Successful Treatment with Tacrolimus in a Case of Lung-dominant Connective Tissue Disease

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Abstract

A 49-year-old man with dyspnea was found to have reticular opacities and ground-glass attenuation with traction bronchiectasis or bronchiolectasis on computed tomography. The patient met the criteria for lung-dominant connective tissue disease (LD-CTD) and histopathologically exhibited a chronic fibrotic interstitial pneumonia illustrating framework of a usual interstitial pneumonia-like pattern. Due to worsening of the disease, therapy was initiated with corticosteroids in combination with cyclosporine A. However, treatment with these drugs was ineffective. Pirfenidone and intravenous cyclophosphamide therapy also proved ineffective. The cyclosporine A was therefore switched to tacrolimus, and the patient’s disease improved, allowing for a reduction in the dose of the corticosteroids. Our experience in this case suggests that treatment with tacrolimus might be useful for treating refractory LD-CTD even when histopathologically chronic fibrotic interstitial pneumonia is evident.

Key words: lung-dominant connective tissue disease, idiopathic pulmonary fibrosis/usual interstitial pneumonia, tacrolimus, undifferentiated connective tissue disease

Introduction

There is insufficient evidence that any specific pharmacologic therapy is effective for idiopathic interstitial pneumonia (IIP) and connective tissue disease-associated interstitial lung disease (CTD-ILD) (1, 2). This report presents the case of a patient with progressive ILD who met the criteria for lung-dominant connective tissue disease (LD-CTD) (3) and histopathologically exhibited a chronic fibrotic interstitial pneumonia illustrating framework of a usual interstitial pneumonia (UIP)-like pattern. Although the patient was initially refractory to corticosteroids, cyclosporine A (CsA), intravenous cyclophosphamide (IVCY) and pirfenidone, replacement of cyclosporine A with tacrolimus resulted in improvement in the condition of ILD.

Case Report

In July 2009, a 49-year-old man with non-alcoholic steatohepatitis was admitted to our hospital due to exercise-induced dyspnea scored as Medical Research Council (MRC) grade 1. The patient’s vital signs were as follows: blood pressure, 100/64 mmHg; respiratory rate, 20 breaths/min; body temperature, 35.9°C. Auscultation revealed endo-inspiratory fine crackles bilaterally in the lower lung fields; however, none of the typical symptoms associated with connective tissue disease (CTD) such as joint swelling, Raynaud’s phenomenon, dry eyes or mouth, skin rashes, myalgia and muscle weakness were observed. The results of the examinations are described in Table. Laboratory examinations revealed the following values: lactate dehydrogenase...
Figure 1. Chest X-ray. Chest radiograph showing bilateral patchy infiltrates predominantly in the middle and lower lung fields and a decrease in the volume of the bilateral basal lungs.

(LDH): 232 IU/L, C-reactive protein (CRP): 0.61 mg/dL, KL-6: 2,330 IU/mL, SP-D: 372 mg/mL, anti-nuclear antibody (ANA): 160 index (cytoplasmic pattern), anti-SS/A antibody: positive, anti-SS/B antibody: (-Ab) plus/minus. Tests for rheumatoid factor, anti-cyclic citrullinated peptide (CCP)-Ab and myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA) were all negative. An analysis of arterial blood gases showed the partial pressures of O₂ and CO₂ to be 70.3 Torr and 36.2 Torr, respectively, on room air. Chest radiograph showed bilateral patchy infiltrates predominantly in the middle and lower lung fields and decreased volume in the bilateral basal lungs (Fig. 1). A pulmonary function test (PFT) revealed constrictive impairment and a reduced diffusion capacity (%VC, 63.8%; %D_LCO, 35.6%; %D_LCO/VA, 73.5%). A six-minute walk test (6MWT) yielded the following data: distance, 132 m; lowest SpO₂, 84%; and baseline saturation, 94% on room air. High-resolution CT (HRCT) images showed patchy areas of intralobular reticular opacities and ground-glass attenuation (GGA) with traction bronchiectasis or bronchiolectasis predominantly involving the subpleural parenchyma of the bilateral lower lung lobes. Although no areas of honeycombing were evident, there was an impression of heterogeneous pulmonary parenchymal impairment. On the basis of the HRCT findings, a possible UIP pattern was considered based on the new ATS/ERS/JRS/ALAT guidelines for idiopathic pulmonary fibrosis (IPF) (2) (Fig. 2A). The abnormalities observed on chest HRCT worsened approximately three years after the initiation of pharmacologic therapy with prednisolone, CsA, IV CY, tacrolimus and pirfenidone followed by the appearance of honeycombing (Fig. 2B). Bronchoalveolar lavage fluid (BALF) obtained from the left lingula revealed an elevated total cell count (4.7×10⁵/mL). The BALF differential cell count consisted of 41% macrophages, 40% lymphocytes and 19% neutrophils. BALF staining and culture revealed no pathogens, and the transbronchial lung biopsy specimens exhibited no specific features. Schirmer’s test and the gum test demonstrated no decreases in tear or saliva production. In August 2009, we performed a video-assisted thoracic surgical lung biopsy of the left lingula and lateral basal segment (S9). The lung biopsy specimens demonstrated a chronic fibrotic interstitial pneumonia illustrating framework of a UIP-like pattern with patchy dense fibrosis, architectural disruption and scattered fibroblastic foci (Fig. 3A, B). Unlike that seen in IPF, findings suggestive of LD-CTD, including lymphoid follicles with marked germinal center plasmacytic infiltration (Fig. 3C) and extensive cellular pleuritis, were evident (data not shown). These findings met none of the criteria for CTD (including Sjögren’s syndrome: SJS). Although the type of IIP in this case was consistent with IPF/UIP according to the new IPF criteria (2), it also met the criteria for LD-CTD (3).

Due to worsening dyspnea and pulmonary function (VC 2.38 to 1.79 L, D_LCO 10.2 to 3.41 mL/min/mmHg) approximately one month after diagnosis and an increase in GGA with traction bronchiectasis or bronchiolectasis evident on chest HRCT (Figs. 1, 4), methylprednisolone pulse therapy
(1,000 mg/day, intravenously for three days) was initiated followed by prednisolone (30 mg/day) in combination with oral CsA (150 mg/day), which led to improvements in the lung parameters (VC 1.79 to 2.04 L, D_{LCO} 3.41 to 8.18 mL/min/mmHg) approximately four months after diagnosis. However, the serum level of KL-6 was elevated (2,330 to 7,240 U/mL), and the lowest SpO₂ value (84% to 81%) and distance on 6MWT (87% and 210 m during the administration of oxygen at 6 L/min) both decreased approximately four months after diagnosis. Because these parameters did not improve despite the addition of oral pirfenidone (1,800 mg/day) and IVCY (500 mg/body, three times), it was impossible to reduce the dose of the corticosteroids. In June 2011, the CsA was switched to oral tacrolimus (3 mg/day), which resulted in improvements in dyspnea, the pulmonary function (VC 1.93 to 3.03 L, D_{LCO} 7.79 to 8.57 mL/min/mmHg), the lowest SpO₂ value and the distance on 6MWT (87% and 210 m during the administration of oxygen at 5 L/min to 81% and 495 m during the administration of oxygen at 2 L/min) and a decrease in the serum level of KL-6 (7,240 to 993 U/mL), allowing for a reduction in the dose of the corticosteroids (40 to 12 mg/day) starting from the initiation of treatment with TAC and up to 14 months thereafter. HRCT images obtained after oral tacrolimus therapy revealed improvements in the areas of GGA and the disappearance of some branches of traction bronchiectasis in the bilateral lower lung zones. Currently, the patient’s clinical condition is good (Fig. 4), and there have been no systemic manifestations of CTD for three years.

**Discussion**

Many patients with ILD exhibit poor responses to any form of pharmacologic therapy (1, 2). In particular, IPF/UIP, a major type of IIP (accounting for approximately 47-62% of all cases), has a grave prognosis with a median survival period of approximately 2-3.8 years (1, 2, 4, 5). Patients with progressive ILD have been treated with corticosteroids in combination with immunosuppressive agents such as CsA, cyclophosphamide and azathioprine and/or antifibrotic drugs, including pirfenidone and N-acetylcysteine (NAC) (6-9). However, such patients are often refractory to these treatments and exhibit an aggressive disease course. Treatment with CsA in combination with low-dose corticosteroids is often effective for progressive ILD (8).

The immunosuppressive actions of CsA are believed to be based on the prevention of T-cell activation through the inhibition of calcineurin, thereby inhibiting the phosphorylation of members of the nuclear factors of activated T-cells (NFAT) family and the activation of the interleukin-2 gene. Moreover, several reports have indicated that CsA exerts antifibrotic effects by blocking the activation of transforming growth factor-β (TGF-β) by activator protein-1 (AP-1) and...
Figure 3. Histopathological analysis of surgical lung biopsy specimens. A surgical lung biopsy (SLB) specimen showing patchy distribution of dense fibrosis along with architectural disruption (A) and scattered fibroblastic foci (B) indicating a chronic fibrotic interstitial pneumonia illustrating framework of a UIP-like pattern. Findings suggestive of connective tissue disease-associated interstitial lung disease (CTD-ILD) were evident, including lymphoid follicles with germinal centers (C).

may have the ability to reduce lung fibrosis, which is the primary factor responsible for worsening of IIP (10). The immunosuppressive mechanisms of tacrolimus are reported to be similar to those of CsA, although the activity of the former is approximately 30-100-fold more potent than that of the latter in vitro (11). Several reports have documented the successful use of tacrolimus for cases of polymyositis/dermatomyositis (PM/DM) or amyopathic dermatitis (ADM)-associated ILD that are refractory to treatment with corticosteroids in combination with CsA and/or cyclophosphamide (12-14). However, to our knowledge, this is the first report to document the effectiveness of tacrolimus for LD-CTD histopathologically showing a chronic fibrotic interstitial pneumonia pattern, a type of ILD that is more refractory to pharmacologic therapy. Previous studies (13) have shown the BALF lymphocyte count to increase in ILD patients with ADM who have been successfully treated with TAC. In the present case, the BALF lymphocyte count was also increased. TAC is well known to be a T-cell-specific immunosuppressant. Therefore, TAC can be effective in LD-CTD patients by preventing the T-cell function in the lungs. Further analysis is needed to verify this issue.

Histopathologically, the present patient exhibited a chronic fibrotic interstitial pneumonia illustrating framework of a UIP-like pattern. However, although serum positivity for ANA and anti-SS/A antibodies suggested a diagnosis of CTD, the physical findings did not meet the defined criteria for CTD. Occult CTD with systemic symptoms and serologic abnormalities may develop into defined CTD during follow-up, even when defined CTD is absent on admission (15). Kinder et al. proposed provisional criteria for undifferentiated CTD (UCTD) on the basis of clinical manifestations and the presence of specific antibodies (16), while Fischer et al. proposed criteria for LD-CTD on the basis of specific antibodies and histopathologic features (3). Because a few histopathologic features in this case (lymphoid follicles with germinal centers and plasmacytic infiltration) matched the criteria for LD-CTD, the patient was diagnosed with LD-CTD and not UCTD.

In summary, we herein reported a case of LD-CTD refractory to treatment with corticosteroids, CsA, pirfenidone and IVCY. Tacrolimus improved the disease activity and resulted in a reduction in the dose of corticosteroids. The findings of the present case suggest that treatment with tacrolimus can be considered in refractory cases of LD-CTD even when histopathologically chronic fibrotic interstitial pneumonia patterns are evident.

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

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Figure 4. Clinical course of this case

CsA: cyclosporine A, TAC: tacrolimus, LTOT: long term oxygen therapy, IVCY: intravenous cyclophosphamide, mPSL: methylprednisolone, 6MWT: six-minutes walk test

References


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