alveolar hemorrhage was due to potential vasculitis. After initiating IVIG therapy, his respiratory function and the bilateral patchy ground-glass opacities and infiltrative shadows on HRCT began to improve (Fig. 3); he was therefore switched from NHF to nasal cannula two days after starting IVIG therapy. After the IVIG therapy, the dosage of mPSL and CyA could be decreased gradually from the 19th hospital day and the 23rd hospital day, respectively. Further, tests for anti-glomerular basement membrane antibody, myeloperoxidase-ANCA, and proteinase 3-ANCA yielded negative results. No other clinical findings supporting the diagnosis of vasculitis were detected.

On the 45th hospital day, he was discharged after the introduction of home oxygen therapy (HOT). The changes observed in the interstitial shadows on HRCT are shown in Fig. 3. CyA was discontinued from about one month after discharge because his renal function deteriorated. One and a half year after discharge, HOT was withdrawn. About two years after discharge, mPSL was discontinued. Drug-induced lymphocyte stimulation test conducted about half a year after the withdrawal of mPSL demonstrated a positive result for Sai-rei-to (stimulation index = 384%). Thus, the final diagnosis was DLI due to Sai-rei-to. The

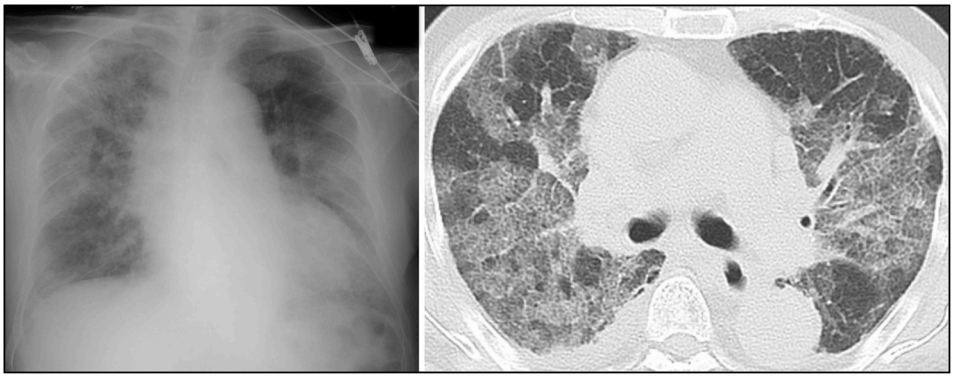

Fig. 1. Chest radiograph and computed tomography scan showing bilateral patchy ground-glass opacities, infiltrative shadows, and pleural fluid.

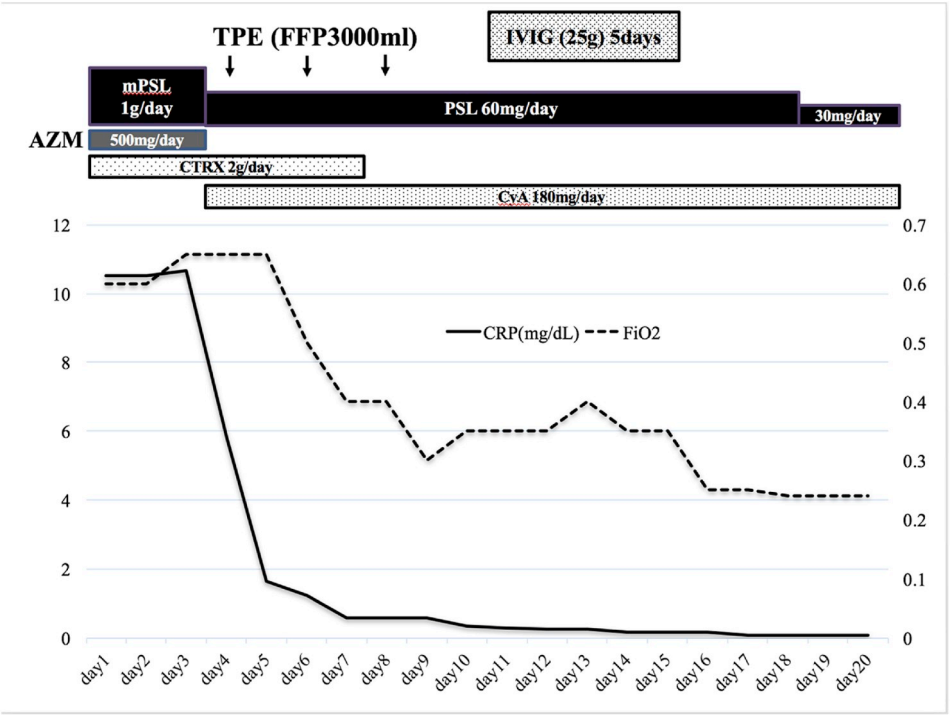

Fig. 2. Clinical course and treatments (AZM: azithromycin, CTRX: ceftriaxone, CyA: cyclosporine, IVIG: intravenous immunoglobulin, mPSL: methylprednisolone, PSL: prednisolone, TPE: therapeutic plasma exchange).

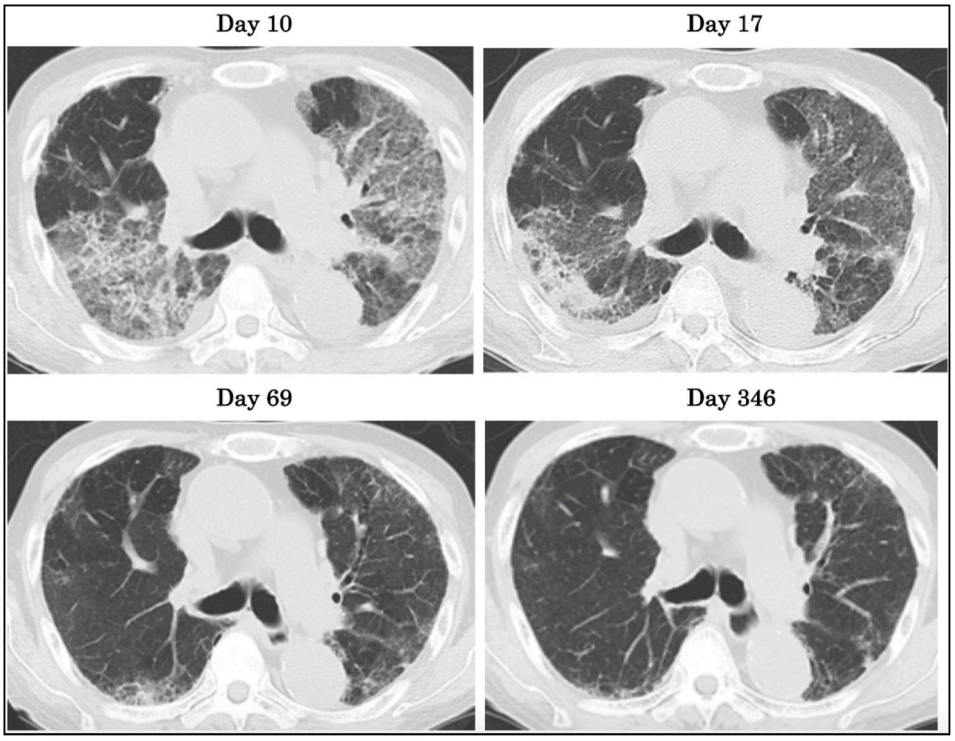

Fig. 3. Computed tomography scans obtained during the treatment. On Day 10, the scan shows deterioration after therapeutic plasma exchange. On Day 17, after 5 days of intravenous immunoglobulin therapy, there is improvement. On Day 69, after the patient had been discharged, the interstitial shadows have almost disappeared. From Day 346, the dose of prednisolone could be tapered.

patient has remained well throughout the follow-up period.

3. Discussion

This case report illustrates that TPE and IVIG may constitute an additional treatment option for DLI with severe acute respiratory failure

when immunosuppressive therapy including glucocorticoid administration is not adequately successful. This case provides new insights into the management of DLI.

No clinical disease type is specific to DLI [1]. DLIs are diagnosed based on clinical examination, diagnostic imaging, and histological findings [1]. Certain clinical presentations of DLI have a favorable clinical course and resolve after drug discontinuation or treatment with corticosteroids [1]. However, some DLIs are fatal and do not respond to this treatment [1]. DLI induced by Chinese herbal drugs, such as Sai-rei-to, have been documented and the number of such cases is increasing [1,12]; some of these show a poor prognosis [13]. In previous studies, including a review of 12 cases, CT findings of Sai-rei-to-induced lung injury revealed mainly a groundglass opacity [3–5]. The average period from the start of Sai-rei-to intake to the onset of DLI was 35 days (range 8–110 days). In this particular case series, discontinuation of Sai-rei-to intake and corticosteroid therapy use were ineffective in one out of 12 cases. The patient developed acute respiratory distress syndrome and eventually died.

There are two basic plausible pathogenetic mechanisms underlying DLI: cytotoxic drugs may have direct toxic effects on lung cells, and the drug may activate immune cells by acting as a hapten or by mimicking an antigen [1]. In general, when specific ILD cases in intensive care units do not show a response to first-line therapy with corticosteroids, immunosuppressive agents, such as CPA and CyA, are considered the second-line therapy [3]. However, there is no definitive therapy for severe DLI in cases where corticosteroid as well as immunosuppressive therapies are ineffective. Our patient with severe DLI was successfully treated using multi-modal therapy that included immunosuppressive therapy, TPE, and IVIG treatment.

The efficacy of TPE for ANCA-associated vasculitis and Goodpasture syndrome has been reported; these studies show that removal of certain pathological autoantibodies and some inflammatory mediators from the plasma will reduce damage progression and even allow the pathological process to be reversed [7,8]. We therefore hypothesize that removal of some pathological antibodies and inflammatory mediators might have contributed to improvement of the severe DLI in this case.

In pulmonary medicine, IVIG therapy is used for some cases of ILD with PM/DM [9]. In addition, IVIG has been used for patients who have vasculitis with persistent disease activity after standard therapy [10,11]. There is no reported evidence of use of IVIG for the treatment of DLI, and it is unclear why IVIG relieves the progression of ILD. Immunoglobulins have several potential anti-inflammatory and immunomodulatory effects, which may have contributed to the resolution of the respiratory failure in this case; these effects may include Fc receptor blockade, inhibition of complement deposition, enhancement of regulatory T cells, inhibition or neutralization of cytokines and growth factors, accelerated clearance of autoantibodies, modulation of adhesion molecules and cell receptors, and activation of regulatory macrophages through the FcγRIIb receptor [14–16]. IVIG was previously administered to a series of five patients with ILD-PM/DM with resistance to high-dose corticosteroid therapy [9]. Of the five patients, one patient with ILD-PM and one patient with ILD-amyopathic survived, while no major complication of IVIG was detected [9]. This result suggests that IVIG treatment is safe and could be an effective salvage therapy for refractory ILD-PM/DM in certain cases. In one randomized placebo-controlled trial, treatment response was found in 14/17 and 6/17 patients of the IVIG and placebo groups, respectively [10]. This study suggests that IVIG may be an alternative treatment for ANCA associated vasculitis when disease symptoms persist after standard therapy [10]. Since the immunosuppressive therapy and TPE had limited effects and we could not exclude vasculitis as a cause of alveolar hemorrhage, we administered IVIG for the potential vasculitis, which rapidly improved respiratory function and the bilateral patchy ground-glass opacities and infiltrative shadows on HRCT; this resulted in successful management of the patient's condition without complications.

Several questions remained unanswered in our case. First, the contributions of corticosteroids and CyA to improvement could not be ignored: since the treatment with TPE and IVIG overlapped with the administration of corticosteroid and CyA, it is possible that the improvement observed in this case was due to delayed effects of the immunosuppressive treatments that had been administered earlier. Even if that were the case, however, we think that IVIG, which yielded immediate beneficial effects, may have helped to prevent the deterioration of the patient's respiratory status until the effects of corticosteroids, CyA, or TPE manifested. Second, the timing of administering TPE and IVIG remains controversial. Adding TPE and IVIG therapy may be useful in cases that appear not to satisfactorily respond to immunosuppressive treatments, thus facilitating patient management until the effects of immunosuppressive therapy start manifesting. Third, the long-term prognosis of such patients is unknown, and the long-term effect of TPE and IVIG treatment of DLI remains to be elucidated. The efficacy of IVIG is considered to diminish quickly [17], and repeated administration may be required to sustain any improvement.

In conclusion, this case report suggests that combining both TPE and IVIG with immunosuppressive agents and corticosteroids may contribute to the improvement of DLI. Therefore, we suggest that the multi-modal therapy with TPE and IVIG in addition to conventional treatment with prednisolone and immunosuppressant may be a useful approach for severe acute respiratory failure due to DLI.

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Declaration of Competing Interest

None.

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