

Effectiveness of Combined Therapy with Pirfenidone and Erythromycin for Unclassifiable Interstitial Pneumonia Induced by HTLV-1-associated Bronchioloalveolar Disorder (HABA)

Naoko Yokohori¹, Akitoshi Sato¹, Mizue Hasegawa¹, Hideki Katsura¹,
Kenzo Hiroshima² and Tamiko Takemura³

Abstract

Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus involved in the pathogenesis of adult T-cell leukemia (ATL) and HTLV-1-associated bronchioloalveolar disorder (HABA). The clinical and pathological findings of HABA have been characterized as either a diffuse panbronchiolitis (DPB) pattern or idiopathic interstitial pneumonia (IIP) pattern. Treatments for HABA include corticosteroids for the IIP pattern and erythromycin for the DPB pattern. We herein report a case of HABA-associated unclassifiable interstitial pneumonia that improved with combined therapy with pirfenidone and erythromycin. This is the first report on the effectiveness of combined therapy with pirfenidone and erythromycin for HABA.

Key words: human T-cell lymphotropic virus type 1 (HTLV-1), HTLV-1-associated bronchioloalveolar disorder (HABA), unclassifiable interstitial pneumonia, HTLV1-proviral pX gene, pirfenidone, erythromycin

(Intern Med 56: 73-78, 2017)
(DOI: 10.2169/internalmedicine.56.6995)

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus involved in the pathogenesis of adult T-cell leukemia (ATL) and non-neoplastic inflammatory diseases of various organs, such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Pulmonary involvement in HTLV-1 carriers is referred to as HTLV-1-associated bronchioloalveolar disorder (HABA) (1, 2). The pulmonary complications of HABA develop in HTLV-1 carriers and have been attributed to an inflammatory reaction to HTLV-1 and its gene products (3-6). The clinical and pathological findings of HABA are characterized by a diffuse panbronchiolitis (DPB) pattern or idiopathic interstitial pneumonia (IIP) pattern, and T-lymphocytic alveolitis (2). Treatments for HABA include corticosteroids for the IIP pattern and erythromycin for the DPB pattern (7, 8). How-

ever, the efficacy of pirfenidone, which is an anti-fibrotic drug used in the treatment of idiopathic pulmonary fibrosis, has not yet been determined for HABA. We herein report a case of HABA-associated interstitial pneumonia that was improved by combined therapy with pirfenidone and erythromycin.

Case Report

A 73-year-old-man was admitted by a local physician with dyspnea on exertion that had begun 2 months earlier. He was diagnosed with interstitial pneumonia, thrombocytopenia, hepatic cirrhosis, and diabetes. He was referred to a hematologist for the thrombocytopenia. He came from Nagasaki, an area in Japan in which HTLV-1 is prevalent. The hematologist diagnosed him as an HTLV-1 carrier with myeloproliferative disorder (essential thrombocythemia). He was then referred to our pulmonary outpatient clinic for in-

¹Division of Respiratory Medicine, Tokyo Women's Medical University Yachiyo Medical Center, Japan, ²Division of Pathology, Tokyo Women's Medical University Yachiyo Medical Center, Japan and ³Division of Pathology, Japanese Red Cross Medical Center, Japan

Received for publication December 17, 2015; Accepted for publication May 12, 2016

Correspondence to Dr. Naoko Yokohori, wbycm409@ybb.ne.jp

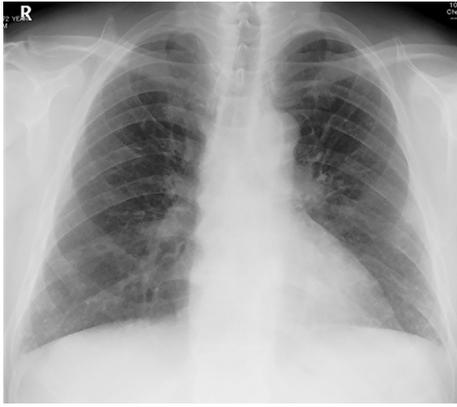


Figure 1. Chest X-ray film showing bilateral GGO in both lower lung fields.

terstitial pneumonia. Fine crackles were heard at the base of the bilateral lungs. He had a family history of interstitial pneumonia, as his brother and sister had both died of interstitial pneumonia, but the etiology of those interstitial pneumonia cases was not identified. Chest X-ray showed bilateral ground-glass opacity (GGO) in both of the lower lung fields (Fig. 1). Chest CT showed bronchovascular bundle-dominant reticular shadows and GGO in the bilateral lung field (Fig. 2, 7a). His percutaneous oxygen saturation in room air was 97% with a Modified British Medical Research Council (mMRC) grade two, and the findings on the pulmonary function test and 6-minute walk test (6MWT) were normal (Table 1). There were no positive data for collagen disease (Table 1). Given that the CT findings were inconsistent with the UIP pattern, we performed video-assisted thoracoscopic surgery (VATS) to confirm a diagnosis of interstitial pneumonia. Lung tissue was obtained by VATS from three parts of the lung (right S3, right S6, and right S8) (Fig. 2). The pathological findings of right S3 and right S6 were similar, and the primary lesions were organizing pneumonia like-lesions and usual interstitial pneumonia (UIP) like-lesions. In contrast, the primary lesions of right S8 were fibrotic non-specific interstitial pneumonia (f-NSIP)-like lesions (Fig. 3, 4). Taken together, the lung specimens revealed various interstitial pneumonia patterns, including UIP like-lesions, f-NSIP-like lesions, and organizing pneumonia-like lesions that were diagnosed as unclassifiable interstitial pneumonia.

Since HTLV-1 was not detected in the plasma or lung tissue, the patient was diagnosed with IIP. Given that some of these lesions showed a UIP pattern, the patient was administered pirfenidone at 1,800 mg/day. The CT findings and the dyspnea on exertion subsequently improved (Fig. 7b); however, the KL-6 and SP-D increased slightly (Fig. 6, clinical course). Gastrointestinal symptoms and depression developed as side effects 3 months after the initiation of pirfenidone at 1,800 mg/day. We reduced the pirfenidone dose to 1,200 mg/day and continued its administration. The symptom of dyspnea on exertion, the percutaneous oxygen saturation in room air, and the findings on the pulmonary function

did not progress (Table 2); however, the CT findings of bronchovascular bundle-dominant reticular shadows and GGO had deteriorated 6 months after the initiation of the pirfenidone treatment (Fig. 7c).

We performed transbronchial lung biopsy (TBLB) and bronchoalveolar lavage (BAL) to rule out the infiltration of leukemic cells or lymphocytic interstitial pneumonia. TBLB specimens and cytology of the bronchoalveolar lavage fluid (BALF) showed no leukemic cells (Fig. 5). However, in the BALF, the percentage of lymphocyte was elevated (37%) and the findings for the HTLV-1 proviral pX gene were positive (Table 2). These results suggested the exacerbation of HABA-associated interstitial pneumonitis. Previous studies have reported the effectiveness of steroids in the treatment of HABA; however, we were concerned about the deterioration of the existing diabetes. We therefore increased the dose of erythromycin, which had been administered for viscous sputum two months earlier, from 200 mg/day to 400 mg/day. The GGO, KL-6, and SP-D improved after combined therapy with pirfenidone and erythromycin (Fig. 6, 7).

This combined therapy with pirfenidone at 1,200 mg/day and erythromycin at 400 mg/day has been continued in this patient for more than 2 years, with no progression of the dyspnea on exertion or abnormalities on chest CT thus far.

Discussion

In 1986, Kimura et al. reported the presence of HTLV-1 antibody in chronic pulmonary disease (9). Sugimoto et al. subsequently detected T-lymphocyte alveolitis in HTLV-1 associated myelopathy in 1989 (10). Following further investigations, pulmonary complications in HTLV-1 carriers were recognized as a concept termed HABA (1). The lung is the preferential site for HTLV-1 infection (5, 11), and this preference has been implicated in the high incidence of pulmonary involvement in HTLV-1 carriers. Although the pathological findings of HABA have not yet been fully established, Sugimoto et al. investigated 32 surgical lung biopsy specimens obtained from HTLV-1-positive patients with diffuse pulmonary disease (12) and found that the pathological findings of HABA consisted of four types of pulmonary involvement: chronic bronchitis, chronic interstitial pneumonia, infiltration of leukemic or lymphoma cells, and lymphoproliferative disease. Most patients were diagnosed with chronic bronchitis (66%), followed by chronic interstitial pneumonia (16%). Two of the patients with chronic interstitial pneumonia were also diagnosed with UIP, while the others had chronic fibrosing interstitial pneumonia.

The clinical and pathological findings of HABA-associated interstitial pneumonia have not yet been investigated in detail. A recent study identified the NSIP pattern for HABA-associated interstitial pneumonia (13, 14). Our HTLV-1 carrier patient presented with bronchovascular bundle-dominant reticular shadows and GGO, which are inconsistent with the UIP pattern (15). The histological findings of the VATS specimens from this patient showed vari-

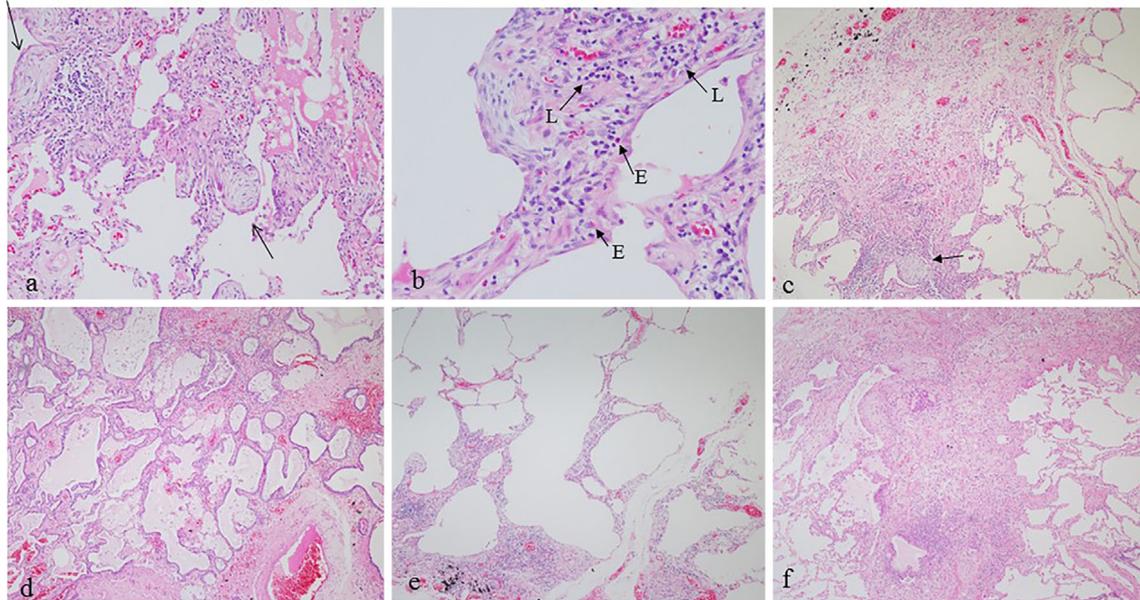


Figure 4. Higher-power images of VATS specimens. (a) Mural incorporation fibrosis of the alveolar wall associated with intra-alveolar exudate in the right S3 section. (b) Slight infiltration of lymphocytes (L→) and eosinophils (E→) in the alveolar wall in the right S3 section. (c) Subpleural fibrosis of the right S3 section showing dense fibrosis, the collapse of alveolar walls, and a fibroblastic focus (↑). (d) Widespread interstitial fibrosis with airspace enlargement and bronchiolar metaplasia in the right lower lobe (S8) section. (e) The patchy involvement of mural incorporation fibrosis in the right S8 section. (f) Subpleural and paraseptal fibrosis in the right S8 section (Hematoxylin and Eosin staining; original magnification a, d, e: ×100, b: ×200, c, f: ×40).

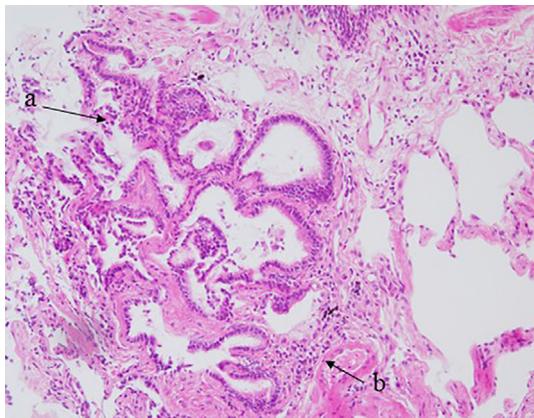


Figure 5. The histological findings of TBLB specimens showing peribronchiolar metaplasia (a→) and slight mononuclear cell infiltration to the bronchiolar wall (b→) (Hematoxylin and Eosin staining; original magnification ×100).

ous lesions (organizing pneumonia-like mural incorporation fibrosis, f-NSIP-like interstitial fibrosis with airspace enlargement, and UIP-like subpleural and paraseptal fibrosis), and the pathological diagnosis was unclassifiable interstitial pneumonia (15, 16).

To our knowledge, this is the first report of a case of HABA-associated unclassifiable interstitial pneumonia. Since most pathological studies have been conducted using a limited volume of lung tissues from a small number of patients, the data obtained may be unsatisfactory for determining a

precise pathological diagnosis. In our case, we were able to evaluate a relatively large amount of lung tissue, which was obtained by VATS from three parts of the lung (rt. S3, rt. S6, and rt. S8). Therefore, these pathological findings may lead to a more precise pathological diagnosis of interstitial pneumonia. While the pathogenic mechanisms of HTLV-1 in lung tissue have not yet been elucidated in detail, the immunological and inflammatory mechanisms induced by HTLV-1 and its gene products may have played a central role in the pathogenesis of unclassifiable interstitial pneumonia associated with the various pathological findings in the present patient.

Although a dose reduction of pirfenidone to 1,200 mg/day induced the deterioration of interstitial pneumonia, the GGO was improved by the administration of pirfenidone at 1,800 mg/day. Pirfenidone (5-methyl-1-phenyl-2[1H]-pyridone; Shionogi & Co., Osaka, Japan) is known to have combined anti-inflammatory, antioxidant, and anti-fibrotic effects in experimental models of pulmonary fibrosis (17-19). Indeed, recent studies have demonstrated that the administration of pirfenidone decreases the rate of decline in vital capacity in patients with IPF (20, 21). Pirfenidone may have exerted anti-fibrotic and/or anti-inflammatory effects on the alveolar lesions caused by interstitial pneumonia in the present patient.

While bronchitis was not detected in the VATS sections, the administration of erythromycin improved HABA-associated interstitial pneumonia in our patient. Macrolide

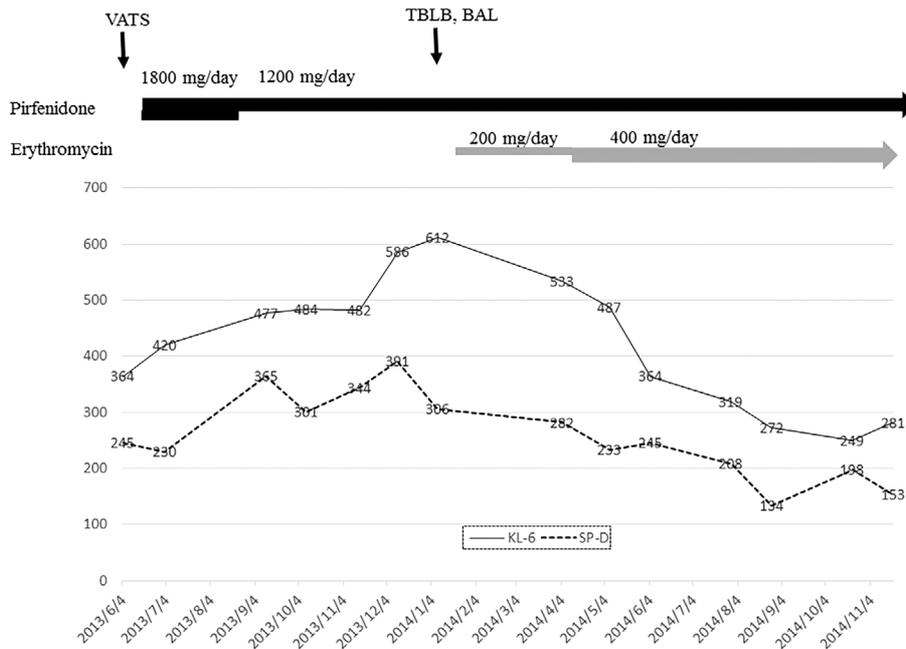


Figure 6. Clinical course.

Table 2. Laboratory Findings after Six Months' Pirfenidone Treatment.

Pulmonary function test		BALF	
VC	3.32L	Total cell count	1.75×10^5 mL
%VC	102%	Macrophages	53%
FVC	3.23L	Neutrophils	7%
%FVC	99.7%	Eosinophils	3%
FEV1.0	2.72L	Lymphocytes	37%
FEV1.0%	84.2%	HTVL-1 proviral pX gene	(+)
DLco	17.8mL/min/mmHg		
%DLco	97.1%		

BALF: Bronchoalveolar Lavage Fluid

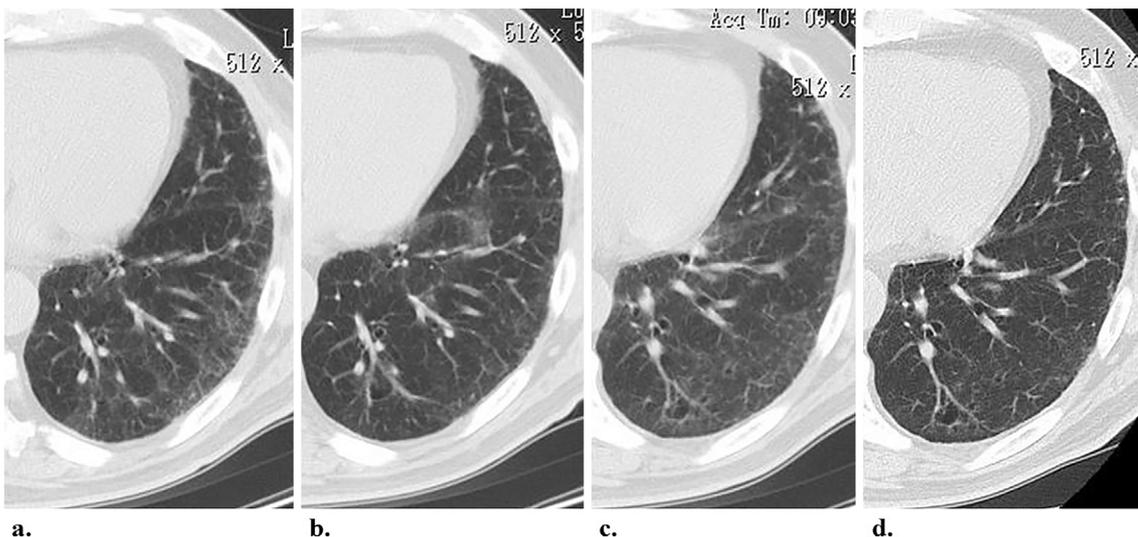


Figure 7. The chest HRCT findings. (a) Before being treated, basal and bronchovascular bundle-dominant reticular shadows and GGO were shown. (b) Two months after treatment with pirfenidone 1,800 mg/day, the reticular shadows and GGO slightly improved. (c) Three months after a dose reduction to 1,200 mg/day, the basal and bronchovascular bundle-dominant reticular shadows and GGO had deteriorated. (d) Nine months after treatment with pirfenidone 1,200 mg/day and erythromycin 400 mg/day, the reticular shadows and GGO continued to improve.

has been reported to exert anti-fibrotic effects (22), and it is an effective treatment for cryptogenic organizing pneumonia due to its anti-inflammatory properties (23). Based on these findings, erythromycin may have also exerted anti-inflammatory and/or anti-fibrotic effects on the alveolar lesions caused by interstitial pneumonia in our patient.

The administration of pirfenidone at 1,200 mg/day did not control the progression of interstitial pneumonia, but combined therapy of pirfenidone at 1,200 mg/day and erythromycin at 400 mg/day improved the GGO, KL-6, and SP-D. These results suggest the synergistic effects of pirfenidone and erythromycin on interstitial pneumonia.

In conclusion, we encountered a case of HABA-associated unclassifiable interstitial pneumonia that was improved by combined therapy with pirfenidone and erythromycin. This is the first report of the effectiveness of such combined therapy in treating HABA.

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

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