CASE REPORT

Severe drug-induced interstitial lung disease successfully treated with corticosteroid plus recombinant human soluble thrombomodulin

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SUMMARY

There is no established therapeutic option for corticosteroid (CS) refractory drug-induced interstitial lung disease (DILD). We report a case of CS refractory severe DILD successfully treated with recombinant human soluble thrombomodulin (rhTM). A 64-year-old Japanese man was admitted with symptoms of fever, dry cough and dyspnoea. A chest radiograph showed bilateral infiltrations. DILD from Nijutsutou, a Chinese medicine, was suspected based on a history of similar interstitial lung disease after its administration 4 years prior and a positive drug-induced lymphocyte stimulation test. Nijutsutou was promptly discontinued and high doses of CS administered, but the patient's bilateral infiltrations remained unimproved. Since coagulation tests also indicated a rapid aggravation of coagulopathy, rhTM was added to the CS therapy. The patient's lung infiltration ameliorated and plasma levels of D-dimer and high morbidity group box 1 (HMGB1) decreased. rhTM may be an alternative agent for CS refractory DILD. Further study is necessary to confirm this.

BACKGROUND

Drug-induced interstitial lung disease (DILD) is a notable adverse event of drug therapy and has many clinical patterns, ranging from benign infiltrates to life-threatening acute respiratory distress syndrome (ARDS). Discontinuation of the causative drug is the first step in the treatment of DILD.¹ Some studies have reported that corticosteroid (CS) treatment is effective for DILD;² however, some cases of DILD worsen, even after CS treatment. There is no further advanced treatment option established for CS-refractory DILD.

A novel biological agent, recombinant human soluble thrombomodulin (rhTM) (Recomodulin, Asahi Kasei Pharma Corporation, Tokyo, Japan), has been approved for clinical use in Japan for the treatment of disseminated intravascular coagulation (DIC). This molecule has been shown to have anti-inflammatory effects as well as anticoagulation effects,³ and to be effective for acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF).⁴ Although no report has shown the effectiveness of rhTM for DILD, we now present a case of severe DILD successfully treated with rhTM in addition to CS therapy.

CASE PRESENTATION

A 64-year-old Japanese man presented with a 3-day history of fever, dry cough and progressive dyspnoea.

On admission, the patient demonstrated tachycardia (115 bpm), tachypnoea (32 respirations per minute) and normotensive blood pressure (128/72 mm Hg). Initial oxygen saturation was 78% under room air conditions. Blood tests revealed elevated transaminase (aspartate transaminase, 177 IU/L; alanine transaminase, 244 IU/L), KL-6 (502.4 U/mL) and surfactant protein D (SP-D) (176.0 U/mL) levels. A chest radiograph showed bilateral infiltrations (figure 1A). A chest high-resolution CT (HRCT) scan revealed bilateral ground glass opacities (GGOs) with alveolar structural changes such as traction bronchiectasis, indicating diffuse alveolar damage (DAD)-type DILD (figure 2A–C). Echocardiography showed normal wall motion with a preserved ejection fraction, indicating no sign of cardiogenic pulmonary oedema. DILD and liver damage were suspected because the patient had been administered the Chinese medicine 'Nijutsutou' for the treatment of right shoulder pain for 2 weeks and had a similar history of interstitial lung disease after the administration of Nijutsutou 4 years prior. A positive drug-induced lymphocyte stimulation test for Nijutsutou supported the diagnosis.

TREATMENT

The patient was initially treated twice with repeated pulse therapies of CS (methylprednisolone 1000 mg/day for 3 days) in addition to cessation of Nijutsutou administration (figure 3). Despite these treatments, the patient's oxygenation and lung infiltrations did not improve 2 weeks after beginning steroid pulse therapy (figure 1B), and D-dimer levels progressively elevated to 8.8 mg/mL, compared to a normal level of <1.0 mg/mL. Although pulmonary thromboembolic disease was suspected, CT pulmonary angiography showed no evidence of pulmonary emboli. Because it was suspected that combined coagulopathy was aggravating the DIC, we then administered a third course of steroid pulse therapy followed by rhTM (380 IU/kg/day for 6 days). Eventually, the D-dimer levels gradually decreased and the patient's oxygenation and lung infiltrations improved (figure 1C). High morbidity group box 1 (HMGB1) levels also decreased after administration of rhTM (figure 3).

DISCUSSION

In the present case, it was suspected that Nijutsutou had induced interstitial lung disease. The cessation of Nijutsutou and high-dose CS therapy did not improve oxygenation or lung

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Figure 1 Chest radiography findings. The changes on chest radiographs are shown. Bilateral infiltrations were detected on admission (A), which worsened 2 weeks after high-dose corticosteroid therapy was initiated (B). The administration of corticosteroid plus recombinant human thrombomodulin ameliorated lung infiltrations (C).

Figure 2 High-resolution CT findings. High-resolution CT imaging on admission showing the upper lung fields (aortic arch level) (A), middle lung fields (tracheal bifurcation level) (B) and lower lung fields (directly above the diaphragm level) (C). Bilateral ground glass opacities, infiltrative shadows (arrows) and the structural changes of traction bronchiectasis (arrowheads) were detected.

infiltrates. Since progressive coagulopathy was suspected to coexist, rhTM was administered in addition to CS therapy, resulting in improvements in the patient's interstitial lung disease as well as coagulopathy.

High-dose CS therapy was administered according to recommendations and guidelines for the treatment of DILD,⁵ but the DILD in the present case did not improve. Although lung histology was not examined in the present case, HRCT findings indicated DAD-type DILD. From a prognostic standpoint, it seems very useful to classify DILD into either DAD type, which generally carries a poor prognosis, or non-DAD, which carries a relatively favourable prognosis.⁵ The imaging findings that characterise DAD-type DILD include those suggestive of structural changes, such as traction bronchiectasis, in addition to extensive consolidation or GGOs.⁶ DAD-type DILD is reported to be refractory to CS therapy similar to other clinical disorders showing DAD, such as ARDS and AE-IPF.⁷

The pathogenesis of DAD is also characterised by disordered coagulation and fibrinolysis.⁸ The modulation of coagulation and fibrinolysis may have beneficial complex effects on haemostatic as well as inflammatory pathways in DAD.⁹ Thrombomodulin is a transmembrane protein expressed on the endothelial cell surface that plays an important role in the regulation of intravascular coagulation by binding thrombin.¹⁰ In the present case, the plasma D-dimer level, which was elevated even after 2 weeks of CS therapy, decreased after administration of rhTM. The present case indicates that rhTM might also have an effect modulating coagulopathy associated with DAD, resulting in an improvement of DILD.

In addition to anticoagulant activity, rhTM has been reported to have an anti-inflammatory role via its ability to neutralise HMGB1, a representative damage-associated molecular pattern molecule for innate immune responses. In the present case, we followed the time course of HMGB1 serum levels, which were increased during the CS pulse therapy and then decreased by the administration of rhTM. It is not reported that CS therapy induces HMGB1. Therefore, the increase of HMGB1 during the CS pulse therapy might reflect the progression of DILD. rhTM might improve DILD by ameliorating lung inflammation via neutralising HMGB1. Thus, rhTM is a possible therapeutic agent for DAD-type DILD with anticoagulant as well as anti-inflammatory effects. Intriguingly, a recent paper reported that rhTM is effective for AE-IPF, where DAD is the central pathological change.⁴ Moreover, rhTM showed potential therapeutic effects on severe ARDS in a murine model.¹¹

rhTM produces anticoagulant and anti-inflammatory properties mainly via activated protein C (APC)-dependent mechanisms, although there are APC-independent mechanisms.¹² Protein C is a vitamin K-dependent anticoagulant serine protease zymogen in plasma which on activation by the thrombin-thrombomodulin complex downregulates the coagulation cascade by degrading cofactors Va and VIIIa by limited

Figure 3 Clinical course. The patient was initially treated with weekly steroid pulse therapy for 2 weeks; however, his oxygenation did not improve and he had elevated KL-6, SP-D, D-dimer and HMGB1 levels. The administration of CS plus rhTM ameliorated his oxygenation deficit and decreased his SP-D, D-dimer and HMGB1 levels. KL-6 levels decreased late. SP-D, surfactant protein D; HMGB1, high morbidity group box 1; CS, corticosteroid; rhTM, recombinant human thrombomodulin.

proteolysis.¹³ In addition to its anticoagulant function, APC also binds to the endothelial protein C receptor in lipid-rafts/caveolar compartments to activate protease-activated receptor 1 (PAR-1), thereby eliciting anti-inflammatory and cytoprotective signalling responses in endothelial cells.¹³

The first step in the treatment of DILD is discontinuation of the suspected drugs. If the patient does not improve after discontinuation of the suspected drugs or the DILD is moderate or severe, the administration of CS therapy is recommended. However, some cases of DILD are refractory to CS therapy and carry a poor prognosis, such as DAD-type DILD. Some case reports suggested effects from a direct haemoperfusion with polymyxin B-immobilised fibre (PMX-DHP) treatment, but to date, the efficacy of PMX-DHP treatment has not been thoroughly validated.⁵ There is no advanced treatment strategy established for severe DILD refractory to CS therapy. In the present case, we demonstrated the potential beneficial effects of CS plus rhTM for DILD with its anticoagulation and anti-inflammation activities. Further studies are necessary to investigate the efficacy of CS plus rhTM for the treatment of CS refractory DILD.

In conclusion, we present the first case of DILD successfully treated with CS and rhTM. rhTM may be an alternative agent for CS refractory DILD. Further study is necessary to confirm its effects.

Learning points

- At present, there is no established therapeutic option for corticosteroid (CS) refractory drug-induced interstitial lung disease (DILD).
- The present case indicates that recombinant human soluble thrombomodulin (rhTM) may be useful as an adjunct to CS therapy in refractory patients.
- Further study is needed to confirm the efficacy of rhTM for the treatment of CS refractory DILD.

Contributors SM was involved in data collection, analysis, interpretation and manuscript writing. MaS was involved in data collection, analysis and interpretation. MiS and MF were involved in data analysis and interpretation. All authors read and approved the final manuscript.

Competing interests None.

Patient consent Obtained.

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