Case report

Nintedanib and intensive immunosuppressive therapy to treat rapidly progressive interstitial lung disease presenting anti-ARS antibodies

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A 59-year-old Japanese man with no past medical history presented with worsening dyspnea of one-month duration. He was a construction worker and had 20 pack-years smoking history. He denied any contact with sick people and had not traveled. On admission, he had a temperature of 37.1 °C, blood pressure of 124/77 mmHg and a heart rate of 76 beats per minute. He was tachypneic with oxygen saturation of 93% with an oxygen mask delivering 8 L/min. Physical examination revealed fine bilateral crackles in his back, but no evidence of the skin rash that typifies dermatomyositis. He demonstrated evidence of "mechanic's hand" (roughening and cracking of the skin) (Fig. 1). An assessment of muscle power was not completed due to severe respiratory failure, but no obvious muscle weakness was observed.

A PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was negative. Increased levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer were noted (17.95 mg/dL, 478 U/L, and <500 U/mL). Serum levels of creatine kinase (CK) and aldolase were not elevated (38 IU/L and 4.1U/L, respectively). Krebs von den Lungen-6 (KL-6) was remarkably increased (3930 U/mL; normal <500 U/mL). Serum levels of creatine kinase (CK) and aldolase were not elevated (38 IU/L and 4.1U/L, respectively). Serological tests for atypical pathogens, including Mycoplasma pneumoniae, were negative. Chest computed tomography (CT) showed consolidations and ground-glass opacities (GGO), predominantly in the bilateral lower lobes with decreased lung volumes, suggesting a radiologic pattern of diffuse alveolar damage (DAD) imposed on non-specific interstitial pneumonia (NSIP) (Fig. 2A).

1. Introduction

Dermatomyositis (DM) is an autoimmune disease that mainly affects the skin and proximal muscles; however, some patients with DM have minimal or no muscle involvement, called clinically amyopathic DM (CADM) [1]. Interstitial lung disease (ILD) is a major complication of DM, with a poorer prognosis than DM without ILD [2]. Rapidly progressive ILD (RP-ILD) in CADM is a life-threatening subtype of myositis-associated ILD that tends to be resistant to high-dose glucocorticoid treatment and immunosuppressants. Anti-aminocyt tRNA synthetase (ARS) antibodies and anti-melanoma differentiation-associated 5 (MDA5) antibodies have been reported with RP-ILD [3]. RP-ILD due to anti-MDAS antibodies is often associated with worse outcomes than RP-ILD due to anti-ARS antibodies [4,5]. Here we report a case of severe onset RP-ILD associated with anti-ARS antibodies that was successfully treated with nintedanib in addition to intensive immunosuppressive therapies.

2. Case report

A 59-year-old Japanese man with no past medical history presented with worsening dyspnea of one-month duration. He was a construction worker and had 20 pack-years smoking history. He denied any contact with sick people and had not traveled. On admission, he had a temperature of 37.1 °C, blood pressure of 124/77 mmHg and a heart rate of 76 beats per minute. He was tachypneic with oxygen saturation of 93% with an oxygen mask delivering 8 L/min. Physical examination revealed fine bilateral crackles in his back, but no evidence of the skin rash that typifies dermatomyositis. He demonstrated evidence of “mechanic’s hand” (roughening and cracking of the skin) (Fig. 1). An assessment of muscle power was not completed due to severe respiratory failure, but no obvious muscle weakness was observed.

A PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was negative. Increased levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer were noted (17.95 mg/dL, 478 U/L, and <500 U/mL). Serum levels of creatine kinase (CK) and aldolase were not elevated (38 IU/L and 4.1U/L, respectively). Serological tests for atypical pathogens, including Mycoplasma pneumoniae, were negative. Chest computed tomography (CT) showed consolidations and ground-glass opacities (GGO), predominantly in the bilateral lower lobes with decreased lung volumes, suggesting a radiologic pattern of diffuse alveolar damage (DAD) imposed on non-specific interstitial pneumonia (NSIP) (Fig. 2A).
Contrast-enhanced CT showed no obvious pulmonary artery thromboembolism or deep vein thromboembolism.

In addition to broad-spectrum antibiotic therapy (intravenous meropenem and minocycline), pulse doses of methylprednisolone (mPSL) were initiated, followed by 50 mg/day of prednisolone (PSL). Further workup revealed positive anti-ARS antibodies (81.9 index; normal <24), which led to a final diagnosis of rapidly progressive interstitial lung disease (RP-ILD) associated with anti-ARS antibodies (The anti-ARS antibodies were later found to be anti-PL-7 antibodies). Despite a second course of mPSL pulses and additional tacrolimus and recombinant thrombomodulin therapy, which were started on day 7, his respiratory condition deteriorated. He was referred to Hamanomachi Hospital on day 11.

On arrival at Hamanomachi Hospital, his PaO₂ was 73 mmHg with...
100% O₂ oxygen. Repeat chest CT showed a new development of mediastinal emphysema with worsening consolidation, GGO, traction bronchiectasis, and loss of lung volume, predominantly in the left lobes, suggesting progressive fibrosis (Fig. 2B). Nasal, high-flow oxygen therapy was started with initial fraction of inspiratory oxygen (FiO₂) at 1.0. His serum ferritin level was elevated at 771 ng/mL. Intravenous immunoglobulin (IVIG; 20g for 5 days) and intravenous cyclophosphamide (IVCY; 900 mg [500 mg/m²]) was initiated. The dose of tacrolimus was increased to 0.05 mg/kg twice a day (8 mg/body), and the goal trough was set to 10 ng/mL. Due to suspicion of thrombotic microangiopathy in the pulmonary microvessels, based on his high levels of D-dimer, continuous intravenous dalteparin (5000 U/day) was started (Fig. 3).

On day 15, although laboratory tests showed improved levels of CRP and D-dimer, there was no improvement of chest X-ray images and the PaO₂/FiO₂ ratio. Serum KL-6 level was further elevated at 5380 U/mL. Therefore, nintedanib (200 mg/day) was started. The serum trough of tacrolimus reached 11.1 ng/ml on day 17. PSL was tapered to 30 mg/day. On day 25, dalteparin treatment was discontinued due to improvement of the D-dimer level. His respiratory condition further improved on day 34 with de-escalation of his oxygen requirement to a regular nasal canula with oxygen at 3 L/min. His chest CT, repeated on day 40, showed improvement of GGO and consolidations (Fig. 2C). Traction bronchieactasis in the peripheral area and lung volume was somewhat improved as well (Fig. 2C).

3. Discussion

We describe a case of fulminant RP-ILD associated anti-ARS antibodies, treated with nintedanib in addition to intensive immunosuppressive therapies. The recommended treatment for CADM-associated RP-ILD is corticosteroid therapy and/or immunosuppressive agents [6]. Immunosuppressive agents (IVCY and tacrolimus) may offer the main benefits in such a case. In addition to this standard therapy, we added nintedanib, based on the assumption that there should be significant fibrogenesis in the lung on day 15.

There are several publications regarding prognostic factors for inflammatory myositis-ILD. Fujisawa et al. reported that acute/subacute onset, older age, lower level of forced vital capacity (FVC), and a diagnosis of CADM predict a poor outcome in inflammatory myositis-ILD [7]. High levels of serum ferritin (>828 ng/mL) on admission constitute a poor prognostic factor in RP-ILD patients with anti-MDA5 antibodies, along with IL-6 [8]. Recently, a multicenter retrospective cohort of cases of myositis-associated ILD from 44 institutions across Japan was established, and several predictors of poor prognosis were reported: age at onset >60 years (hazard ratio (HR) = 4.3, 95% CI: 2.4, 7.5), CRP >1 mg/dL (HR = 2.6, 95% CI: 1.5, 4.8), peripheral capillary oxygen saturation <95% (HR = 2.0, 95% CI: 1.2, 3.4) and anti-MDA5 antibodies (HR = 7.5, 95% CI: 2.8, 20.2) [9]. Higher levels of KL-6 (>1000 U/ml) were an additional, independent risk factor (HR = 2.0, 95% CI: 1.2, 3.3; p = 0.01) [9]. In this case, acute onset with desaturation, extensive findings on chest CT, and higher levels of CRP and KL-6, except for the
absence of anti-MDA5 antibodies, all suggested a poor prognosis and provided the rationale for intensive treatment.

The anti-ARS antibodies were later found to be anti-PL-7 antibodies. Marie et al. investigated clinical manifestations and outcomes of 15 patients with anti-PL-7 positive anti-synthetase syndrome [10]. They found that 93.3% (14/15) of anti-PL-7 patients exhibited ILD. 7.1% (1/14) showed acute onset of ILD. No patient had resolution of ILD, and 35.7% (5/14) of patients experienced deterioration [10]. This report suggests that additional therapies such as anti-fibrotic agents may be needed for disease remission.

It is becoming recognized that there is a progressive phenotype in non-idiopathic pulmonary fibrosis (IPF)—progressive fibrosing interstitial lung disease (PF-ILD)—the disease behavior of which is similar to IPF [11,12]. Thus, it is reasonable to consider application of antifibrotic agents—nintedanib or pirfenidone in PF-ILD, including from a Chinese institution reported that nintedanib therapy might contribute to favorable outcomes. Clinical trials using nintedanib in the anti-fibrotic, but also anti-inflammatory effects, which should further nintedanib treatment suppresses interleukin (IL)-1β from a Chinese institution reported that nintedanib therapy might reduce the incidence of RP-ILD and might improve survival in inflammatory myositis-ILD patients [15].

Moreover, nintedanib has anti-inflammatory activity [16]. Ninte-
danib treatment suppresses interleukin (IL)-1β and KC in both bleomycin-treated lung and silica-treated lung in mice [17]. Nintedanib inhibits the release of mediators, including IL-2, IL-4, IL-5, IL-10, IL-12p70, IL-13 and interferon-γ from human peripheral blood mononuclear cells or T-cells [18]. Thus, nintedanib could have not only anti-fibrotic, but also anti-inflammatory effects, which should further contribute to favorable outcomes. Clinical trials using nintedanib in the acute phase of RP-ILD are warranted to assess and quantify the benefits of nintedanib. We hope that this case report will contribute to a thorough discussion of the use and timing of nintedanib for RP-ILD.

Patient consent for publication

Written, informed consent was obtained from the patient.

Declaration of competing interest

All authors of the manuscript declare that there are no conflicts of interest.

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