Official Case Reports Journal of the Asian Pacific Society of Respirology
Respirology Case Reports
OPEN ACCESS

Coexistence of diffuse panbronchiolitis and asthma: reciprocity of neutrophilic and eosinophilic inflammation

Kiyoshi Takeyama, Yuri Shimizu, Masanobu Ishii, Hiroko Hara, Mitsuko Kondo & Jun Tamaoki

First Department of Medicine, Tokyo Women's Medical University School of Medicine, Tokyo, Japan.

Keywords
Chronic sinusitis, erythromycin, FeNO, macrolide, Th1/Th2.

Correspondence
Kiyoshi Takeyama, MD, First Department of Medicine, Tokyo Women's Medical University School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: takeyama.kiyoshi@twmu.ac.jp

Received: 27 January 2017; Revised: 28 February 2017; Accepted: 7 March 2017; Associate Editor: Arata Azuma.

***Respirology Case Reports*, 5 (3), 2017, e00232**

doi: 10.1002/rcr2.232

Abstract

Diffuse panbronchiolitis (DPB) and asthma are obstructive airway diseases, the former being characterized by Th1-type and the latter by Th2-type airway inflammation. Differential diagnosis is often a problem, but coexistence has rarely been reported. A 76-year-old man with asthma was admitted to our hospital because of one-month history of dyspnoea on exertion with bilateral diffuse granular shadows. He also had a history of chronic sinusitis. Auscultation of the lungs showed coarse crackles and wheezes. Laboratory data revealed an elevated total serum immunoglobulin E and a high titre of cold agglutinin. Bronchoscopic evaluations of the shadows revealed compatible pathological findings in both DPB and asthma. Low-dose macrolide caused a prompt reduction of symptoms, along with improvements in radiographic findings and pulmonary functions, whereas the eosinophilic airway inflammation transiently worsened. When DPB and asthma coexist, the balance of Th1/Th2 immune response may be reciprocally altered by therapeutic intervention.

Introduction

Diffuse panbronchiolitis (DPB) is a chronic inflammatory disease that diffusely involves respiratory bronchioles. Th1-driven inflammatory cells, including CD8+ lymphocytes, neutrophils, and foamy macrophages, play important roles in the pathogenesis of DPB. However, asthma is known typically as a Th2-driven inflammatory disease where eosinophils and mast cells act as central effector cells in inflamed airways. Because typical symptoms including productive cough, wheezing, shortness of breath, and chest tightness are common in both DPB and asthma, the patients with DPB have often been misdiagnosed with asthma. However, coexistence cases in which two different types of immune response, Th1 and Th2, are observed in the airways have rarely been reported. In this study, we present a case of DPB that also showed clinical and pathological features of asthma. In this case, both neutrophilic and eosinophilic inflammation coexisted in the airways, and were reciprocally altered by low-dose macrolide therapy.

Case Report

A 76-year-old man was admitted to our hospital because of one-month history of dyspnoea on exertion, cough, and viscous sputum. He has been diagnosed with asthma since he was 62 years, and has been partially controlled (score 20 in Asthma Control Test) with inhaled corticosteroids/long-acting β_2 agonist (ICS/LABA). When he was 75 years old, he noticed lymphadenopathy, and was diagnosed with follicular lymphoma. He received six courses of rituximab combined with pirarubicin-cyclophosphamide, vincristine and prednisolone (R-THP-COP) therapy, and a complete remission was achieved. After the chemotherapy, he noticed shortness of breath, cough, and viscous sputum. As chest computed tomography (CT) revealed diffuse granular shadows in bilateral lungs, he was referred to our hospital. He had a surgical history of chronic sinusitis at 28 years of age, and had a 30-pack-year history of smoking until the age of 62. Physical examination revealed hypoxia, peripheral capillary oxygen saturation (SpO_2) 92% with a low-grade fever. Auscultation of the lungs showed coarse

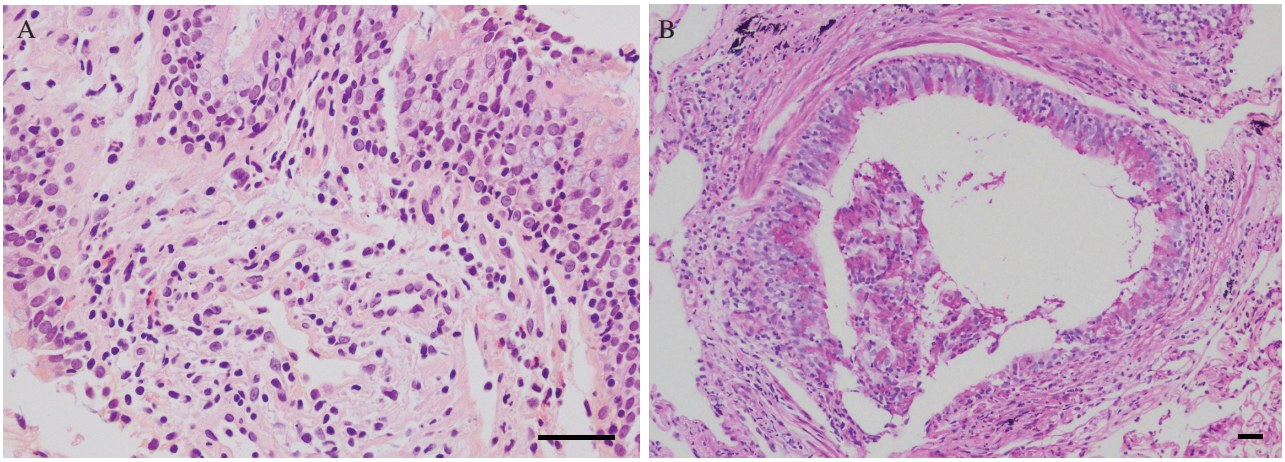

Figure 1. Pathological exhibition in transbronchial lung biopsy. The walls of respiratory bronchioles were thickened by infiltration of lymphocytes, plasma cells, and foamy macrophages (A: haematoxylin and eosin staining, scale bar = 40 μm). In addition, goblet cell hyperplasia with thickness of basement membrane was observed in the airway epithelium (B: periodic acid-Schiff staining, scale bar = 40 μm).

crackles and wheezes in both lung fields. On laboratory findings, white blood cell counts increased to 8670/μL with neutrophilia (72.6%). C-reactive protein level was 7.82 mg/mL. *Pseudomonas aeruginosa* was detected in sputum culture. The level of total immunoglobulin E was 288 IU/mL, and a titre of cold agglutinin was >64. Fibre-optic bronchoscopy was performed to evaluate the shadows; the cellularity of bronchoalveolar lavage fluid (BALF) was increased to 1.91×10^5/mL with increased proportion of both neutrophils (86.4%) and eosinophils (8.2%). Transbronchial lung biopsy revealed mild infiltration of lymphocytes, plasma cells, and foamy macrophages around the respiratory bronchioles, which was compatible with DPB, and goblet cell hyperplasia with thickness of basement membrane, which was compatible with asthma (Fig. 1). As he fulfilled the diagnostic criteria for DPB, we started low-dose macrolide therapy. After erythromycin (400 mg/day) was added to ICS/LABA, his symptoms reduced, along with the improvements in pulmonary function, diffuse granular shadows, and airway clearance determined by saccharin test (Table 1). Conversely, the level of fractional exhaled nitric oxide (FeNO), a biomarker of eosinophilic airway inflammation, increased 2 weeks after the macrolide therapy. The level of FeNO then gradually decreased (Table 1).

Discussion

In this study, we report a patient who was confirmed to have clinical and pathological features of both DPB and asthma. DPB mostly affects East Asian countries, where the patients with DPB have often been misdiagnosed and treated for severe asthma. In Korea, Park et al. reported that five patients with DPB who had been presenting clinical manifestations of severe asthma were well managed with macrolides [1]. Thus, in patients with severe asthma who do not respond to ICS/LABA, DPB should be taken into consideration. In this case, diffuse nodular shadows appeared after R-THP-COP therapy for follicular lymphoma. During the chemotherapy, granulocyte-colony stimulating factor was given to recover from neutropenia, and the resultant increase in neutrophils in the airways might have aggravated DPB.

Coexistence of DPB and asthma has rarely been reported. The characteristics of airway inflammation of the two diseases are contrasting. Asthma is explained typically as a Th2-driven inflammatory disease in which eosinophils play important roles. On the other hand, Th1-driven

Table 1. Effect of macrolide therapy.

	Before	After 2 weeks	After 4 weeks
SpO_2 room air (%)	92	96	97
FVC (L)	2.80	3.10	3.17
FEV_1 (L)	0.92	1.03	1.26
FEV_1/FVC (%)	32.9	33.2	39.8
PEF (L/sec)	2.07	2.88	2.97
DL_{co} (mL/min/mmHg)	49.2	63.9	59.9
CAT score	28	9	6
Saccharin test (min)	50	20	
FeNO (ppb)	22	73	41

CAT, chronic obstructive pulmonary disease assessment test; DL_{CO}, diffusing capacity of the lung carbon monoxide; FEV_1; forced expiratory volume in 1 sec; FVC, forced vital capacity; PEF, peak expiratory flow; SpO_2, peripheral capillary oxygen saturation.

inflammatory cells, neutrophils, play important roles in DPB. In our case, both neutrophilia and eosinophilia were evident in BALF. Moreover, compatible histological findings of both DPB and asthma were simultaneously present, thereby confirming coexistence of the two diseases. In addition, he had a 30-pack-year history of smoking, and the forced vital capacity/forced expiratory volume in 1 sec (FEV_1/FVC) was still less than 0.70 even after treatment with erythromycin and ICS/LABA, suggesting an overlap of chronic obstructive pulmonary disease (COPD) with asthma.

Low-dose macrolide therapy has been shown to produce dramatic improvement in patients with DPB [2]. In this case, erythromycin reduced clinical symptoms, along with the improvements in diffuse granular shadows, pulmonary function test, and saccharin test. These results indicate favourable influences on both obstructive lesions and mucociliary transport in the airways. Interestingly, the level of FeNO increased after the macrolide therapy. It has been reported that treatment with low-dose erythromycin causes a significant increase in the levels of Th2 cytokine, interleukin (IL)-4, IL-5, and IL-13, and a significant decrease in Th1 cytokines, IL-2, and interferon-γ in BALF [3]. Thus, the macrolides could shift the immune systems from Th1 to Th2 pathways, which induce eosinophilic airway inflammation. Indeed, a case report showed that macrolide therapy without steroids induced asthma in a patient with DPB [4]. Another reason for the increase in FeNO may be the reduction in neutrophilic airway inflammation. Several oxidants concomitantly produced by neutrophils are known as scavengers of nitric oxide [5]. Consequently, eosinophilic airway inflammation has transiently worsened after the macrolide therapy.

We have experienced a coexistence case of DPB and asthma. It is interesting that clinical features of either DPB or asthma might become apparent by treatment of neutrophilic airway inflammation with macrolides or eosinophilic airway inflammation with corticosteroid, and vice versa.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

References

1. Park KH, Park HJ, Lee JH, et al. 2012. Single center experience of five diffuse panbronchiolitis patients clinically presenting as severe asthma. J. Korean Med. Sci. 30:823–828.
2. Kudoh S, Uetake T, Hagiwara K, et al. 1987. Clinical effects of low-dose long-term erythromycin chemotherapy on diffuse panbronchiolitis. Nihon Kyobu Shikkan Gakkai Zasshi 25:632–642.
3. Park SJ, Lee YC, Rhee YK, et al. 2004. The effect of long-term treatment with erythromycin on Th1 and Th2 cytokines in diffuse panbronchiolitis. Biochem. Biophys. Res. Commun. 324:114–117.
4. Matsuno O, Ueno K, Hayama Y, et al. 2010. Deterioration of asthma in a patient with diffuse panbronchiolitis (DPB) after macrolide therapy. J. Asthma 47:486–488.
5. Wewel AR, Crusius JA, Gatzemeier U, et al. 2006. Time course of exhaled hydrogen peroxide and nitric oxide during chemotherapy. Eur. Respir. J. 27:1033–1039.