The First Report of Diffuse Panbronchiolitis in Korea: Five Case Reports
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Diffuse panbronchiolitis (DPB), which is prevalent in Japan, is known to be rare outside Japan. Although a case of diffuse panbronchiolitis in a second generation Korean was reported in Japan in 1986, no case has been reported in Korea. Recently we found 5 cases of diffuse panbronchiolitis in Korea, two histologically proven and three clinically and radiologically suspected. All 5 cases had the typical respiratory symptoms and signs and a history of chronic sinusitis. In three clinically and radiologically suspected cases, high resolution computed tomography showed the typical findings of DPB and other diseases such as pulmonary emphysema, bronchial asthma, chronic bronchitis and bronchiectasis could be ruled out. More cases of DPB are expected to be found in Korea in the near future.

Introduction

Diffuse panbronchiolitis (DPB) is a chronic inflammatory lung disease of unknown etiology which has characteristic clinical, radiological and pathological features (1, 2). Clinically, patients with DPB have chronic cough, exertional dyspnea, sputum and hypoxemia. The chest radiograph is characterized by hyperinflation and small nodular shadows, up to 2 mm in diameter, present throughout both lungs. Recently it was reported that DPB has characteristic high resolution computed tomography (HRCT) findings (3). Histologically it is characterized by thickening of the walls of respiratory bronchioles, with infiltration of lymphocytes, plasma cells, and histiocytes, and extension of these inflammatory changes toward the peribronchiolar tissues. Accumulation of foamy histiocytes with lymphoid cells in the wall of respiratory bronchioles and adjacent alveolar ducts and alveoli was reported to be the typical pathologic features of DPB (4).

In Japan, Homma and co-workers reported 82 histologically confirmed and more than 1,000 clinically suspicious DPB cases (2). But only a few cases have been reported outside Japan (5–7). Although there was a case report of DPB in a second generation Korean male in Japan (8), there has been no reported case of DPB in Korea. Here, we report 5 cases of DPB in Korea, two histologically confirmed and three clinically and radiologically suspected.

Case History

Case 1
A 48-year-old man was admitted to Seoul National University Hospital (SNUH) because of chronic cough and sputum production for 20 years. Prior to this admission he had not been treated because the symptoms were tolerable. Thirteen years ago, he had surgical treatment for paranasal sinusitis. He had no history of smoking. From 2 months before admission, he experienced dyspnea and wheezing and as the cough and dyspnea became aggravated, he visited the hospital.

Physical examination on admission revealed neither cyanosis nor orthopnea. Blood pressure was 100/80 mmHg; pulse rate, 108 beats/min; respiration rate, 28/min; and body temperature, 36.3°C. The chest was symmetric. On auscultation, inspiratory crackles were heard in the both lower lung fields. No other abnormal

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findings were observed.

Laboratory data were as follows: The hemoglobin concentration was 15 g/dl and leukocyte count was 5,000/mm³. Chest radiograph showed hyperinflated lung with diffuse small nodular densities (2–3 mm) and thickened bronchial wall, especially in lower lung fields (Fig. 1). On thin section high-resolution CT (HRCT), nodular and branching linear shadow was seen at 1–3 mm inside the pleural surface which represent bronchiolar lesions within the central portion of the secondary pulmonary lobule. Medium sized bronchi showed thickened walls and mild dilatation. There was diffuse hyperinflation of the lung, especially in both lower lung fields. Paranasal sinus (PNS) view showed pansinusitis. Pulmonary function test (PFT) showed FVC 2.281 (62.3% of the predicted value), FEV₁ 1.371 (50.7% of the predicted value), FEV₁/FVC 60%, FRC 4.271 (124% of the predicted value), RV 3.661 (254% of the predicted value) and TLC 6.581 (120% of the predicted value). Blood gas analysis showed pH 7.47, PaCO₂ 37 mmHg and PaO₂ 70 mmHg on room air. Sputum gram stain showed numerous G(+) cocci, G(−) rods and few G(−) cocci, but no specific pathogen was isolated.

Under the impression of diffuse panbronchiolitis, open lung biopsy was carried out. A specimen (4 x 1 x 1 cm) was taken from the superior segment of right lower lobe. Histologic examination of the lung specimen at low magnification revealed punctate accentuation of bronchioles by the inflammatory cells around the terminal bronchioles and respiratory bronchioles. The peri-bronchiolar infiltrations consisted mainly of lymphocytes and plasma cells. Small follicular collections of lymphocytes were seen around the larger bronchioles but they were not associated with germinal center formation. The bronchiolar epithelial cells were intact but their lumina contained mucus, some denuded epithelial cells and neutrophils. Foamy histiocytes were scattered at the interstitium around the respiratory bronchioles and adjacent alveolar septa. Distal alveolar spaces were widely open or sometimes, hyperinflated but without any inflammatory change (Fig. 2).

Based on the histologic findings the patient was treated with erythromycin (250 mg b.i.d.). Eight months after treatment, his symptoms improved and chest X-ray also showed slight improvement. His PFT revealed remarkable changes, that is, FVC 3.401 (92.6% of the predicted value) and FEV₁ 2.091 (77.1% of the predicted value).

Case 2

A 27-year-old non-smoking man was admitted to SNUH because of worsening cough, sputum production and dyspnea. He had been well until 7 years prior to this admission when he noticed cough and whitish sputum. Four years prior to this admission dyspnea on exertion appeared in addition to cough and sputum, so he visited the outpatient clinic and was diagnosed to have bronchiectasis. His symptoms did not improve despite the treatment. Two years before admission, he had been treated with antituberculosis drugs for 6 months under the clinical impression of pulmonary tuberculosis.

Physical examination on admission showed fine inspiratory crackles, expiratory rhonchi and intermittent wheezing in both lower lung fields on auscultation. Chest radiograph showed hyperinflation and diffuse nodular and linear shadow of 2–4 mm in diameter, especially in the lower lung fields. The thickened bronchial wall with...
tram-line shadows in both lower lung fields suggested bronchiectasis (Fig. 3). On HRCT, there were diffuse small nodular lesions which frequently showed eccentric radiolucency of about 1 mm in diameter, suggesting patent terminal or respiratory bronchiole within the center of the secondary lobule. There was thickening and dilatation of the medium sized bronchi. Hyperinflation was evident especially in the peripheral lung field where bronchiolar lesions are more prominent. PNS view revealed chronic pansinusitis. The leukocyte count was 10,300/mm³ with a left shift and the hemoglobin concentration was 15.1 g/dL. Arterial blood gas analysis breathing room air revealed PaO₂ of 77 mmHg; PaCO₂ of 39 mmHg; and pH 7.38. PFT showed FVC of 3.14 L (75.1% of the predicted value); FEV₁ 2.04 L (59.5% of the predicted value); and the specific diffusing capacity was 5.29 ml/min/mmHg (92.5% of the predicted value).

Under the impression of diffuse panbronchiolitis open lung biopsy was done. A specimen (1.5 x 1.0 x 0.4 cm) was taken from the anterior segment of the right upper lobe. Microscopic examination of the lung revealed peri-bronchiolar and alveolar inflammation. The terminal bronchioles and respiratory bronchioles showed intact epithelial lining cells but there was associated peri-bronchiolar lymphocytic infiltration and fibrotic change. The alveolar septa near the respiratory bronchioles showed focal and patchy collections of foamy histiocytes. In addition to the bronchiolar lesions, the distal alveolar spaces also showed patchy collections of neutrophils and alveolar destruction (Fig. 4).

At first prednisolone (60 mg/day) was started with only slight improvement of symptoms, and the symptoms persisted. Therefore, erythromycin (250 mg t.i.d.) was used after tapering prednisolone. Six months after treatment with erythromycin, his symptoms improved slightly and follow-up HRCT also showed some improvement.

Case 3
A 59-year-old male non-smoker was admitted to SNUH because of wheezing and dyspnea which had persisted for 3 years. He was said to have had measles during his childhood. Since the age of 20, he had suffered from productive sputum which was sometimes bloody.

Physical examination on admission revealed inspiratory crackles on the both lower lung fields. Chest radiograph revealed severely hyperinflated lung, showing diffuse relatively fuzzy margiated nodular and linear shadows especially in lower lung fields. Bronchial wall thickening and dilatation was evident in lower lungs (Fig. 5). HRCT of the chest showed centrilobular nodular and branching bronchiolar lesions associated with tubular bronchiectasis of medium and small sized bronchi (Fig. 6). PNS view revealed chronic pansinusitis. The leukocyte count was 11,100/mm³ with a left shift and the hemoglobin concentration was 15.3 g/dL. Arterial blood gas analysis breathing room air revealed PaO₂ 58 mmHg; PaCO₂ 43 mmHg; and pH, 7.45. PFT showed FVC 2.04 L (57.1% of the predicted value) and FEV₁ 0.72 L (28.9% of the predicted value). For further evaluation he visited Kyoto University in Japan where he was confirmed to have DPB, and has been treated.

Case 4
A 51-year-old woman transferred to SNUH under the impression of miliary tuberculosis. Since 20 years prior
to this admission, she had suffered from dyspnea. She had no history of smoking. Four months before admission, cough and sputum production became aggravated.

Physical examination on admission revealed inspiratory crackles on both lower lung fields. Chest radiograph showed hyperinflation and diffuse nodular shadow with thickened bronchial wall especially in lower lung fields (Fig. 7). HRCT showed branching linear structure as well as small nodular lesions suggesting bronchiolar lesions. Thickening of medium sized bronchial wall was also seen. Associated pneumothorax, because of transbronchial lung biopsy, was noted (Fig. 8). The leukocyte count was 9,900/mm³ and hemoglobin concentration was 12.5 g/dl. Arterial blood gas analysis breathing room air revealed PaO₂ 68 mmHg; PaCO₂ 43 mmHg; and pH 7.47. PFT showed FVC 1.14 l (48.7% of the predicted value); FEV₁ 0.74 l (35.9% of the predicted value). Sputum smear for acid-fast bacilli was negative three times.

Under the impression of DPB, transbronchial lung biopsy was performed, but the specimen was inadequate for evaluation. Based on the clinical diagnosis of DPB, the patient was treated with erythromycin (250 mg b.i.d.). Two months after treatment symptoms and chest radiographic findings improved slightly.

**Case 5**

A 57-year-old female patient was admitted because of worsening cough, sputum production and dyspnea. Seven
years prior to admission she had dyspnea and was diagnosed to have bronchial asthma at a local clinic. Her dyspnea had waxed and waned since that time. Five months prior to this admission, cough and purulent sputum production became aggravated. She had had Caldwell-Luc operation because of chronic sinusitis 10 years before admission, and she had no history of smoking.

Physical examination on admission revealed coarse breath sound and inspiratory crackles on both lower lung fields on auscultation. Inspiratory wheezing was also heard in both upper lung fields. Chest radiograph showed hyperinflation, nodular lesions and bronchial wall thickening predominantly in lower lung fields (Fig. 9). Under the impression of DPB, HRCT was done, which showed nodular and linear shadows predominantly at the peripheral lung fields. These lesions frequently showed adjacent (1 mm size) round radiolucency indicating patent bronchioles (Fig. 10). Arterial blood gas analysis breathing room air revealed PaO₂ 56 mmHg; PaCO₂ 38 mmHg; and pH 7.44. RA factor was positive at 1:320 dilution, and cold agglutinin was also positive at 1:64 dilution.

PFT showed FVC 1.41 l (60.8% of the predicted value); FEV₁ 1.11 l (56.1% of the predicted value); and RV 2.58 l (169.7% of the predicted value).

Based on the clinical diagnosis of DPB, medical treatment with erythromycin (250 mg b.i.d.) was started. Six months after treatment she felt no respiratory symptoms, and physical examination of the chest showed no crackle. PFT revealed marked improvement, that is, FVC 2.41 l (97.6% of the predicted value), and FEV₁ 2.03 l (106.3% of the predicted value).

Discussion

Since Yamanaka et al (1) described a chronic obstructive pulmonary disease distinguished from bronchial asthma, chronic bronchitis, chronic pulmonary emphysema, bronchiectasis, or alveolitis, and termed it as DPB, many cases have been reported in Japan. A nation-wide survey in Japan from 1978 to 1980 revealed more than 1,000 clinically suspected DPB cases (2). But outside Japan only a few cases were reported in China, Italy (6) and North America (7). The reason why DPB is prevalent only in Japan is not known. But a recent study on HLA typing indicated that HLA Bw54, of which 14.1% of Japanese have, might be a factor (9). Recent studies on HLA antigens in DPB patients disclosed that HLA-Bw54 was found most frequently in DPB cases (68.4%,...
relative risk 16.8) compared with controls (11.4%) (10). Because HLA-Bw54 is known to be specific for Mongolians (9) and the frequency of HLA-Bw54 of Korean people was known to be about 10.6% (11), there is a possibility that some cases of DPB might be found in Korea.

The five cases described here have the typical clinical findings according to Homma's definition (12). Chronic cough, sputum and dyspnea with crackles and rhonchi on auscultation were noted. And typical chest X-ray findings of diffusely disseminated fine nodular shadows led us to suspect DPB. The history of chronic sinusitis which all five cases had was also helpful. But HLA typing was not available in all cases.

The histopathologic characteristics of DPB are described to be thickening of the wall of the respiratory bronchiole with infiltration of lymphocytes, plasma cells and histiocytes, and extension of these inflammatory changes towards the peribronchiolar area (2). Collection of foamy histiocytes in alveolar septa and alveoli is described to be one of the important histologic differential points (4).

The first case is histologically typical of DPB, but the second case showed neutrophilic alveolar exudates and alveolar destruction, which are features contrary to DPB. However, the inflammatory lesion in the respiratory bronchioles and collections of foamy histiocytes are unique pathologic changes of DPB and therefore may be DPB. Needless to say, the histologic examination of a small biopsy specimen never represents the morphology of the whole lung lesion; clinical and histological follow-up studies will likely clarify the pulmonary lesion of the second case.

Roughly one-half of the clinically defined cases of DPB showed histologically different lesions from the classical DPB among the cases of Kyoto University (Kitaichi M, personal communication, 1990). Therefore, the present three clinically and radiologically suspected cases might require histological confirmation. Homma et al (2) originally described the plain radiographic findings of DPB to be diffusely disseminated fine nodular shadows, mainly in the lower lung fields with hyperinflation of the lungs. Further description includes a small branching linear shadow which indicates bronchiolar shadows; sub-pleural sparing of nodular shadow, tram-lines and ring shadows which means small and medium sized bronchial shadow (13).

HRCT findings of DPB include: 1) small branching linear opacities derived from bronchioles, 2) small rounded opacities frequently at the terminal portion of the linear opacities, 3) wall thickening and dilatation of medium-sized bronchi, 4) inequality of lung density (hypolucent sub pleural lung). Akira et al (3) classified HRCT findings of DPB into four types reflecting the clinical stages and pathologic process: small nodules around the end of bronchovascular branching (type I), small nodules in the centrilobular area connected with small branching linear opacities (type II), nodules accompanied by ring-shaped or small ductal opacities connected to the proximal bronchovascular bundle (type III), large cystic opacities accompanied by dilated proximal bronchi (type IV). In the present cases, high resolution CT's were very helpful in determining the diagnosis, especially in the three cases in which a histological confirmation...
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was not obtained.

As long-term treatment with erythromycin has been known to be beneficial in the treatment of DPB with few side effects (14), we administered low-dose erythromycin to all of the present patients. Fortunately, most of the patients showed subjective and objective improvement, and to date no progression of disease has been noted. Finally, as DPB has only recently been introduced to Korean pulmonologists, it is expected that many cases of DPB will be reported in Korea in the near future.

References