Mod Rheumatol (2008) 18:52–56
DOI 10.1007/s10165-007-0002-3

CASE REPORT

Severe airflow limitation in two patients with systemic lupus erythematosus: effect of inhalation of anticholinergics

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Received: 1 December 2006 / Accepted: 2 August 2007 / Published online: 20 December 2007

Abstract Airway involvement clinically presenting as dyspnea and an obstructive ventilatory defect is a rare but clinically important complication in systemic lupus erythematosus (SLE), since the airway manifestation is often progressive and resistant to systemic immunosuppressive therapy. Here we report two SLE patients with slowly progressive airflow limitation, which was clinically thought to be bronchiolitis obliterans. Both patients showed obvious improvement after inhalation of anticholinergics was started. Because anticholinergics are highly safe and never immunosuppressive, inhalation of these drugs might be useful in the therapeutic strategies for airflow limitation accompanying SLE or other collagen diseases.

Keywords Airflow limitation · Anticholinergics · Bronchiolitis obliterans (BO) · Obstructive ventilatory defect · Systemic lupus erythematosus (SLE)

Introduction

Respiratory system involvement sometimes occurs in systemic lupus erythematosus (SLE). SLE patients presenting with uncontrollable lung abnormalities may need special clinical attention, since decreased pulmonary function greatly hampers the patients' activities of daily living. The airway is a relatively rare site of pulmonary complication in SLE. However, chronic progression of airflow limitation, for which a diagnosis of bronchiolitis obliterans (BO) is clinically suspected, has been generally recognized as a potentially life-threatening, difficult-to-treat complication in SLE, although its precise pathogenesis and incidence remain unclear [1, 2]. Here, we report two SLE patients with slowly progressive airflow limitation that showed obvious improvement after inhalation of anticholinergics was started.

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Case report

Case 1

A 42-year-old female complained of slowly progressive exertional dyspnea and showed severe airflow limitation at a follow-up visit to our outpatient clinic in January 2003.

At the age of 20, SLE was diagnosed on the basis of lymphocytopenia, proteinuria (lupus nephritis type V), anti-nuclear autoantibodies, anti-ds DNA antibodies (54 IU/mL) and hypocomplementemia, and corticosteroid treatment was started. At the age of 37, a pulmonary function test had revealed an obstructive abnormality, but without any complaint of dyspnea. Two years later, exertional dyspnea developed and gradually worsened. Although a β_2-agonist partially improved her FEV1 from 1.06 to 1.57 L, her dyspnea was not affected by further treatment with a long- or short-acting β_2-agonist, corticosteroid inhaler and oral theophylline, in addition to oral prednisolone at 10–17 mg daily plus cyclosporine A, azathioprine or mizoribine. At the age of 41, her FEV1 was 0.77 L. Her serum IgE level was 7 IU/mL, and neither IgE specific for house dust mites nor blood eosinophilia was detected.

In January 2003, her FEV1 declined to 0.56 L (Fig. 1a, b). The diffusing capacity was well preserved. A chest X-ray (Fig. 1c) demonstrated no obvious abnormalities in either lung field. Chest CT, taken in both the inspiratory and expiratory states, did not show air-trapping patterns, but it indicated mild thickening of the bronchial walls without bronchiectatic changes (Fig. 1e, f). Although she showed prolonged expiration, there were no episodes suggesting asthma, such as nocturnal attacks of wheeze or cough. She had never smoked. Association of rheumatoid arthritis and/or Sjögren's syndrome was ruled out. Inhalation of oxitropium bromide at a total daily dose of 600 μg was started, and her dyspnea was slightly alleviated in the evening of the first inhalation day. One month later, her dyspnea, initially rated as Hugh-Jones grade II or III, completely disappeared. Three months later, her flow-volume curve and FEV1 were obviously improved (Fig. 1a, b). Other anticholinergics, i.e., flutropium bromide and tiotropium bromide, were tried, and their clinical efficacy on her symptoms was similar to that of oxitropium. The patient said that her dyspnea returned when she forgot the inhalation for even 1 day. She has continued the oxitropium inhalation for the following 3 years and has experienced no respiratory symptoms. A chest X-ray taken during the course of this anticholinergic therapy (Fig. 1d) showed slight elevation of the bilateral diaphragm compared with the X-ray of Fig. 1c, suggesting that there had been mild air-trapping before the inhalation was started.

Case 2

A 66-year-old female was admitted to our hospital in September of 2005 with a complaint of slowly progressive exertional dyspnea.

At the age of 56, a diagnosis of SLE was made based on serositis, thrombocytopenia, lymphocytopenia, proteinuria, anti-ds DNA antibodies (12 IU/mL), antiphospholipid antibodies and hypocomplementemia, and corticosteroid treatment was started. Three years later, exertional dyspnea manifested and gradually worsened. Lung function studies revealed obvious obstructive changes, but the total lung capacity (TLC) and diffusing capacity were relatively preserved (Fig. 2a). She had never smoked. Although a β_2-agonist inhaler partially improved her FEV1 from 0.62 to 0.89 L, that treatment plus a corticosteroid inhaler showed little effect on her dyspnea. Her serum IgE level was 36 IU/mL. Neither IgE specific for house dust mites nor blood eosinophilia was detected.

A respiratory function test on admission showed a severe obstructive pattern, suggesting that airflow limitation was responsible for her slowly progressive symptoms (Fig. 2a, b). Association of rheumatoid arthritis and/or Sjögren syndrome was ruled out. Chest X-rays (Fig. 2c) showed no obvious abnormalities in either lung field except for a dull left-side costophrenic angle due to past splenectomy. A chest CT scan, taken in both the inspiratory and expiratory states, failed to show air-trapping patterns, although mild thickening of the bronchial walls was seen (Fig. 2e). There were no episodes of wheeze or attacks, suggesting that bronchial asthma was unlikely. Based on the clinical course of Case 1, we decided to try inhalation of an anticholinergic in this patient; tiotropium bromide was chosen because of its high affinity for M3 muscarinic receptor. Surprisingly, her dyspnea disappeared on the day of the first inhalation. One week later, her flow volume curve and FEV1 showed great improvement (Fig. 2a, b). Six months later, an airway response to β_2-agonist inhalation was not obvious (before inhaling: FVC 2.04 L, FEV1 0.86 L; after inhaling: FVC 2.09 L, FEV1 1.01 L). She has continued tiotropium inhalation for the following 12 months and has experienced no worsening of her respiratory symptoms. A chest X-ray taken during the course of this anticholinergic treatment (Fig. 2d) showed no changes, although her pulmonary function was greatly improved.

Discussion

Besides SLE, the patients described in this report did not have any other rheumatic diseases, such as Sjogren's syndrome or rheumatoid arthritis, because there were no findings of dry eye and dry mouth, arthritis, rheumatoid factor or anti-Ro/La autoantibodies. The key finding reported here is that both of the SLE patients who had presented with slowly progressive exertional dyspnea and an obstructive ventilatory defect demonstrated obvious improvement soon after inhalation of an anticholinergic was started. The clinical responses of the patients demonstrated that multiple agents belonging to the anticholinergics are effective, supporting the notion that their bronchodilating effects come from blockage of M3 receptors, thereby inducing antagonistic reduction of the vagal cholinergic tone of the airways [3]. Months to years of anticholinergic use successfully maintained the improved condition in both patients. No adverse events were observed. This is the first report of the effect of anticholinergics on the airway obstructive abnormality accompanying SLE.

SLE is a multisystem autoimmune disorder whose exact etiology remains unknown. Pulmonary involvement sometimes occurs in SLE, including acute or chronic interstitial pneumonitis, alveolar hemorrhage and bronchiolitis obliterans organizing pneumonia (BOOP)/cryptogenic organizing pneumonia (COP) [2]. On the other

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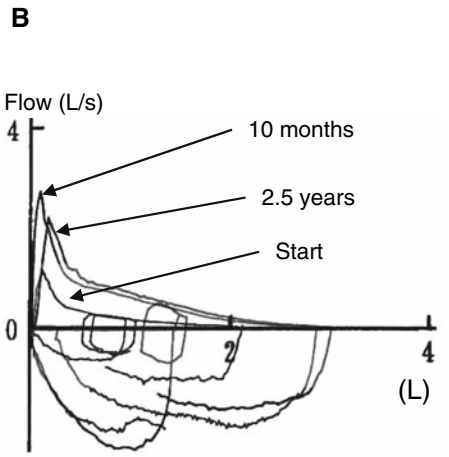
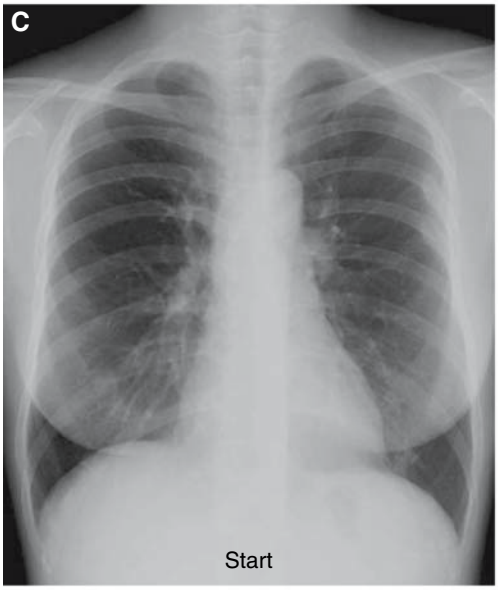
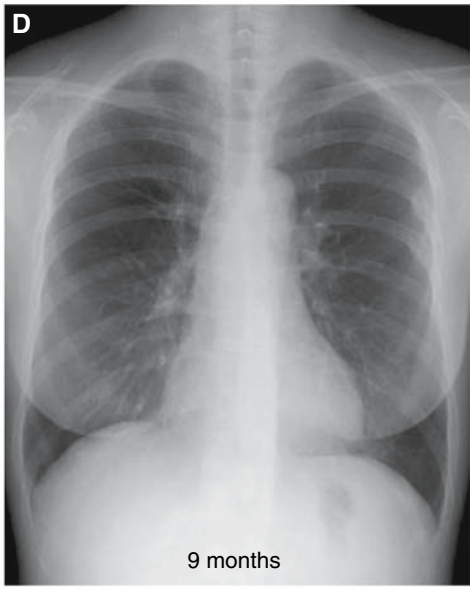
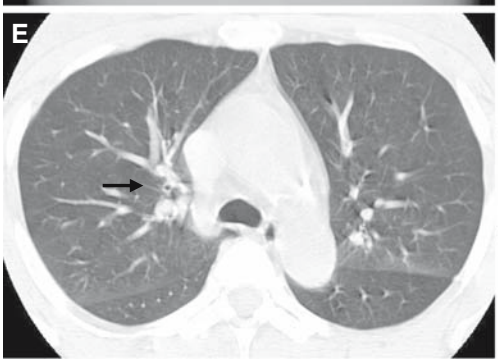
	11mo before	Start	3mo after	10mo after	2.5yr after
VC (L)	2.54	2.26	3.12	3.15	3.23
%VC	94	84	116	117	121
FEV1 (L)	0.77	0.56	1.00	1.04	1.16
FEV1%	30	25	32	33	36
PEFR (L/s)	1.33	1.18	2.10	2.72	2.20
V50 (L/s)	0.27	0.16	0.34	0.37	0.45
V25 (L/s)	0.11	0.09	0.11	0.10	0.13
TLC (L)	4.16	3.87		5.06	4.69
IRV (L)	0.99	0.75		1.34	1.30
TV (L)	0.44	0.45		0.44	0.45
ERV (L)	1.09	0.99		1.37	1.48
RV (L)	1.64	1.68		1.91	1.46
RV/TLC(%)	39.4	43.4		37.7	31.1
DLco	17.9	19.7		16.1	15.7
%DLco	94	104		86	80
DLco/VA	5.38	5.32		4.04	3.59









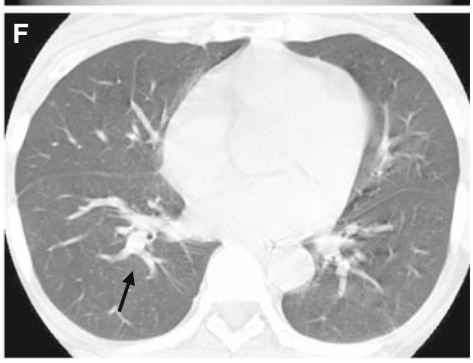


Fig. 1 **a** Results of pulmonary function tests in Case 1. The functional residual capacity was measured by the N_2 dilution method. Diffusion was assessed by the single-breath-holding method. *VC* vital capacity, *FEV1* forced expiratory volume in one second, *PEFR* peak expiratory flow rate, *TLC* total lung capacity, *IRV* inspiratory reserve volume, *TV* tidal volume, *ERV* expiratory reserve volume, *RV* residual volume, *VA* alveolar volume. **b** Flow volume curves just before ("start") and 10 months and 2.5 years after initiation of the anticholinergic inhalation therapy. **c** Chest X-ray taken before the inhalation was started. **d** Chest X-ray taken 9 months after anticholinergics inhalation was introduced. **e**, **f** Chest CT in the inspiratory state. *Arrows* indicate mildly thickened bronchial walls

hand, it is relatively rare for SLE to be accompanied by airflow limitation, and the available pathophysiological information is limited since lung biopsy is often contraindicated due to poor lung function in such patients. A small number of reports, in addition to autopsy studies, suggest that slowly progressive airflow limitation without lung parenchymal shadows may be due to a small-airway disorder called BO [4–6]. Based on the clinical courses of our two patients, both presenting a marked discrepancy between initially silent respiratory symptoms and only slight abnormalities in imaging studies versus severe abnormalities in lung functional tests, we believe that BO is the most accurate diagnosis for these patients. Furthermore, the slight thickening of the bronchial walls observed

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	7 yr before	3 yr before	Start	1 wk after	16 mo after
VC (L)	1.86	1.79	1.97	2.11	2.13
%VC	79	79	89	96	98
FEV1 (L)	0.94	0.60	0.65	0.93	0.99
FEV1%	50	34	33	44	46
PEFR (L/s)	2.45	1.48	1.47	2.47	2.65
V50 (L/s)	0.51	0.19	0.25	0.40	0.40
V25 (L/s)	0.21	0.08	0.07	0.12	0.14
TLC (L)	3.84	3.73	3.69	3.76	3.54
IRV (L)	0.84	0.66	0.70	0.63	0.63
TV (L)	0.58	0.46	0.46	0.68	0.63
ERV (L)	0.44	0.67	0.81	0.80	0.87
RV (L)	1.98	1.94	1.72	1.65	1.41
RV/TLC(%)	51.6	52.0	46.6	43.9	39.8
DLco	13.7		14.1	13.2	12.9
%DLco	84		92	87	85
DLco/VA	5.00		5.24	4.60	4.47

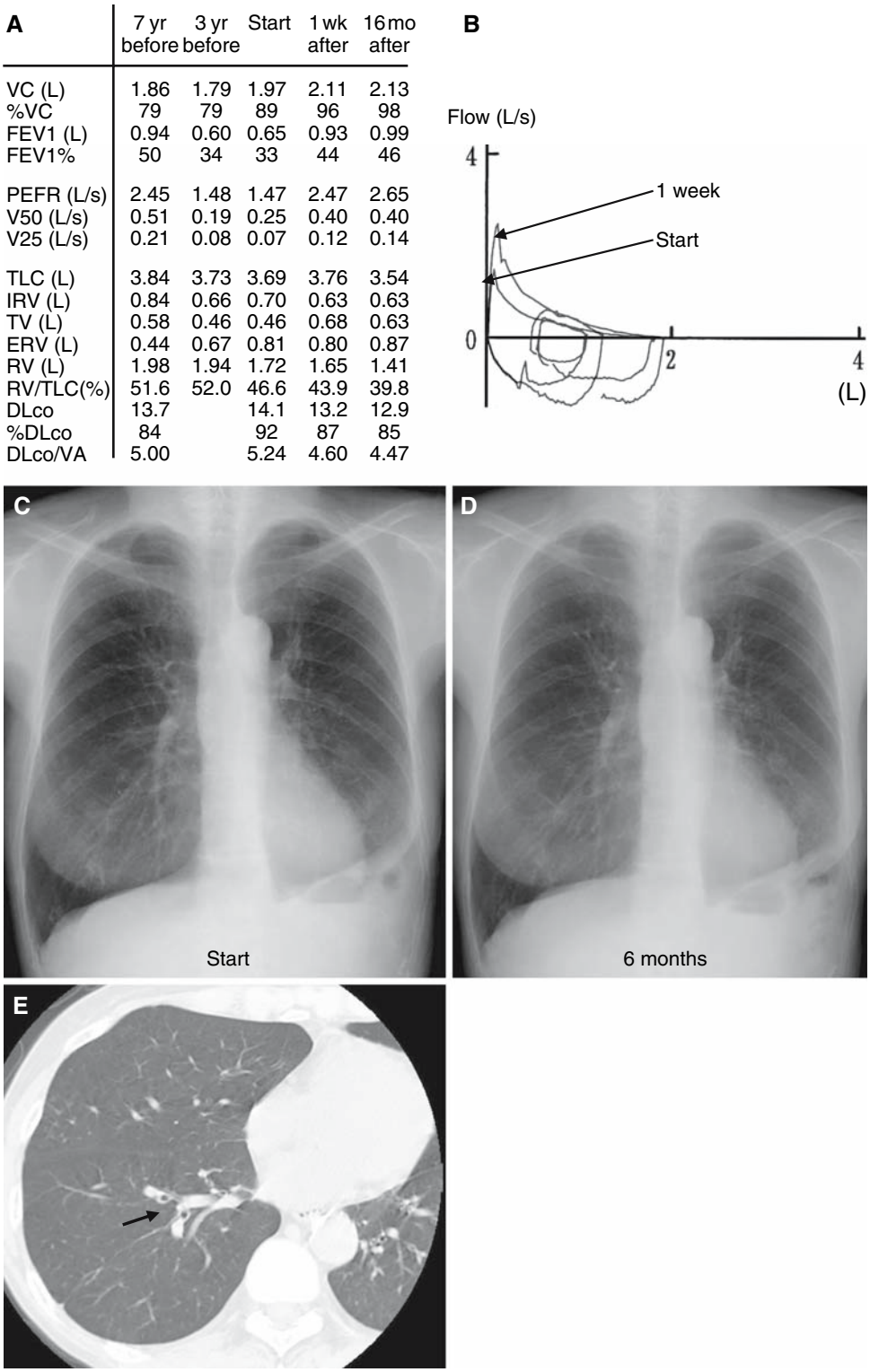

Fig. 2 **a** Results of pulmonary function tests in Case 2. **b** Flow volume curves just before ("start") and 1 week after initiation of the anticholinergic inhalation. **c** Chest X-ray taken before the inhalation was started. **d** Chest X-ray taken 6 months after anticholinergic inhalation was started. **e** Chest CT in the inspiratory state. *Arrow* indicates mildly thickened bronchial walls

in CT images in addition to the rapid response to anticholinergics may suggest involvement of the large airways; this may partly account for the airflow limitation in our patients. In both of our patients the obstructive ventilatory defect responded partially to an inhaled β_2-agonist. At present, however, we do not know whether an asthmatic component was involved, but their clinical courses, lacking recurrent wheeze and nocturnal dyspnea, seem obviously different from that of typical asthma. Neither blood eosinophilia, elevation of serum IgE nor a family history of

asthma was observed. Anti-asthmatic medications were tried but did not relieve dyspnea in either patient.

It is generally thought that BO is not a single disease with a uniform etiology. In addition, pathological study is often impossible in severe cases suggestive of BO. In this regard, BO "syndrome" is often used as the clinical diagnosis of this disorder in the absence of precise pathological information [7]. Collagen vascular diseases such as rheumatoid arthritis and SLE rarely accompany BO syndrome. The clinical presentation was different and specific features were not detected in our two patients. Moreover, in both patients the disease activity of SLE was low, based on the clinical and serological parameters and the SLE disease activity index (SLEDAI). In addition, recent progress in leukemia therapy has revealed that BO more often occurs following bone marrow transplantation, and that development of BO is an important factor that may limit the posttransplantation life expectancy [8, 9]. Indeed, irrespective of the nature of the primary disease, BO often progresses slowly and is highly resistant to systemic immunosuppressive therapy and β_2-agonist bronchodilators, although anecdotal reports mention a few cases that responded to immunosuppressants [6, 10]. Although the usual therapeutic regimen for BO does not include anticholinergics [11], one very recent case report suggested that an anticholinergic, inhaled tiotropium bromide, might be effective in some posttransplantation patients clinically presumed to have BO [12]. Our cases further demonstrate that anticholinergic inhalation may also be effective on autoimmune-based BO accompanying SLE and possibly other collagen diseases. At present we do not have a reasonable explanation for why anticholinergics were so effective in our patients. However, in view of that effectiveness, functional dysregulation of the cholinergic nerve system in the airways may be implicated in the pathogenesis of the airway abnormalities in our patients with SLE. We speculate that autoimmune-related airway damage may be responsible for the excessive activity of the cholinergic nerve system and the mild bronchial wall thickening seen in our patients; further assessment analyzing whether specific antibodies or subsets of lymphocytes are involved in their lung abnormalities is warranted, and, importantly, respiratory function tests revealed a decrease in the residual volume/total lung capacity (RV/TLC) ratio in both patients several months after starting medication. These results suggest that anticholinergic agents may have both early and late effects, and the late and sustained improvement of air-trapping indicates that the anticholinergics may even have affected small airway remodeling and/or the fibrosing process.

Anticholinergic agents are considered highly safe, based on the cumulative experience from extensive use of these drugs in patients with smoking-related chronic obstructive pulmonary diseases [13]. Thus, assessment of the clinical efficacy of inhaled anticholinergics seems warranted in patients with SLE or other autoimmune diseases accompanied by progressive dyspnea and obstructive respiratory abnormalities suggestive of BO.

Acknowledgment The authors thank Dr. Hirokazu Yamada for discussion on this manuscript.

References

1. Orens JB, Martinez FJ, Lynch JP 3rd. Pleuropulmonary manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am. 1994;20:159–93.
2. D'Cruz, D, Khamashta MA, Hughes G. Pulmonary manifestations of systemic lupus erythematosus. In: Wallace DJ, Hahn BH, editors. Duboi's lupus erythematosus. 7th ed. Lippincott Williams & Wilkins; 2007. p. 678–99.
3. Costello RW, Fryer AD. Cholinergic mechanisms in asthma. In: Barnes PJ, Grunstein MM, Leff AR, Woolcock AJ, editors. Asthma. Lippincott-Raven Publishers; 1997. pp. 965–84.
4. Kinney WW, Angelillo VA. Bronchiolitis in systemic lupus erythematosus. Chest. 1982;82:646–9.
5. Katzenstein AL, Myers JL, Prophet WD, Corley LS 3rd, Shin MS. Bronchiolitis obliterans and usual interstitial pneumonia. A comparative clinicopathologic study. Am J Surg Pathol. 1986;10:373–81.
6. Godeau B, Cormier C, Menkes CJ. Bronchiolitis obliterans in systemic lupus erythematosus: beneficial effect of intravenous cyclophosphamide. Ann Rheum Dis. 1991;50:956–8.
7. Boehler A, Estenne M. Post-transplant bronchiolitis obliterans. Eur Respir J. 2003;22:1007–18.
8. Estenne M, Hertz MI. Bronchiolitis obliterans after human lung transplantation. Am J Respir Crit Care Med. 2002;166:440–4.
9. Sharples LD, McNeil K, Stewart S, Wallwork J. Risk factors for bronchiolitis obliterans: a systematic review of recent publications. J Heart Lung Transplant. 2002;21:271–81.
10. Weber F, Prior C, Kowald E, Schmuth M, Sepp N. Cyclophosphamide therapy is effective for bronchiolitis obliterans occurring as a late manifestation of lupus erythematosus. Br J Dermatol. 2000;143:453–5.
11. Reilly JJ Jr. Chronic lung transplant rejection: bronchiolitis obliterans. UpToDate 2006.
12. Matsuyama W, Yamamoto M, Machida K, Oonakahara K, Watanabe M, Higashimoto I, Osame M, Arimura K. A case of bronchiolitis obliterans syndrome successfully treated by Tiotropium bromide (in Japanese). Nihon Kokyuki Gakkai Zasshi. 2006;44:404–9.
13. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Pharmacological treatment: bronchodilators. 2003, NIH pp. 67–71.