**A CASE OF AUTOIMMUNE PULMONARY ALVEOLAR PROTEINOSIS WITH FLUCTUATING LUNG SHADOWS IN PARALLEL WITH CIGARETTE SMOKE BURDEN**

Ayumu Takahashi, Etsuro Yamaguchi, Toshiyuki Yonezawa, Kenshi Kosaka, Ayako Matsubara, Masaki Nishimura, Hiroyuki Tanaka, Norihito Yokoe, Akihito Kubo

Division of Respiratory Medicine and Allergology, Department of Medicine, Aichi Medical University School of Medicine

**Abstract.** The association between the development of pulmonary alveolar proteinosis (PAP) and dust inhalation has been established; however, the link between PAP and smoking is less clear. A 46-year-old man with mild bronchial asthma and a 52-pack-year smoking history was diagnosed with autoimmune PAP (APAP) based on computed tomography (CT) shadows, pathologic findings of the lung, and a high serum level of anti-granulocyte macrophage colony-stimulating factor (GM-CSF) IgG autoantibody. Smoking was stopped and he was treated three times with unilateral whole lung lavage (WLL). However, his respiratory failure did not improve because of incomplete WLL due to bronchospasm and decreased compliance of the ventilated lung during WLL. A fourth WLL was planned, but was cancelled because his respiratory status and lung shadows on CT scan unexpectedly improved immediately before WLL. During the follow-up period without smoking, the lung shadows resolved almost completely. However, the abnormalities relapsed after he resumed smoking and then modestly improved after changing to cigarettes containing less tar. Serum levels of anti-GM-CSF IgG were not compatible with the lung shadows. These observations in this patient suggested a link between smoking and APAP. Since variable smoking rates in patients with APAP have been reported in epidemiologic studies, a definite conclusion requires precise case-control studies in the future. (*Sarcoidosis Vasc Diffuse Lung Dis* 2017; 34: 257-259)

**Key Words:** autoimmune pulmonary alveolar proteinosis, smoking, autoantibody

**Introduction**

A hallmark feature of autoimmune pulmonary alveolar proteinosis (APAP) is accumulation of excessive amounts of surfactant in the lung. The fundamental mechanism was proven to be production of autoantibodies against granulocyte macrophage colony-stimulating factor (GM-CSF), which is essential for surfactant clearance by maturation and proliferation of alveolar macrophages (AM) (1,2). Smoking and inhalation of dust have been suggested to accelerate the occurrence of APAP (3,4), but precise epidemiologic studies have not been performed. A case of APAP that appeared to be linked to smoking is presented.

**Case Report**

A 46-year-old man with mild bronchial asthma presented with dyspnea and widespread shadows
in the lung. He had a 52-pack-year smoking background. Lung computed tomography (CT) scan revealed diffuse ground glass opacities with peripheral sparing. Bronchoalveolar lavage, transbronchial lung biopsy (Figure 1), and measurement of serum anti-GM-CSF IgG yielded results consistent with APAP.

Since his PaO$_2$ was below 60 mmHg on room air, he was advised to stop smoking 40 cigarettes with high tar content (10 mg) per day and to continue inhalation of medium-dose fluticasone/salmeterol before undergoing three times of unilateral whole lung lavage (WLL). Despite these preparations, the WLL procedures failed or were incomplete because of bronchoconstriction and decreased compliance of the ventilated lung. Because he still needed oxygen inhalation and lung shadows on CT scan improved minimally, a fourth unilateral WLL was planned. One day before the scheduled WLL, he was noted to be stable without the need for oxygen inhalation and lung shadows were markedly improved. Therefore, the fourth WLL was canceled and he was followed-up instead.

Five months after the last WLL, the patient was doing very well and lung shadows improved further (Figure 2). He had continued cessation of cigarette use at that time. However, at 13 months after the last WLL, an apparent relapse was observed on CT scan (Figure 2). He confessed that he had resumed
smoking 20 cigarettes (10 cigarettes with 6 mg of tar and 10 cigarettes with 1 mg of tar) daily after the previous visit. Despite our strong recommendation of abstention from smoking, the best he could do was change the cigarette brand to one with less tar content (20 cigarettes with 1 mg of tar per day). Apparent but modest improvement of lung shadows was observed 2 months later (Figure 2). Shadows of similar density persisted at 5 months after transition to low-tar cigarettes. Serum autoantibody levels transiently decreased following WLL, but these returned to the initial levels at the time of remission and remained constant while the lung shadows changed (Figure 1). On the other hand, serum levels of Krebs von den Lungen-6 (KL-6), a sialylated glycoprotein expressed by alveolar type 2 cells and one of the biomarkers of alveolar proteinosis, well paralleled the changes in the lung shadows (Figure 1). Respiratory function and percutaneous oxygen saturation did not change significantly while the lung shadows fluctuated.

Discussion

In this case, the changes in lung shadows as seen by CT scan seemed to be strongly affected by smoking. Spontaneous resolution and exacerbation were least likely, given the consistent close correlation between disease fluctuation and smoking. In addition, the development of APAP might have been accelerated by heavy smoking. The extent of the CT shadows well correlated with the total amounts of tar indicated on the cigarette packs. The amount of tar in a given cigarette brand is measured by an inhalation machine under the condition stipulated and may not be an accurate indicator of the amount of tar actually inhaled by smokers. Nevertheless, the amounts can be surrogate indicators of not only tar content, but also nicotine and all other constituents in cigarette smoke, as the amounts of constituents in cigarettes are correlated with each other (5). Smoking has been reported to impair the phagocytic activity of AM, which may be relevant to the pathogenesis of APAP (6,7).

In conclusion, the present case supported the idea that smoking may be a risk factor for the development and persistence of APAP in some patients. However, the reported incidence of smoking in patients with APAP at disease onset has been variable (8-10). Well-designed case-control studies are needed to draw a definite conclusion on this issue.

Acknowledgement

Authors would like to thank Ms. Kamiya and Ms. Takagi for their excellent technical assistance.

Funding/Support:
This case report was supported in part by a grant from the Strategic Research Foundation Grant-aided Project for Private Universities from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (MEXT, 2011-2015, S1101027); JSPS KAKENHI Grant Number 26461169; and by a grant from Rare Lung Diseases (pulmonary alveolar proteinosis, congenital interstitial lung disease) from Japan Agency for Medical Research and Development.

References

1. Kitamura T, Tanaka N, Watanabe J, Uchida K, Kanegasaki S, Yamada Y, et al. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 1999; 190: 875-880.
2. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med 2003; 349: 2527-2539.
3. Seymour JF, Presnell JL. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 2002; 166: 215-235.
4. Tanino Y, Misa K, Fukuhara N, Nikaido T, Sato S, Fukuhara A, et al. Increase in autoimmune pulmonary alveolar proteinosis after the 2011 Fukushima disaster. Allergol Int 2016; 65: 326-333.
5. Bodnar JA, Morgan WT, Murphy PA, Ogden MW. Mainstream smoke chemistry analysis of samples from the 2009 US cigarette market. Regul Toxicol Pharmacol 2012; 64: 35-42.
6. Ortega E, Hueso F, Collazos ME, Pedrera MI, Barriga C, Rodriguez A. Phagocytosis of latex beads by alveolar macrophages from mice exposed to cigarette smoke. Comp Immunol Microbiol Infect Dis 1992; 15: 137-142.
7. Hodge S, Hodge G, Ahern J, Jersmann H, Holmes M, Reynolds P. Smoking alters alveolar macrophage recognition and phagocytic ability: implications in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol 2007; 37: 748-755.
8. Inoue Y, Nakata K, Arai T, Tazawa R, Hamano E, Nukiwa T, et al. Epidemiological and clinical features of idiopathic pulmonary alveolar proteinosis in Japan. Respirology 2005; 6 Suppl S: S5-S60.
9. Xu Z, Jing J, Wang H, Xu F, Wang J. Pulmonary alveolar proteinosis in China: a systematic review of 241 cases. Respilation 2009; 14: 761-766.
10. Bonella F. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. Respir Med 2011; 105: 1908-1916.