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Clinical profiles of 12 Chinese patients with diffuse panbronchiolitis.

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Abstract. *Background:* Diffuse panbronchiolitis (DPB) is an uncommon idiopathic inflammatory disease, characterized by chronic sinusitis, respiratory bronchiolitis and progressive airway obstruction. Without correct diagnosis and treatment, DPB may progress to bronchiectasis, respiratory failure and even death. *Objective:* To help other clinicians deal with DPB. *Methods:* Twelve Chinese patients (six women; mean (SD) age 50(14.7) years) who were diagnosed as DPB were assessed retrospectively for clinical, radiological, lung function, microbiological, and other "characteristic" laboratory parameters. *Results:* Most patients presented with chronic cough, copious purulent sputum production, and exertional dyspnoea, end-inspiratory crackles, and a history of sinusitis. Unlike DPB cases from Japan, cold agglutination test in 11 out of 12 patients were negative, and the CD4/CD8 lymphocyte ratio in all patients were normal or low. All patients had moderate to severe small airway disfunction and hypoxemia. The mean values of FEV1/FVC, and RV/TLC were 58.9%, and 41.5%, respectively. The most common HRCT findings from this cohort of patients were bronchiectasis and bronchiolitis, with nodular shadows distributed in a centrilobular pattern. Morphological examination revealed peribronchiolar and bronchiolar wall inflammation composed of lymphocytes, plasma cells, and histocytes. Few cases were not confirmed by diagnostic criteria from Japan but clinically diagnosed as DPB due to satisfied treatment response and typical clinical features. *Conclusions:* More DPB cases need to be analyzed from Chinese population due to different presentations compared to Japanese population. This experience should help other clinicians in the investigation and management of DPB in non-Japanese patients. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 300-307)*

Key words: Chinese, Clinical presentations, Diagnostic criteria, Differential diagnosis, Diffuse panbronchiolitis

Introduction

In 1969, Yamanaka and his colleagues (1-3) proposed the name diffuse panbronchiolitis(DPB) to distinguish it from chronic bronchitis. In the early 1980s, the international scientific community became aware of this new entity (1). "Diffuse" refers to the distribution of the bronchial lesions throughout both lungs, and "pan" refers to the involvement of inflammation in all layers of the respiratory bronchioles. DPB has distinctive clinical and pathological features characterized by chronic pulmonary inflammation in the respiratory bronchioles of the lung and paranasal sinuses (4). Although no report on prevalence, DPB is an uncommon disease in China (5). The first case of DPB in China was reported in 1996 (6). Since then, an increasing number of cases have been reported. Most clinicians are not familiar with DPB, and it may be ac-

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tually under-recognized and under-reported in China (7). DPB is often misdiagnosed as other diseases such as bronchiectasis, chronic bronchitis, miliary tuberculosis, sarcoidosis, primary ciliary dyskinesia, cystic fibrosis or alveolar cell carcinoma (8). In this study, we reported 12 cases of Chinese patients with DPB who had different clinical features compared to Japanese cases, aiming to facilitate diagnosis differentiation of DPB in Chinese population.

Materials and methods

Patients

From October 2005 to August 2012, 12 patients were diagnosed as DPB in Zhongshan Hospital, Fudan University. Diagnosis of DPB was based on the diagnostic criteria proposed in 1998 by a working group of the Ministry of Health and Welfare of Japan (9)(Table 1). Three patients without paranasal sinusitis were confirmed by histopathological examination. After institutional review board approval, collected quality assurance data were reviewed.

Data collection

The laboratory examinations included routine blood tests, arterial blood gas analysis, serum cold hemagglutinin testing, sputum cultures, Ziehl-Neelsen (ZN) method for the detection of acid-fast bacilli(AFB) in sputum, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), quantitative immunoglobulins, auto-antibodies(include anti-CCP, rheumatoid factor, ANA), T-spot. TB test and saccharin test to evaluate mucociliary function.

The HRCT scan was analyzed by three experienced radiologists. HRCT scans were graded as described previously by Tsang KW *et al* (10): each lung was divided into three zones: upper (apex to carina), middle (carina to venous confluence), and lower(venous confluence to bases). Six lung zones were therefore evaluated individually for each patient. Grading for nodular profusion was made according to the extent of involvement in each lung zone as: 0 (normal), 1 (<25% of lung zone involvement), 2 (>25% but <50%), and 3 (>50%). Bronchial dilatation was similarly graded by comparing bronchial caliber with that of the accompanying artery: 0 (normal bronchial caliber), 1 (<1.5 times caliber of accompanying artery), 2 (>1.5 but <2.0 times), and 3 (>2 times). Bronchial thickening was graded as 1 (mild), 2 (moderate), and 3 (severe).

Pulmonary function and cardiac color ultrasound (UCG) tests were conducted in 11 patients. In total, six patients obtained lung histopathological examination, in which one patient went through open lung biopsy.

Statistical analysis

SPSS 13.0 software was used to analyze the data. Continuous data was presented as mean ± standard deviation (SD), while categorical data was presented as number and percentage.

Results

Demographic data and distribution

Six of the cases were male and six were female, aged 24-70 years (50±14.7). Three cases (25%) of these patients have been smoking for at least 10 years. The

Table 1. Diagnostic criteria for diffuse panbronchiolitis

1. Persistent cough, sputum and exertional dysponea
2. History of chronic paranasal sinusitis
3. Bilateral diffuse small nodular shadows on a plain chest radiography film or centrilobular micronodules on chest computed tomography images
4. Coarse crackles
5. FEV1/FVC <70% and PaO2 <80 mmHg
6. Titer of cold haemogglutinin ≥64

Cases definitely established should fulfill criteria 1, 2 and 3, along with at least two of criteria 4, 5 and 6. These parameters are useful for carrying out an epidemiological analysis. In countries in which the disease is very rare, surgical lung biopsy is required to make a diagnosis. Criteria are taken from a working group of the Ministry of Health and Welfare of Japan (9).1 mmHg=0.133 kPa.

average time from the onset of the symptoms to the diagnosis of the disease was 18 months to 39 years. The nationality of the patients were all the Han. All the patients were treated with azithromycin at the time diagnosed with DPB. One patient who had sputum with isolated aspergillus for twice in the follow-up was treated intravenously with itraconazole besides azithromycin. All the patients were treated with Azithromycin for at least 6 months.

Clinical manifestations

There were 11(91.7%) cases presented with chronic cough, copious purulent sputum production, and exertional dysponea and 5 of these 12 cases had hemoptysis. One patient had only hemoptysis. Seven cases (58.3%) had a fever. All patients were found to have end-inspiratory crackles in their chest on physical examination, and three (25%) of them had wheezes simultaneously, while only 2 (16.7%) patients had digital clubbing. All but 3 (75%) patients had a history of sinusitis. One patient complicated with asthma. One patient had a history of malignant thymoma and vitiligo for 11 years before he was diagnosed as DPB.

Laboratory findings

The neutrophil count was found higher than normal only in one case (8.3%). Nine cases (75%) had high ESR and ten cases (83.3%) had increased CRP. All of the patients received serum cold hemagglutinin testing, and results showed only one case had more than 16-folds higher titer than the normal value and others were all negative. Sputum cultures were done in all of the 12 cases. *P. aeruginosa* was isolated from 7(58.3%) patients, and *aspergillus* from one patient. The other 4 cases had no identifiable pathogen in the sputum. The results of AFB-stained sputum were all negative. CD4/CD8 lymphocyte ratio performed from peripheral blood were normal (8 cases) or low (4 cases) in all cases. Results of the auto-antibody and quantitative immunoglobulins were all negative. Results of T-spot.TB were all negative in the 8 patients who had this test. All patients have a negative result in saccharin test (saccharin transport time from inferior turbinate to oropharynx was less than 60 minutes), which further ruled out the diagnosis of primary ciliary dyskinesia (PCD).

Pulmonary function and UCG assessment

Pulmonary function test was measured in 11 patients. The results showed there was a significant airflow limitation. Eight cases (72.7%) had obstructive ventilation functional impairment, 3 cases (27.3%) demonstrated mixed obstructive-restrictive lung function impairment, and 3 cases (27.3%) had reduced diffusion capacity. All patients had severe small airway functional impairment. V_{max} 50 and V_{max} 25 decreased significantly. The mean predicted values of FEV_1/FVC, and RV/TLC were 58.9%, and 41.5%, respectively. The blood gas analysis showed that all the cases had hypoxemia, 3 patients (25%) had type I respiratory failure. UCG showed that two patients had pulmonary hypertension.
All of the above clinical and lab data are displayed in Table 2.

HRCT assessment

HRCT findings, together with histological examination, provided better approaches to distinguish DPB from other sinobronchial disorders (11). All 12 patients underwent thoracic high resolution computerized tomography (HRCT) scanning at the time of diagnosis and were scanned in supine position (scan thickness 1 mm and slice interval 10 mm) at the end of inspiration. In our study, there were four types based on HRCT findings, including type 1, nodules associated with bronchovascular branching; type 2, nodules branching in appearance("tree-in-bud"); type 3, nodules connected to ring-shaped or ductal opacities(bronchiolectasis); and type 4, dilatation of proximal terminal bronchioles and bronchi(predominantly at the peripheral airways). These four types of imaging were graded as described previously by Akira et al (12).The most common HRCT findings were bronchiectasis and bronchiolitis, which were seen in all patients. Most (11 cases) bronchiectasis and bronchiolitis were seen in the right middle lobe and both lower lobes. Nodular shadows were distributed in a centrilobular fashion, occupying in about half of the whole lung zones (Table 3). Another typical finding from HRCT was bilateral and diffuse centrilobular nodules connected to thickened and dilated bronchioles which were seen in almost all the cases (Table 3, Figure 1).

Table 2.1. Characteristics of patients with clinical and lab data

Patients	Age at onset (years)	Age at assessment (years)	Nasal symptoms (years)	Physical examination	Sputum pathogen	Concurrent illness	ESR (mm/h)
1 man	48	51	None	crackles	Flavobacterium	Malignant thymoma, vitiligo	28
2(woman	55	61	5	crackles	Commensals	Hypertension	5
3(woman	26	33	10	crackles	G(-) non-fermenting bacteria	Nil	10
4 man	1	38	None	crackles	P aeruginosa	Asthma	12
5(woman)	57	59	15	wheezes/crackles	Candida albicans	Nil	84
6(man)	36	56	20	crackles	P aeruginosa	Nil	40
7(woman)	55	70	15	wheezes/crackles	P aeruginosa	Duodenal ulcer	64
8(man)	10	60	None	crackles	P aeruginosa	Nil	24
9(man)	27	57	35	crackles	P aeruginosa	Irritable Bowel Syndrome	36
10(man)	20	24	4	crackles	Aspergillus	Nil	55
11(woman)	37	47	10	crackles	P aeruginosa	Nil	75
12(woman)	21	34	13	wheezes/crackles	P aeruginosa	Nil	23

Table 2.2. lung function and lab results

Patients	Serum IgE(<200)	Blood WBC count(×109/ml)	CRP (mg/l)	FEV1 (%predicted)	FVC (%predicted)	FEV1/FVC (%)
1	210	7.1	37.5	58	90	53
2	190	6.7	3.5	59.7	85.6	56
3	174	8.8	5	80	92	82
4	160	9.9	13.5	22.5	57.4	32.6
5	218	6.1	56	58.8	81.1	82.5
6	_	8.8	33	27.4	42.2	53.8
7	121	4.7	58	63.2	64.2	72.8
8	172	8.2	42.6	22.8	48	31.5
9	186	9.4	30.5	64	72	64.2
10	91	4.8	150.7	_	_	_
11	483	12.5	161	50	54	56
12	29	8.0	26	78	84.1	64.5

Pathological changes

In order to further confirm the diagnosis, five patients underwent transbronchial lung biopsy and one patient underwent open lung biopsy. Four of them showed typical pathological changes of DPB(Figure 2) as diffuse, bilateral chronic airways inflammation with some centrilobular chronic interstitial inflammation, the classic feature of foam cells in the walls of respiratory bronchioles, alveolar ducts and alveoli, intraluminal acute inflammation, follicular bronchiolitis, bronchiectasis/bronchiolectasis, organizing pneumonia, and post-obstructive lipoid pneumonia.

Table 2.3. lung function results (continued)

Patients	RV (%predicted)	RV/TLC (%)	Vmax50 (%predicted)	Vmax25 (%predicted)	Kco	Pulmonary artery pressure	PaO2 (mmHg)	PaCO2 (mmHg)
1	102	32	26.2	24.1	4.2	45	58	47
2	113	35	15.9	23.5	5.9	20	62	35.4
3	98	42	12.2	11.3	6.8	Normal	86	32
4	128	32.6	7.9	10.5	6.4	18	86	46
5	90	39.5	21.5	17.6	5.8	Normal	69	42
6	105	59.1	9.7	12.9	5.8	_	66	46
7	76.1	50.2	34.6	35.2	5.7	Normal	79	41.6
8	89	43.6	23.2	21.5	5.3	42	56	38
9	95	41.4	29.4	30.1	4.9	27	70	40.3
10	_	_	_	_	_	50	47	34
11	102	51.4	12.5	11.4	4.6	18	49	34
12	115	30	32.5	35.3	5.4	Normal	80	32

"-":patients did not accept this check for some reasons. FEV1=forced expiratory volume in one second; FVC=forced vital capacity; RV=residual volume; TLC=total lung capacity; Kco=carbon monoxide transfer coefficient; PaO2=arterial oxygen tension.

Table 3. HRCT assessment

Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	mean ±SD
Nodular profusion	1.7	1.8	1.3	2.3	1.8	1.8	1.7	2.0	2.0	1.3	2.2	2.0	1.83±0.3079
Bronchial dilatation	1.0	1.3	0.8	2.0	0.7	2.2	1.5	2.3	1.8	1.3	2.5	1.5	1.58±0.5926
Bronchial thickening	0.7	0.8	0.5	1.5	0.3	1.8	1.3	2.0	1.5	1.0	2.0	1.2	1.22±0,5702

Discussion

It has been more than 40 years since first DPB report in Japan (1-3). Studies on the etiology of DPB have revealed a genetic predisposition that is unique to Asians (13). DPB was mostly seen in East Asia, especially in Japan, and only a limited number of patients have been reported in non-Asian populations (14-20). Compared with the relative high DPB prevalence in Japan, the incidence of DPB in China is relatively low (5), maybe underestimated partially due to less recognization and report. The distinctive imaging and histological features, the coexisting sinusitis, and the isolation of *Haemophilus influenzae* and *Pseudomonas aeruginosa* in the sputum increases awareness of DPB. Histologically, DPB is characterized by chronic inflammation, localized mainly in the respiratory bronchioles and adjacent centrilobular regions, with characteristic interstitial accumulation of foamy histocytes, neutrophils and lymphocyte infiltration. Neutrophils and T lymphocytes, particularly CD8+ cells, together with the cytokines interleukin-8 and macrophage inflammatory protein-1, are supposed to play key roles in the development of DPB (11).

Laboratory findings from this study suggest immunological abnormalities, which is similar to the report by Sugiyama Y (4). However, we also find that cold agglutination test in 11 patients were negative, and the CD4/CD8 lymphocyte ratio in all patients were normal or low, that were different from Japanese patients, suggesting that these two tests might not be as important for the diagnosis criteria of DPB in Chinese as in Japanese (8,21,22). Microbiological analysis showed that 58.3% of these 12 patients had positive *P.aeruginosa* isolation in their sputum. The

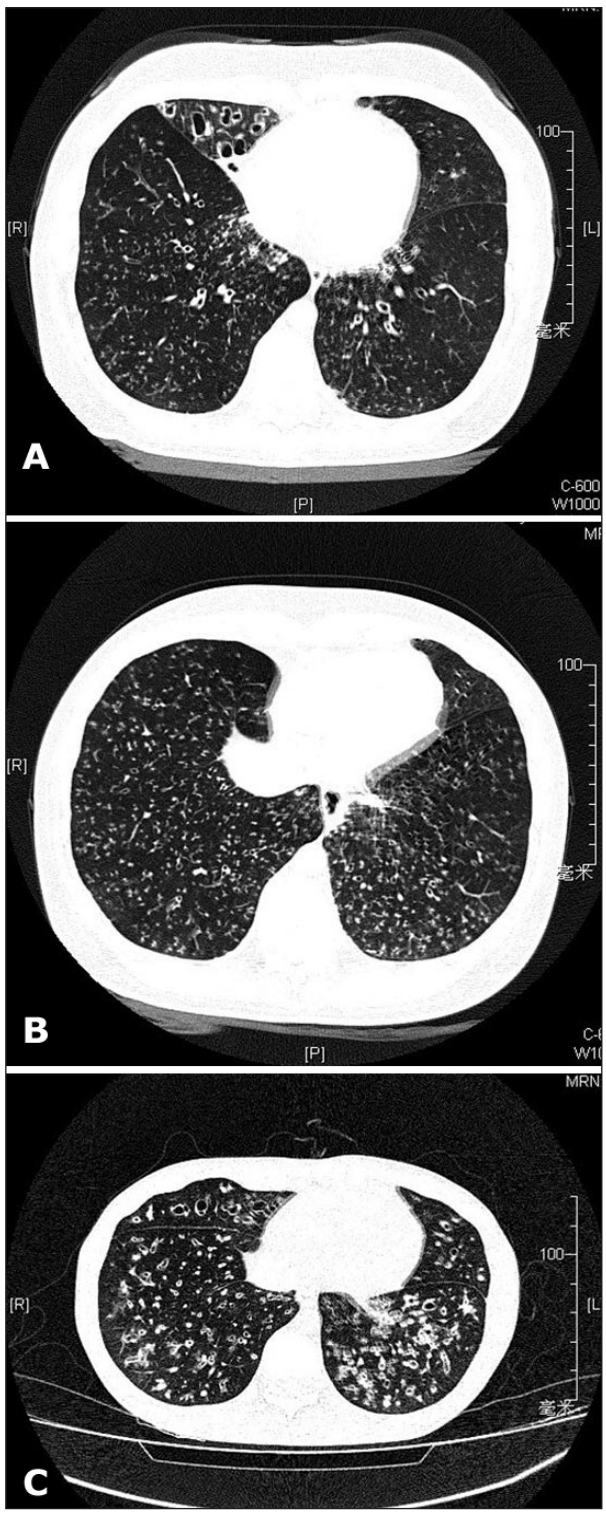

Fig. 1. HRCT showed bronchiectasis and bronchiolitis, ring-shaped or ductal opacities in upper, middle, and lower lungs, some of these changes were accompanied by small nodules. bronchiectasis were seen in right middle lobe and left lingual lobe.

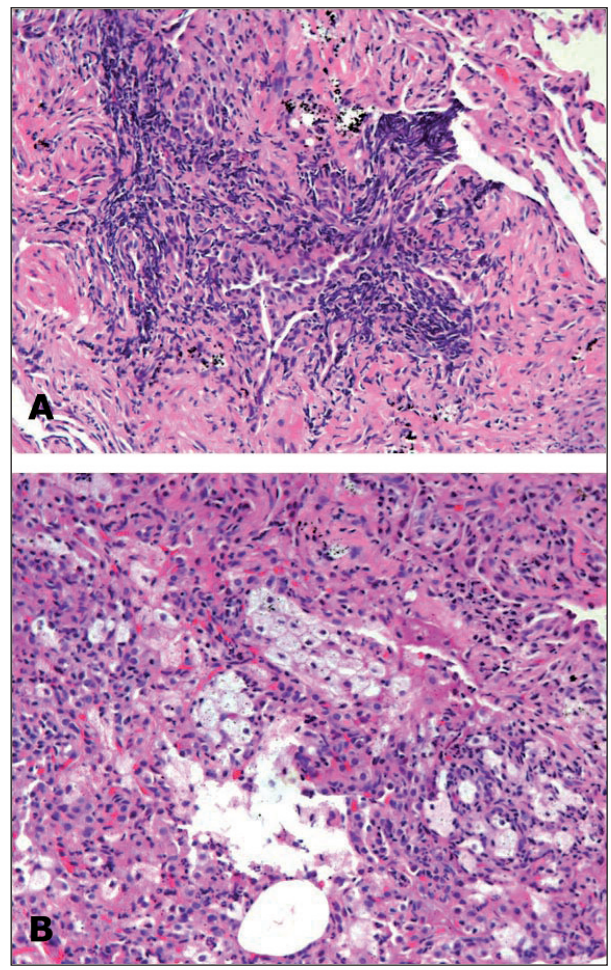

Fig. 2. Part of alveolar space collapsed with fibrous tissue hyperplasia, inflammatory cell infiltration and histocytic reaction. Carbon powder deposition was seen in local area. Chronic inflammatory cell infiltration and foamy phagocytes groups were seen in small bronchioles and interstitial lung tissue.

clinical feature of these patients were at least 10 years since appearance of symptoms, and their symptoms were usually more serious than other patients. The colonization of *P.aeruginosa* further reduces the lungs' capacity for gas exchange, which promote disease progression that ultimately leads to hypoxemia and, later, hypercapnia.

The value of HRCT scans in assessing small airways disease in DPB is obvious with confirmed pathological-radiological correlation (12,23,24). According to the grading of HRCT scan, we found that bronchodilatation is more severe in the patients with a history of more than ten years. However, from these few cases, lung function measurement showed

the grading of HRCT finding was not consistent with pulmonary function test. So more cases should be collected in future to confirm the correlation.

According to current guidelines, all patients were treated with azithromycin once diagnosed with DPB. Azithromycin (500 mg, once a day) was administrated intravenously in the first 5 days and was then taken orally (500 mg, once a day) while their symptoms and CT findings was progressively improved. Ten patients were followed up to 6 months. After at least 6 months of treatment with azithromycin, the presenting symptoms of dyspnea on exertion, cough, sputum production, and nasal symptoms improved or stabilized in 9 patients. One patient died two months after he was diagnosed as DPB because of the lethal pulmonary infection with *Aspergillus*.

All 12 patients had been misdiagnosed as other respiratory diseases before they were confirmed to have DPB, including bronchiectasis, chronic bronchitis, miliary tuberculosis, cryptogenic organizing pneumonia (COP), asthma, and lung cancer, among which bronchiectasis and miliary tuberculosis were the most common misdiagnosis entities. There were three patients in our study who had ever been diagnosed as miliary tuberculosis and received anti-tuberculosis treatment for at least 6 months. Patient with miliary tuberculosis also can present with chronic cough, sputum production and hemoptysis, and the CT features also can present with granular nodular or miliary shadow imaging. Sputum smear were done in all 12 patients with negative findings. T-Spot.TB test showed negative results in the 8 patients who received this test.

Other differentiation disease includes PCD and alphal$_1$-antitrypsin (AAT) deficiency. The key criterias to diagnose PCD are bronchiectasis in respiratory, dextrocardia, male infertility due to impaired sperm motility and female ectopic pregnancy in genitourinary (25-27). The saccharin test and the specific diagnosis requiring examination of cilia by light and electron microscopy (28) could facilitate the diagnosis of PCD. For ATT, the major presentation is pulmonary emphysema at third or fourth decade of age and liver disease, which typically presents early in infancy as neonatal hepatitis with a diverse degree of liver involvement and outcome (29). All of the 12 patients received the examination of liver function and abdominal ultrasonography, and the AAT was detected in two patients who had the symptom since their childhood, both of the results were normal.

In conclusion, we reported here 12 Chinese patients with DPB who had similar clinical presentation as Japanese patients but they also had different laboratory examination showing negative results in serum cold hemagglutinin testing. Beneficial effects from erythromycin treatment suggests early interference could significantly delay disease progress. If DPB is left untreated, the patient's condition deteriorates more rapidly than other chronic lung conditions, and the outcome is fatal (30). Thus, the early correct diagnosis and differential diagnosis is critical. Our experience is that typical HRCT imaging, clinical symptoms, lung function impairment in small airways, and exclusion criteria are key components to diagnose DPB. At certain conditions, empirical treatment with erythromycin or azithromycin might be considered if the clear diagnosis could not be made and follow up is needed to confirm the diagnosis. Further investigation in more DPB patients is warranted to accumulate more evidence for DPB diagnosis and treatment in Chinese population.

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