Diffuse Panbronchiolitis, the First Case Reports in Thailand

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Abstract

Diffuse panbronchiolitis (DPB) is an important cause of progressive obstructive lung or chronic suppurative lung disease in the Far East (Japan, China and Korea). It is a distinctive sino-bronchial syndrome with typical radiological and histologic features. We have identified three patients who have typical clinical manifestation and pathological confirmation. DPB should be suspected in patients who have clinical manifestations of chronic cough, productive sputum and shortness of breath. The chest radiograph often shows diffuse nodular shadows on a background of hyperinflated lungs. High resolution computed tomographic (HRCT) can guide the diagnosis and differentiate from other diseases. Finally, the most important issue of DPB is the treatment. Chronic treatment with low-dose erythromycin can improve the survival of patients.

Key word : Diffuse Panbronchiolitis, Bronchiectasis

Diffuse panbronchiolitis (DPB) was first described in Japan nearly three decades ago as a new clinicopatological entity. The histological features are chronic inflammation, localized predominantly in the small airways, with infiltration of mononuclear and plasma cells leading to chronic airway obstruction(1). A large number of neutrophils and activated T lymphocytes are present in the distal airspaces(2). These lesions diffusely affect both lungs and often extend to the proximal bronchioles, leading to secondary bronchiectasis. However, the lesions are not found in the alveolar areas away from the centrilobular lesions(3). Recently, soluble adhesion molecules especially selectins have been found elevated in DPB patients, and may be regulated by cytokines that are produced in the lungs(4).

Clinical features of DPB are chronic cough with mucopurulent sputum, shortness of breath, coarse crackles and wheezing on lung auscultation.

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Past history often reveals chronic sinusitis. The chest radiograph typically shows hyperinflation and diffuse nodular shadowing predominantly in the lower lung fields[3,5]. High resolution computed tomographic (HRCT) scanning is characteristic[6]. In addition, abnormalities in lung function tests are obstructive and/or restrictive pattern which resist bronchodilator therapy[7].

The natural history of DPB is progressive respiratory failure and had a poor prognosis until the introduction of prolonged treatment with macrolide antibiotics[8]. Corticosteroids, usually successfully suppress the inflammation in many diseases, had been empirically prescribed to DPB patients without success in decreasing morbidity and mortality[3].

DPB is not a rare disease in Japan and has been reported almost exclusively in Asians, which included Japan, Korea, Taiwan and China[9,10]. In this report, we describe three patients who have clinical and histologic confirmation of DPB. This condition must be considered in the differential diagnosis of bronchiectasis and chronic airway limitation diseases because the therapy now increases the survival rate[11].

METHOD

Study population

Between 1997and 1998, three patients were diagnosed as DPB at the Pramongkutklao Hospital, Thailand. The diagnosis was based on the clinical, physiologic, radiographic and pathologic diagnostic criteria established by Homma and Yamanaka[11]. The diagnostic criteria for DPB are as follows.

1. Symptoms: chronic cough, sputum and shortness of breath on exertion.

2. Signs: coarse crackles, rhonchi or wheezes on auscultation of the chest.

3. Chest radiographic findings: bilateral small nodular shadows, mainly in the lower lung fields with often hyperinflation of the lungs.

4. Lung function test and arterial blood gas analysis: FEV1 < 70 per cent and PaO_2 < 80 mm Hg.

5. Elevated cold-agglutinin titer.

6. Past history or coexistence of chronic parasinusitis.

7. Histology: show thickness of the respiratory bronchiole wall with infiltration of lymphocytes, plasma cells and foamy histiocytes expanded into the peribronchiolar area. DPB also included patients with bronchiectasis considered to be in different stages of DPB.

Recently, HRCT was introduced to make the diagnosis of DPB and the appearance is characteristic[6]. Typical abnormalities are 1-3 mm centrilobular nodules, branching linear areas of attenuation and hypoattenuation in the peripheral lung as a result of air trapping. Varicose and cylindrical bronchiectasis can be observed in the more advanced stage.

Table 1. Clinical and demographic features.

Case	Age	Sex	Race	Presenting Complaint C S D WL	Preceding Chronic Sinusitis	Illness duration (yr)*	Smoking History	Physical exam.			Treatment and outcome
								Crackle	Wheezes	Clubbing	
1	63	F	Chinese Thai	++++	-	10	NS	+	+	-	Alive (7 months on erythromycin)
2	60	F	Thai	++++	+	8	NS	+	+	-	Alive (5 months on erythromycin)
3	68	M		+++-	+	5	NS	+	-	-	Alive (2 months on erythromycin)

Definition of abbreviations :
F = Female; M = Male; C = cough; S = sputum; D = dyspnea; WL = weight loss; NS = never smoker
* Based on productive cough and / or dyspnea prior to diagnosis

The clinical and demographic features of the patients are shown in Table 1. All three patients had open or fiber-optic bronchoscope lung biopsies to confirm the diagnosis. The radiographic (Fig. 1 and 2) and pathological features (Fig. 3) are summarized in Table 2.

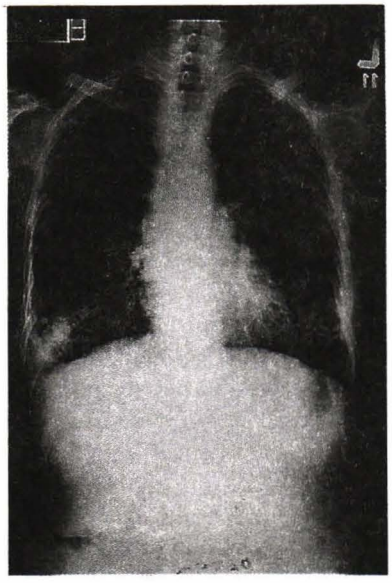

Fig. 1. Chest radiograph on presentation of case 1; showing diffuse reticulonodular shadowing, hyperinflation and cystic opacities in both lower lungs. There is a fungal ball at the right lower lobe.

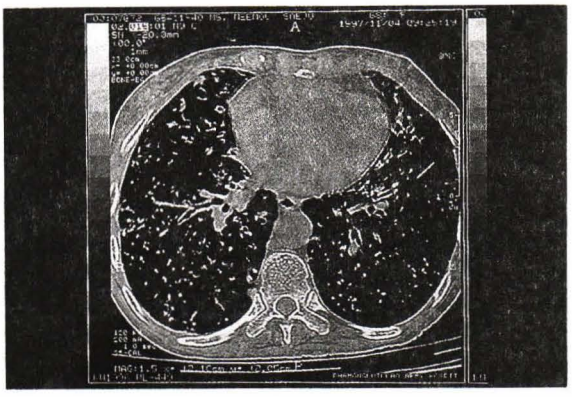

Fig. 2. High resolution computed tomographic of case 1; showing diffuse centrilobular nodules and brochiectatic changes in both lungs.

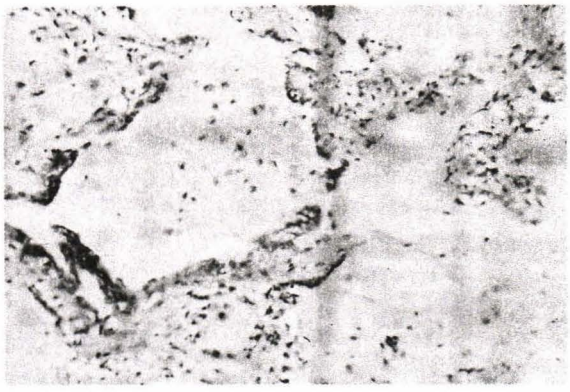

Fig. 3. Pathological features of case 1; showing bronchiolocentric infiltration of lymphocytes, plasma cells and foamy macrophages.

Table 2. Radiographic and pathologic features.

Case	Chest radiograph	HRCT	Pathology
1	Diffuse reticulonodular shadowing, hyperinflation and cystic opacities both lower lungs	Diffuse centrilobular nodules and brochiectatic changed both lower lungs. There is a fungal ball at right lobe	Bronchiolocentric infiltration of lymphocytes, plasma cells and foamy macrophages
2	Diffuse small nodular shadowing and hyperinflated lung	Centrilobular nodules; Dilated and thickened bronchioles	Same
3	Diffuse small nodular shadowing and hyperinflated lung	Centrilobular nodules and air trapping; suggestive small airway disease	Same

Case 1

A 63-year-old woman presented with a history of chronic productive cough, purulent sputum and shortness of breath for 10 years. She had been diagnosed as having asthma since then and the treatments never succeeded to relieve her symptoms. Her medication included bronchodilators and long-term oral prednisolone. She developed respiratory failure and needed ventilator support one time. The patient was a non-smoker. Physical examination revealed marked dyspnea, diffuse coarse crackles and expiratory wheezes. Sputum cultures initially demonstrated a growth of *Haemophilus influenzae*, but on follow-up later, cultures revealed *Pseudomonas aeruginosa*. Pulmonary function test revealed a moderate airflow limitation (FEV_1 56% of predicted) combined with restrictive pattern and air trapping (RV / TLC 55%). Arterial hypoxemia was present. The CXR showed bilateral reticulonodular and small cystic shadowing in both lungs. Her HRCT scan indicated diffuse centrilobular nodules with dilated bronchioles, cystic and tramline shadowing. An open lung biopsy was performed and the pathological report was bronchiolocentric infiltration of lymphocytes, plasma cells and foamy macrophages. The patient has reported subjective improvement since the initiation of daily low-dose erythromycin therapy.

Case 2

A 60-year-old woman who had a 10-year history diagnosed as sinusitis and allergic rhinitis. She developed chronic cough symptoms which produced a moderate amount of purulent sputum and progressive shortness of breath for the last 8 years. She had never smoked a cigarette. Physical examination revealed diffuse crackles, wheezes and had no clubbing of fingers. Pulmonary function test showed severe airflow limitation and an arterial blood gas analysis revealed hypoxemia. A sputum culture showed *Pseudomonas sp.* The chest radiograph demonstrated diffuse bilateral nodular infiltration with lung hyperinflation. The HRCT showed diffuse centrilobular nodules and bronchiectatic change in both lungs. Transbronchial lung biopsies were done and revealed DPB. The patient was treated with low-dose erythromycin which successfully improved her cough symptoms.

Case 3

A 68-year-old male retired officer presented with a 5-year history of chronic cough and progressive dyspnea. He was diagnosed as having pulmonary tuberculosis 5 years ago and treated for a 6-month period without improving his symptoms. In the previous two years, his cough had become more persistent and increasingly productive of yellow sputum and the diagnosis was parasinusitis. Over the same period he had been aware of shortness of breath during walking or exercise. He was a lifelong non-smoker. On examination, he appeared thin and had no clubbing of the fingers. The chest examination revealed hyperinflated lungs and minimal coarse crackles of both lower lungs. Abdominal examination was normal. Complete blood count and other blood chemistries were normal. His chest radiograph showed diffuse small nodules and lung hyperinflation, which had not changed from the previous four years. HRCT showed centrilobular interstitial thickening of both lungs with tree-in-bud sign. Mosaic perfusion was also noted in the expiratory scan. His lung function test showed a moderate degree of obstructive lung disease (FEV_1 58% of predicted) which did not respond to bronchodilators. Transbronchial lung biopsies were done and revealed the characteristics of DPB.

DISCUSSION

DPB is a cause of chronic suppurative lung disease that has been reported mostly from Japan, Korea, Taiwan and China[9,10]. Only twelve patients with this disease have been described from North America and Europe[12]. We have recently identified three Thai patients who met the diagnostic criteria for DPB. Tissue biopsies were performed in these patients and showed the typical characteristics for the disease.

The age of patients with DPB ranged from 20 to 70 years old[11]. However, the peak incidence happens between the fourth and seventh decades of life and the mean age at presentation is 50 years[1]. The patients is this report were between 60 and 68 years old. Chronic sinusitis was found in two of our patients compared with 75 per cent of Japanese patients. All of our patients presented with chronic cough, purulent sputum and shortness of breath. The illness duration ranged from 5 to 10 years. The previous diagnoses were asthma, pansinusitis and pulmonary tuberculosis. Chest examination revealed coarse crackles and wheezes of both lower lungs

Lung function test typically shows an obstructive defect and hypoxia is commonly found

(13). All three patients had abnormal tests which revealed moderate and severe obstructive airway diseases. One patient had combination with restrictive pattern. The chest roentgenogram of DPB is characterized by diffuse small nodular shadows on a background of hyperinflated or normal-sized lungs. The HRCT findings may show centrilobular nodules, branched linear areas of attenuation and decreased lung attenuation in peripheral areas due to air trapping. The HRCT has been found to correlate well with pathological findings(6). These abnormalities were demonstrated in all three of our patients.

The histological features characteristic of DPB are thickening of the respiratory bronchiole walls with infiltration of lymphocytes, plasma cells and foamy macrophages. The lumen of affected bronchioles are filled with acute inflammation cells and mucus. These lesions diffusely affect both lungs and often extend to the more proximal airways, leading to secondary bronchiectasis(3,13). In countries where the prevalence of DPB is high, tissue diagnosis is usually unnecessary. In this report open lung biopsy was performed on one patient while two other patients had transbronchial lung biopsies through a fiber-optic bronchoscope. Pathological reports of our three patients confirmed the diagnosis.

Diffuse panbronchiolitis is markedly different from other chronic suppurative lung diseases because it can be treated with low-dose erythromycin(9,13). The effectiveness of erythromycin and other macrolide drugs in DPB is due to their anti-inflammation rather than antimicrobial effect(3,14). Interleukin-8 (IL-8). which is released by monocytes, macrophages, fibroblast and epithelium cell, is a potent neutrophil chemoattractant and activating factor. The level is increased in bronchoalveolar fluids from patients with DPB and can be inhibited by macrolide drugs(15). The other mechanism of macrolide antibiotics is reduced mucus secretion, so that the drug can decrease sputum production(16).

The natural history of DPB was miserable and included the development of diffuse bronchiectasis, cor pulmonale and progressive respiratory failure. Five year survival of untreated cases was approximately 50 per cent(13). Nevertheless, erythromycin can improve clinical symptoms which include dyspnea, productive cough and chest X-ray manifestations(8). HRCT study also showed improvement of nodular shadowing, the amount of mucus plugging and the extent of airway thickening after erythromycin therapy(17). More recently, Kudoh et al have reported the improvement of survival of DPB patients treated with low-dose erythromycin. They pointed out that effectiveness of erythromycin therapy would be poor in advanced cases of DPB(11). All patients in this report were treated with erythromycin at a dose of 500 mg daily. Their symptoms and signs improved dramatically after two months of therapy. However, lung function tests and chest radiographs were not changed significantly after the treatment.

In conclusion, we reported three cases of DPB who had typically clinical manifestations and pathological confirmations. DPB should be suspected in adult patients who have clinical manifestations of chronic cough, productive sputum and shortness of breath. The chest radiograph often shows diffuse nodular shadows on a background of hyperinflated lungs. HRCT can guide the diagnosis and differentiate from other diseases. Finally, the most important issue of DPB is the treatment. Chronic treatment with low-dose erythromycin can improve the survival of patients. So it is crucial to recognize the disease before starting the appropriate therapy.

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REFERENCES

1. Homma H, Yamanaka A, Tanimoto S, et al. Diffuse panbronchiolitis: a disease of the transitional zone of the lung. Chest 1983; 83: 63-9.
2. Ichikawa Y, Ninomiya H, Koga H, et al. Erythromycin reduced neutrophils and neutrophil-derived elastolytic-like activity in the lower respiratory tract of bronchiolitis patients. Am Rev Respir Dis 1992; 146: 196-203.
3. Koyama H, Geddes DM. Erythromycin and diffuse panbronchiolitis. Thorax 1997; 52: 915-8.
4. Mukae H, Kadota J, Ashitani J, et al. Elevated levels of soluble adhesion molecules in serum of patients with diffuse panbronchiolitis. Chest 1997; 112: 1615-20.
5. Schwarz MI. ACCP-seek board review question of the month. Chest 1998; 113: 1123-4.
6. Nishimura K, Kitaichi M, Izumi T, Itoh H. Diffuse panbronchiolitis: correlation of high resolution CT and pathological findings. Radiology 1992; 184: 779-85.
7. Koyama H, Nishimura K, Mio T, Ikeda A, Sugiura N, Izumi T. Bronchial responsiveness and acute bronchodilator response in chronic obstructive pulmonary disease and diffuse panbronchiolitis. Thorax 1994; 49: 540-4.
8. Nagai H, Shishido R, Yoneda R, Yamaguchi E, Tamura A, Kurashima A. Long-term low dose administration of erythromycin to patients with diffuse panbronchiolitis. Respiration 1991; 58: 145-9.
9. Izumi T. Diffuse panbronchiolitis. Chest 1991; 100: 596-7.
10. Tsang KWT, Lam W, Ip M. Latter to the editor: Diffuse panbronchiolitis in the United States. Am J Respir Crit Care Med 1997; 155: 2114.
11. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. Am J Respir Crit Care Med 1998, 157: 1829-32.
12. Fitzgerald JA, King TE, Lynch DA, Tuder RM, Schwarz MI. Diffuse panbronchiolitis in the United States. Am J Respir Crit Care Med 1996; 154: 479-503.
13. Sugiyama Y. Diffuse panbronchiolitis. Clin Chest Med 1993; 14: 765-72.
14. Yangihara K, Tomono K, Sawai T, et al. Effect of Clarithromycin on lymphocytes in chronic respiratory Pseudomanas aeruginosa infection. Am J Respir Crit Care Med 1997; 155: 337-42.
15. Takizama H, Desaki M, Ohtoshi T, et al. Erythromycin modulates IL-8 expression in normal and inflamed human bronchial epithelial cells. Am J Respir Crit Care Med 1997; 156: 266-71.
16. Rubin BK, Druce H, Ramirez, OE, Palmer R. Effect of Clarithromycin on nasal mucus properties in healthy subjects and in patients with purulent rhinitis. Am J Respir Crit Care Med 1997; 155: 2018-23.
17. Ichikawa Y, Hotta M, Sumita S, et al. Reversible airway lesions in diffuse panbronchiolitis. Detection by high-resolution computed tomography. Chest 1995; 107: 120-5.

Diffuse panbronchiolitis ในประเทศไทย: รายงานผู้ป่วย 3 ราย

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รายงานผู้ป่วยโรค Diffuse panbronchiolitis ในผู้ป่วยชาวไทย 3 ราย ผู้ป่วยมีอาการไอมีเสมหะเรื้อรัง ร่วมกับอาการหอบเหนื่อยมาหลายปี ภาพรังสีทรวงอกมีลักษณะ Diffuse interstitial shadowing และ hyperinflated lungs ผู้ป่วยทุกรายได้รับการทำ Lung biopsy ซึ่งมีลักษณะทางพยาธิวิทยาที่เข้าได้กับโรคนี้ แพทย์ผู้ดูแลรักษาผู้ป่วยควรคำนึงถึงโรคนี้ เพื่อให้การรักษาได้ถูกต้อง

คำสำคัญ : แพนบรองคิโอไลติสชนิดแพร่กระจาย, หลอดลมพอง

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